Current Management in Child Neurology

Fourth Edition

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PREFACE

The fourth edition of Current Management in Child Neurology contains succinct reviews on the evaluation and treatment of the most common neurological complaints in pediatric practice. The highly respected authors have produced superb "how-to" chapters rather than comprehensive reviews on etiology, pathogenesis, and therapeutic controversies, as found in a perfect companion standard textbook such as Child Neurology edited by Menkes, Sarnat, and Maria. The chapters contain carefully selected readings and Web resources for practitioners and patients who seek relevant information but do not want to be overwhelmed by unfiltered online sources.

The book has 111 chapters organized into three sections. In the first section, Clinical Practice Trends, the reader will learn more about the frequency of the most common neurological conditions seen in practice as well as information about the practitioner's "toolbox" for providing clinical and service excellence. Chapter 1, for example, introduces readers to the scope of inpatient and outpatient child neurology practice. Chapter 3 is a wonderful review of the neurologic examination that should be mandatory reading for rotating medical students and residents. Chapter 4 addresses practical use of neurodiagnostic tests in child neurology practice, a rare find in modern neurology texts.

In The Office Visit section, subheadings are organized according to the frequency of conditions seen in office or outpatient clinic settings. The section offers updated management reviews on headache, seizures and epilepsy, neurobehavioral disorders, school readiness, developmental delay, and a range of other conditions, including new chapters on acquired microcephaly, neurodegenerative disorders, chromosomal disorders, epilepsy in adolescence, epileptic encephalopathy, pediatric neurotransmitter disorders, and tropical child neurology.

The third section, The Hospitalized Child, has chapters addressing current therapy issues for trauma, meningitis and encephalitis, injury to the preterm and term brains, status epilepticus, and a host of other conditions associated with hospital care. New chapters include the approach to neonatal or infantile facial dysmorphism and congenital muscular dystrophies.

Since the third edition was published, there has been an exponential increase of online resources and Web sites that can serve families, primary care practices, and pediatric specialists. However, with the ever-increasing volume of available information, people no longer ask "Where can I find more information?" but rather "What can I believe?" Thus, it is hoped this new edition of Current Management in Child Neurology will continue to provide succinct expert opinion on clinical management as well as direction on how to obtain highly relevant and high-quality additional information.

I wish to express my sincere appreciation to a distinguished group of authors for sharing their knowledge, skills, values, and attitudes in caring for children with nervous system problems. I would also like to thank my dedicated clinical research assistants Virginia Williams and Felina Kostova who worked tirelessly on this 4th edition. Lastly, I would to thank all those who serve children daily by practicing medicine, teaching and mentoring, and conducting research.

Bernard L. Maria, MD, MBA

To Barbara and Alex,
Always.

Contents

Section 1

Clinical Practice Trends

Chapter 1

Common Neurologic Complaints and Conditions

Bernard L. Maria, MD, MBA

One in 10 children seen in primary-care practice and 25% of hospitalized children have a neurologic complaint or condition. General practitioners frequently encounter patients with neurologic problems, but many report considerable difficulty in adequately managing the most common disorders, such as migraine, attention-deficit hyperactivity disorder (ADHD), febrile seizures and first unprovoked seizures, and uncomplicated epilepsy. By gaining knowledge and skills in child neurology, practitioners will grow increasingly confident about treating children who have common neurologic complaints.

Child neurology in the United States can be thought of as a discipline that manages four common problems—attention-deficit hyperactivity disorder (ADHD), developmental delay, epilepsy, and headache—and an estimated 2,000 rare disorders that affect the developing nervous system. The spectrum of complaints and conditions, however, varies considerably across communities and borders, and across the world. The high variability in "content" of a child neurology practice in a given community around the world can be explained by regional health conditions and concerns, caregiver expectations and needs, referring physician training, self-confidence and needs, child neurology interest and expertise, specialty availability and accessibility, health care funding and third-party funding policies, and economic and cultural realities of a given region, country, or continent.

Generally, primary-care physicians in the United States are quick to consult neurologists and other specialists about patients who have neurologic problems due to the high expectations of caregivers, fear of litigation, low self-confidence in neurologic skills, ready availability of experts in some communities, and difficulty in keeping up with rapid advances and current practices. In that context, the successful management of children with common neurologic problems demands a partnership between the primary-care physician and the specialist. Judicious use of the expert for more complex clinical questions is important to building efficiencies and cost-effectiveness in health services delivery. Some argue that all neurologic problems should be managed exclusively by the neurologist; others hold the extreme position that management of common conditions is the exclusive purview of primary care. To optimally serve caregivers, I believe that primary-care physicians and child neurologists must communicate, support one another, educate one another, and jointly manage complex cases. The decision by a primary-care physician to independently manage a child with a common condition depends on many factors, including factual knowledge, skills, values, and attitudes. This book aims to assist practitioners from many disciplines with the management of common neurologic conditions by providing succinct opinions from leading authorities on a comprehensive range of neurologic complaints and conditions.

In Chapter 7, "Excelling at the Art of Medicine," Luallin underscores the fact that health services insurers value practitioners who can deliver cost-effective medical care and ensure a high level of patient satisfaction. Excelling in the art of medicine is something we must all strive for. One of the most important ways for practitioners to excel is to develop self-confidence in managing patients with the most common complaints. However, a high level of confidence in managing neurologic problems in children does not necessarily

translate into judicious use of ancillary laboratory testing or cost-effective care. Data show that even confident pediatricians refer the great majority of patients to neurologists. Thus, educational efforts in pediatrics and neurology must emphasize the need for high-quality "gatekeeping" by primary-care physicians.

If one accepts the notion of the pediatrician or other primary-care provider as the "gatekeeper," it becomes essential to identify the most common neurologic complaints and conditions and then to obtain diagnostic and treatment information pertaining to those conditions. Accordingly, we obtained survey data from practicing pediatricians to gain insight into the nature of the pediatric office practice and to determine what predicts a high level of confidence in independently managing children with neurologic conditions. In addition, we obtained information on the actual frequency of inpatient admissions for children with neurologic conditions over a 6-year period (1996–2002) in Florida, where approximately 1,500 pediatricians serve an estimated pediatric population of 3.5 million. In addition, we obtained data on outpatient visits in Florida and across the United States in 2003.

The remaining chapters of this book include advanced diagnostic and treatment information on the most common neurologic conditions encountered in children. The overall goal is to better prepare primary-care physicians to care for more children with common neurologic complaints in both the office and hospital-based settings for three important reasons. First, there is an inadequate supply of neurologists, and trends indicate an increasing undersupply of child neurologists; second, practitioners want to contribute more directly to patient satisfaction, which is one criterion used to measure quality of care; and third, parents of pediatric patients adhere more carefully to recommendations when they are satisfied with the care they receive.

Managing Neurologic Complaints in Primary Care

In Chapter 2, Reigart reviews his approach to managing common neurologic problems in his general pediatric practice. In 1993, we published a survey of 190 practicing pediatricians who defined their clinical practice as related to neurologic problems (see Suggested Readings). More than 90% of pediatricians saw more than 50 children per week in practice, and 60% of practitioners saw more than 100 children per week. One in 10 children seen by pediatricians had a primary neurologic complaint. The survey requested information regarding the frequency of 40 emergency-related and non-emergency-related neurologic problems seen in practice. On the basis of the percentage of physicians citing neurologic problems in their practice, the top four conditions were ADHD, epilepsy, developmental delay, and headache (Table 1-1).

In the same study, self-assessment scores were obtained from pediatricians and pediatric trainees. Not surprisingly, pediatricians scored significantly higher ($p < .01$) than the 35 pediatric trainees in the five questions testing (1) knowledge and skill in performing a neurologic examination, (2) ability to interpret neurologic findings, (3) knowledge of factual information about the diseases of the nervous system, (4) ability to determine the need for investigations, and (5) ability to develop a positive attitude toward neurologic diseases. No significant difference was noted in self-assessment scores between pediatricians who had practiced for more than 10 years and those practicing for 10 years or less. On a scale of 1 to 10 (1 being poor and 10 being excellent), pediatricians had an average total self-assessment score of 7.08 (± 1.58).

Our 1993 study revealed two particularly interesting additional findings. First, 60% of pediatricians referred 8 in 10 children to the neurologist, and 54% referred 9 in 10 patients. Second, pediatricians who referred more than 90% of children to neurologists had significantly lower self-confidence in performing a neurologic examination ($p < .001$). Thus, acquiring and updating child neurology examination skills, as reviewed by Griesemer in Chapter 3, "The Neurologic Examination," may be important to trainees and primary care physicians who would like to be more confident in managing common neurologic complaints.

The lowest self-assessment score for pediatric trainees was in "factual information about diseases of the nervous system." For practicing pediatricians, "ability to interpret neurologic findings" had the lowest score, and "factual information about diseases of the nervous system" had the second lowest. This book provides primary-care physicians, neurologists, and trainees with factual information on how to evaluate and treat children with the most common diseases of the nervous system.

Although health care has changed considerably in the past decade, it seems unlikely to us that 1993 survey data

TABLE 1-1. Top 10 Neurologic Conditions (Pediatric Survey Data)

1.	Attention-deficit hyperactivity disorder (ADHD)
2.	Seizures and epilepsy
3.	Developmental delay
4.	Headache
5.	Newborn disorder
6.	Mental retardation
7.	Microcephaly/macrocephaly
8.	Motor disturbance
9.	Central nervous system infection
10.	Neuromuscular disturbance

would be much different today in the United States. Why is that? The cynical view is that there is an inherent conflict of interest for child neurologists who derive much of their income from volume practice to motivate and educate primary-care referring physicians to manage more children on their own. Although encouraging the willing pediatrician to begin carbamazepine for new-onset complex partial seizures may be the "right thing" for the patient, pediatrician, and child neurologist to do, the reality is that such patients are swiftly directed to the pediatric neurologist's office practice. Given that people will work to maximize their own economic well-being (cost-effective primary and specialty-care practices), and that patterns of referral to specialists are deeply rooted behaviorally and culturally in both primary and specialty care, it is hard to imagine that the burden of neurology care for common complaints and conditions could shift to the primary-care setting, where it resides in much of the rest of the world. However, it seems likely that the inadequate supply of child neurologists in the United States will force pediatric and family medicine trainees and program directors to revisit neurology educational expectations to prepare for a new "real world." We hold the view that primary-care physicians should be equipped to independently manage the most common disorders, such as ADHD, headache, developmental delay, febrile seizures, first unprovoked seizure, and uncomplicated epilepsy.

The Office Visit

Actual outpatient data for the most common neurologic problems encountered in pediatric practice were obtained from the Outpatient Forecaster database maintained by Inforum, a division of The Medstat Group. The data within Outpatient Forecaster are derived from three sources: MarketScan, an employer claims database furnished by Medstat; the National Ambulatory Medical Care Survey (NAMCS); and the Health Care Financing Administration (HCFA) Standard Outpatient Analytical File. Visit volumes are reported at the three-digit *International Classification of Diseases* (ICD-9) Clinical Modification (CM) diagnosis level, which are groupings of individual ICD-9-CM codes. Visit volumes refer to episodes of service, as opposed to the number of patients served. Reporting patients by head counts would underestimate the frequency of problems or diagnoses. Conversely, each episode of service is reported once, even where individual patients have multiple neurologic diagnoses. Consequently, these data understate the incidence of individual diagnoses across the United States to the extent that they are reported as secondary diagnoses.

The 2003 Florida and United States outpatient visit data (Table 1-2) and the 1996 Florida outpatient visit data shown in the second edition of this book match up remarkably well with information provided in the 1993 survey of pediatricians in Florida, ADHD, or hyperkinetic syndrome, is a dominant ICD-9-CM diagnosis among neurologic conditions, accounting for 71% of the top six conditions. Specific developmental delays, nervous or musculoskeletal problems, infantile cerebral palsy, epilepsy, and migraine are also among the most common conditions encountered in pediatrics. Epilepsy was perceived by Florida pediatricians as the second most common neurologic condition in primary care, but it actually ranks fifth in Florida and United States databases. However, the database was unable to provide information on febrile seizures and first unprovoked seizure-related visits to the pediatrician. Headache was ranked the fourth most common by pediatricians, and migraine actually accounts for over 288,000 outpatient visits across the country. The prevalence of migraine is 5 to 7% in the school-age population, and studies have shown that a small percentage of children with migraine come to medical attention. Given a 2003 U.S. pediatric population of 53 million over age 5 years, and a conservative 5% prevalence of migraine (2,650,000 children), one would expect a significantly larger number of outpatient visits than what has been recorded. Thus, the actual number of visits for migraine in 1 year across the country (288,551) strongly suggests that a small fraction (less than 1 in 10) of children with migraine seek medical care and are diagnosed as having migraine. One survey of school aged children found that 12.8% of children 5–15 years of age suffered from headache and that migraine was the commonest of these headaches (10.6%). Furthermore is has been estimated that 28% of adolescents 15–19 years of age suffer from migraine headaches. Other studies have reported even higher prevalence of headache in young school children and adolescents. One prospective study of headaches in children reported 16% of 6 year old children and 19% of 12 year old children suffered from headaches. Of 572 children referred to one major headache center, 99% had a clinical diagnosis of migraine and 85% met the International Classification of Headache Disorders II (ICHD II) criteria for migraine. Despite these reports of high prevalence and high morbidity of headaches in children and

TABLE 1-2. Frequency of Outpatient Visits in 2003 for the Most Common Neurologic Conditions among Patients under the Age of 18 in Florida and across the United States

Condition	Florida Visits	U.S. Visits
Migraine	14,943	288,551
Hyperkinetic syndrome	242,809	4,685,906
Nervous and musculoskeletal systemic symptoms	19,037	367,581
Epilepsy	15,169	292,761
Infantile cerebral palsy	17,414	336,155
Specific developmental delays	34,354	662,886

adolescents, they are infrequently reported as diagnoses at office visits. A review of the national Ambulatory Medical Care Survey 2004 reported only 1.2% of all visits were for headache and only 0.43% were diagnosed as migraine. Headache is clearly one of the most important conditions for which practitioners should develop expertise in recognition, evaluation, and treatment. Given that headache is a common cause of school absenteeism (third after respiratory infection and asthma), and that migraine is severely under-diagnosed (and yet very treatable), practitioners should actively educate caregivers and schools about detection and modern management.

ADHD ranks first in the 1993 pediatrician survey and in 2003 Florida and U.S. outpatient data (see Table 1-2). Because ADHD has a prevalence of 3 to 5% of school-age children, one would have predicted 4,380,000 biannual visits if all children over age 5 years with ADHD were seen and diagnosed. In Florida in 1996 (see the second edition of this book), 25,000 visits were recorded for ADHD with the same databases, though 200,000 visits had been predicted based on epidemiologic data. Several explanations may have accounted for this discrepancy in the past, including under-diagnosis of ADHD or undercoding of hyperkinetic syndrome. Whatever the reason, it now seems that it has been corrected, because over 240,000 were diagnosed with ADHD in Florida in 2003. It would seem that ADHD, in contrast to migraine, is diagnosed significantly more often than in the past in Florida or across the country. Thus, public health education efforts should address the problem of migraine underdiagnosis to reduce headache-related school absence.

Seizures and epilepsy rank among the most common neurologic conditions. Several important facts about seizures and epilepsy justify a key role for primary care physicians: (1) 90% of seizures at age 2 years are febrile and the great majority of such patients do not develop epilepsy, (2) only 50% of children having a single unprovoked seizure will develop recurrent unprovoked seizures (epilepsy), (3) diagnostic evaluations such as magnetic resonance imaging and electroencephalography can be easily obtained in most communities, (4) after initiating a single antiepileptic drug for epilepsy, most children will not have recurrent seizures, and (5) most children on a single antiepileptic drug can be successfully weaned off after a period of 1 to 2 years seizure-free. Although not all children have simple febrile seizures or uncomplicated epilepsy, it seems clear that well-informed primary-care physicians should be independently managing many children with seizures. The subjects of seizures and epilepsy are reviewed in this book.

Pediatricians ranked developmental delay the third most common neurologic complaint and motor disturbance as eighth. In reviewing outpatient visit data, specific developmental delays and cerebral palsy ranked as the second and fourth most common specific conditions respectively. This book contains several excellent chapters on the evaluation and treatment of developmental delay, cerebral palsy, and associated complications.

The Hospitalized Child

The frequencies of inpatient diagnoses were obtained from the State of Florida's Agency for Health Care Administration. For the sake of consistency with the outpatient data, diagnoses were grouped at the three-digit level, and only the principal diagnosis is included for each discharge.

Not surprisingly, children hospitalized for neurologic conditions have a very different mix of diagnoses from that of children seen in the outpatient setting (Table 1-3). The most common neurologic conditions requiring admission from 1996 through 2002 were enteroviral meningitis and epilepsy. Epilepsy accounts for many admissions to neurology services across the country. Central nervous system infections, such as enteroviral meningitis, are a common cause for admission, but patients who have these conditions often are managed independently by general pediatricians and infectious disease specialists. A child neurology consultation may be obtained for seizure emergencies, evaluation of altered state of consciousness, assessment of neurologic function, and provision of a developmental prognosis. In 1999 and 2002, the principal diagnosis of hyperkinetic syndrome ranked third among all causes for hospitalization. Although ADHD is a common comorbid condition to epilepsy, for example, it is surprising to note that 636 children were admitted to Florida hospitals in 2002 with the primary diagnosis of hyperkinetic syndrome, an increase of 72% since 1996, and 18% since 1999. However, 80% of ADHD cases have one or

TABLE 1-3. Frequency of Discharges from Acute-Care Hospitals in Florida for the Most Common Neurologic Conditions among Inpatients under the Age of 18 Years in Calendar Years 1996, 1999, and 2002

Condition	1996	1999	2002	Change (2002 vs 1999)
Enteroviral meningitis	759	957	937	20
Epilepsy	780	831	848	17
Hyperkinetic syndrome	369	538	636	98
Concussion	265	323	442	119
Skull base fracture	363	330	363	33
Skull vault fracture	287	280	352	72
Fracture of face bones	259	240	255	15
Meningeal hemorrhage	172	171	223	52
Bacterial meningitis	183	168	151	17
Other brain injury	527	70	49	21
	3,964	3,908	4,256	348

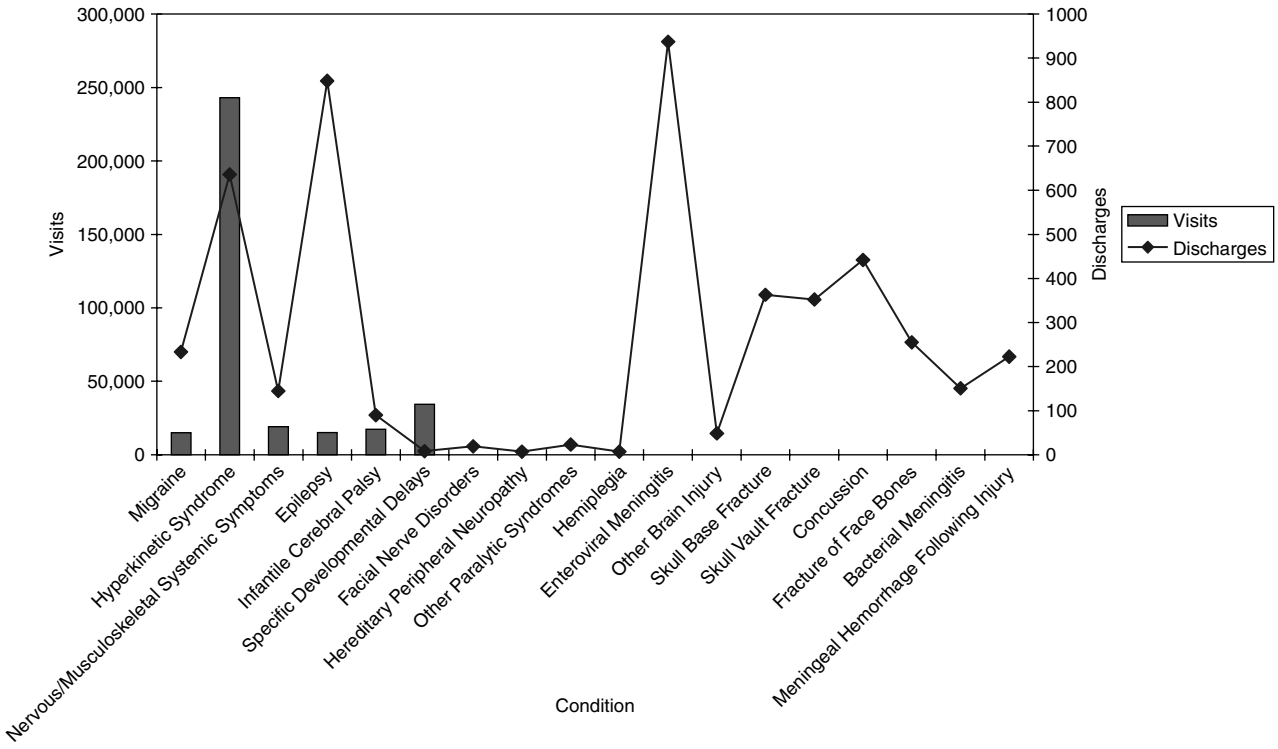

FIGURE 1-1. The frequency of diagnosis in the inpatient setting for the calendar year 2002 and in the outpatient setting for the calendar year 2003.

more secondary diagnoses, and 50% have two or more secondary medical or psychiatric diagnoses that require hospitalization. Thus, although ADHD is cited as a frequent cause of hospitalization, comorbid conditions are primary reasons for admission. If one combines all specific conditions resulting from trauma (skull base fracture, skull vault fracture, fracture of face bones, and concussion), then head injury is the leading cause for hospitalization of children with a neurologic condition. Figure 1-1 presents a combined view of the most frequent conditions treated in both the inpatient and outpatient settings. Note the difference in the rankings of clinical conditions between inpatient and outpatient data. It seems clear that, with the exception of ADHD, the scope of conditions seen in the outpatient setting is different from what one sees in the hospital. A number of neurologic conditions requiring hospitalization, including the most common ones discussed above, are reviewed in this book.

Implications

There continues to be considerable debate about who should be expected to first manage neurologic complaints in children. For example, in some communities, it is customary for families of children with ADHD to first seek out interdisciplinary programs run by developmental pediatricians, child neurologists, or child psychiatrists. In contrast, in communities where comprehensive ADHD programs do not exist, family physicians and general pediatricians are expected to evaluate and treat children with ADHD; the family may not have ready access to a specialist. The busy, fast-paced nature of primary care makes it essential for physicians to have up-to-date information and guidelines for the management of ADHD and the other most common neurologic complaints.

If one accepts the American Academy of Neurology's premise that 75% of patients with neurologic complaints should be cared for by a neurologist, then the United States currently has an inadequate supply of neurologists. Because primary-care providers contribute 85 to 90% of referrals to neurologists, the answer to the inadequate supply of neurologists could be for pediatricians to assume a more active role in managing common neurologic conditions, as do pediatricians in Canada and the United Kingdom. Thus, in an ideal world, primary-care physicians would accept more responsibility in providing principal care.

The rank order of neurologic complaints in primary care differs somewhat from actual outpatient data. It is, nevertheless, reasonable to conclude that ADHD, developmental delay, seizures, cerebral palsy, and headache represent five of the most common specific conditions

that pediatricians should be most confident in managing. A second important point is that regular exposure of pediatric trainees to inpatient neurologic conditions in no way ensures they are prepared for neurologic complaints and conditions in pediatric primary care. Figure 1-1 illustrates the fact that the most common neurologic conditions are very different in outpatient and inpatient settings. This has important implications for educational programs, especially when one considers that conditions requiring hospitalization are often complex and should be managed by child neurologists rather than general pediatricians. In Chapter 5 in this section, Larson and Brumback review issues on education of trainees.

Some may argue that the child with intractable epilepsy admitted to the hospital for videotelemetry monitoring, insertion of a vagal nerve stimulator, or epilepsy surgery is all the "teaching material" required to discuss the management of more common conditions, such as febrile seizure, first unprovoked seizure, or well-controlled epilepsy, which do not require hospitalization. However, it is our bias that to ensure exposure to a wide range of neurologic conditions they will ultimately encounter in practice, trainees should learn neurology in the clinic under the supervision of child neurologists who can attend to improving their neurologic knowledge, skills, values, and attitudes. In fact, experienced community pediatricians advise our residents to spend as much time as possible in the clinic learning neurology and the neurologic examination. Compliance with that recommendation has been problematic, and many (perhaps most) graduating pediatricians have far *less* exposure to child neurology than in the past when neurology rotations were mandatory. It seems that many trainees with primary-care career interests and their program directors must cope with a variety of educational competing interests and regulatory issues (eg, 80-hour work week) that preclude more intense neuroeducation.

Pediatricians entering practice express uncertainty about their readiness to manage the most common neurologic conditions. Survey data of practicing pediatricians support this assertion. The educational problem can be summarized as follows: (1) most neurology teaching takes place on the wards, where patients with complex conditions are hospitalized for very short periods of time; (2) neurology rotations are elective during pediatric training —for more than a decade, it has been common practice in many programs for pediatricians to graduate without having completed a neurology rotation or had meaningful outpatient neuroeducation; (3) good performance by residents on the written pediatric in-training examinations is viewed by pediatric program directors as evidence that neurology education is adequate; (4) didactic lectures rather than hands-on experience may be viewed by trainees and program directors as adequate to ensure competency; (5) the emphasis on providing trainees with general pediatric continuity clinic experience fails to recognize that neurology must be learned from a child neurologist; when the continuity-care clinic patient is referred to the neurologist, continuity is lost for the pediatric resident; and (6) training programs have not systematically examined what knowledge, skills, values, and attitudes are required in the health services marketplace. If one were to use the time-honored business approach of giving customers what they need, we would have to ask how many program directors have data on the expectations of those who will employ graduating pediatricians.

Conclusion

The practice of primary care is demanding and fast paced. Pediatricians, family physicians, and house staff report considerable difficulty in adequately managing the most common neurologic conditions and promptly refer patients to the neurologist. By improving knowledge and skills in child neurology, the practitioner should become more confident in offering principal care to the child with a common neurologic complaint. Child neurologists should continue to encourage pediatric trainees to learn about the management of common neurologic conditions, with emphasis placed on the outpatient setting. The chapters of this book are authored by some of the leading authorities in the field to provide primary-care physicians, neurologists, and trainees with succinct reviews on the evaluation and treatment of the most common neurologic conditions. We believe the book's content can improve practitioner self-confidence and increase the number of children with neurologic complaints who are managed well in the primary-care setting.

Suggested Readings

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Chapter 2

Managing Common Neurological Disorders: Role of the Primary Care Practitioner

J.R. Reigart, MD, FAAP

Primary care practitioners have an important role in managing common neurologic complaints and conditions. The evidence is that headache and migraine are under-diagnosed despite the fact that they account for high rates of school absences. Febrile seizures and first unprovoked seizures are often first managed in pediatric practice. In this chapter, we review current management practices for headaches, seizures, head injury, developmental delay, and autism.

Primary care physicians are regularly called upon to evaluate a wide variety of symptoms in infants and children that may represent neurological disease. The challenge for the primary care provider is to determine which of these children are indeed suffering from neurological disorders, decide the urgency of the problem for diagnosis and management, and then to decide which children need evaluation and management by a pediatric neurologist. The most common referrals to neurologists are seizures and other movement disorders, headaches, attention disorders, and developmental delay. Many children with these conditions can be diagnosed and treated in the pediatric office, without the need to refer to a pediatric neurologist or developmental specialist.

Advances in neuropharmacology have allowed pediatricians the opportunity to actively participate in the care of children with properly diagnosed neurological conditions. The primary care physician prescribes the majority of medications for attention-deficit disorder (ADD) and attention-deficit hyperactivity disorder (ADHD). Likewise, the pharmacologic management of children with headaches should be the responsibility of the primary physician. Given the large number of antiepileptic drugs (AEDs) available for management of epilepsy, it is important for the primary care physician to participate in monitoring for therapeutic response and side effects. In this chapter, we will review the challenges of managing common complaints in primary care practice.

Headaches

Headaches have been reported to be among the major causes of school absenteeism. Though reliable data are lacking, one survey of school-aged children found that 12.8% of children 5 to 15 years of age suffered from headache, and migraine was the commonest of these headaches (10.6%). Furthermore, it has been estimated that 28% of adolescents in 15 to 19 years of age suffer from migraine headaches. Other studies have reported even higher prevalence of headache in young school children and adolescents. One prospective study of headaches in children reported 16% of 6 year old children and 19% of 12 year old children suffered from headaches.

Of 572 children referred to one major headache center, 99% had a clinical diagnosis of migraine and 85% met the International Classification of Headache Disorders II (ICHD II) criteria for migraine. Furthermore, headache has been reported to cause major decrements in quality of life. Children with headaches differed from children without headaches in overall quality of life and in all subscales on a standard evaluation. The greatest effect was in school functioning, and the effect here was comparable to children with cancer and rheumatologic diseases. Despite these reports of high prevalence and high morbidity of headaches in children and adolescents, they are infrequently reported as diagnoses at office visits. A review of the National Ambulatory Medical Care Survey 2004 reported only 1.2% of all visits were for headache and only 0.43% were diagnosed as migraine. It is not clear whether this low rate of visits for headache reflects a lower prevalence of headaches than in surveys or whether parents do not choose to consult their physicians for headache diagnosis and management. Since there are a variety of relatively specific therapies for headache, particularly migraine, it would appear to be beneficial to children to have primary providers more commonly diagnose migraine if prevalence is as reported.

The primary care physician should be comfortable with diagnosing headaches and accepting that most headaches are primary headaches. They should understand that primary headaches are chronic and recurrent, not acute and progressive. Like ADHD, migraine has a high degree of heritability and thus family or maternal history of "sick" headaches is strongly suggestive of a primary headache diagnosis. It has been reported that 85% of brain tumor headaches are associated with neurological findings within 8 weeks of onset and in virtually all cases by 24 weeks. The common findings in these secondary headaches are papilledema, diplopia, hemiparesis, and ataxia. Children with headaches of several months duration and normal examination rarely require imaging for the evaluation of headache. A careful history of the headaches, evaluation of the family history, and a good neurological exam should suffice to rule out increased intracranial pressure that can mimic migraine in children.

Though they have been reported to lack sensitivity, the ICHD II criteria for diagnosis of migraine are useful in assessing children with headaches as shown in Table 2-1. Most primary headaches in children can be managed by simple analgesics and randomized control trials favor use of ibuprofen over acetaminophen. Complementary and alternative therapies have shown some success in children as well. In particular, cognitive behavioral therapy and relaxation therapy have shown excellent results in placebo-controlled randomized trials for migraine and other headaches in children. When simple analgesics and nonpharmacologic therapies are not successful, consideration may be given to the use of triptans, which have proven very effective in the treatment of migraine in adults. However, a recent systematic literature review of triptans in children identified only four randomized, blinded clinical trials. These lent only modest support for the use of triptans in children, perhaps due to the fact that migraines seem to have a shorter duration in children than adults and because of the high placebo effect in the control group. Since they may be only modestly effective and are not Food and Drug Administration approved for use in preadolescents, it is perhaps best at this time to refer patients who may benefit from these agents to a neurologist, especially if maximal doses of ibuprofen prove ineffective. In terms of preventative therapy, cyproheptadine, β-blockers, tricyclic antidepressants, and AEDs, such as valproate and topiramate, are commonly used. If cyproheptadine or propanolol is ineffective in preventing migraine headache, then referral to the neurologist is recommended.

TABLE 2-1.

A.	At least five attacks fulfilling criteria B–D
B.	Headache attacks lasting 1–72 h
C.	Headache has at least two of the following characteristics:
	1. Unilateral location, may be bilateral, frontotemporal (not occipital)
	2. Pulsing quality
	3. Moderate or severe pain intensity
	4. Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D.	During the headache, at least one of the following:
	1. Nausea and/or vomiting
	2. Photophobia and phonophobia, which may be inferred from behavior
E.	Not attributed to another disorder

In summary, the primary pediatric provider should be able to differentiate primary from secondary headaches. He should be familiar with the diagnosis of migraine and be able to manage most cases in his office. He should seek to make the diagnosis more frequently than has been true in the past in order to better manage debilitating symptoms.

Seizures

The primary care provider is often called on to assist in the diagnosis and management of seizures and other movement disorders. The commonest problem confronting primary care physicians in children aged 6 months to 5 years is the simple febrile seizure. The simple febrile seizure has been defined as a seizure lasting less than 15 minutes occurring in a child in this age group who has a fever but does not have a central nervous system infection. Up to 20 to 30% of children have more than a single febrile seizure within 24 hours. The American Academy of Pediatrics (AAP) has published several practice parameters

relative to this problem. Four specific recommendations supported by available studies have been made in reference to the evaluation of this problem. The AAP does not recommend an electroencephalography (EEG) or neuroimaging for febrile seizures. Due to the fact that there is no evidence that routine blood studies are of value in the evaluation of such children, it does not recommend routine measures of blood chemistries, including serum electrolytes, calcium, phosphorus, magnesium, and complete blood count or blood glucose in such children. If the child has symptoms suggestive of hypoglycemia other than the seizure, blood glucose may be performed. The AAP recommends a diagnostic lumbar puncture for children less than 12 months of age since seizures in 13 to 16% of young infants may be the presenting symptom of meningitis.

Although 50% of children under 12 months of age with febrile seizures have recurrent seizures, the considerable majority do not develop epilepsy. The AAP has evaluated the risks and benefits of antiepileptic therapy in such children and concluded that the risk of continuous therapy outweighs any benefit of such therapy. It is, therefore, a responsibility of the primary care provider to provide education and support to parents of such children with reassurance that these seizures are highly unlikely to be injurious to their child and do not suggest a high likelihood for the development of epilepsy. The Home Management of Breakthrough Seizures, including use of rectal diazepam, is addressed in Chapter 23 "First-Choice Antiepileptic Drugs" of this book.

Seizures without fever present a somewhat different problem for the primary care provider. It has been reported that one-third of the population has at least one seizure at some time in their life, though most do not develop epilepsy (two or more seizures). A brief generalized seizure in an otherwise well child does not require extensive evaluation though most parents expect some type of brain imaging, even if the yield is very low. Although abnormal EEG increases the risk of seizure recurrence, an EEG abnormality in of itself does not justify starting an AED. If the history suggests the possibility of past seizures, such as unexplained drooling on the pillow, developmental delay, or neurological abnormalities on examination, then magnetic resonance imaging, EEG, and laboratory evaluations should be ordered. In this case, prompt evaluation by a neurologist is also indicated. AEDs should not be initiated until a diagnosis of epilepsy has been made.

When the diagnosis of epilepsy has been made, then a decision should be made about selecting an AED. The chapter of this book on "First-Choice Antiepileptic Drugs" reviews the approach to initiating therapy. Though there is no need for the primary care physician to be familiar with the indications for each of the drugs available, he should be aware of the potential side effects and drug interactions. Drugs of choice such as oxcarbazepine, topiramate, or levetiracetam do not require routine laboratory monitoring of blood counts or liver enzymes but others, such as carbamazepine and valproate, require periodic laboratory tests. The primary care pediatrician should become comfortable with therapeutic drug monitoring and establish relationships with persons proficient in pharmacokinetics and modifications of drug dosing to achieve appropriate therapeutic drug levels.

A related and difficult problem is nonepileptic movement disorders in children. While some of these are familiar to pediatricians, such as simple breath holding spells, others may be difficult to evaluate, diagnose, and manage. In such situations, it is important to obtain a careful history of the movement disorder and to perform a careful examination of the child. In such cases, it can be exceptionally useful to have the parents videotape episodes for review by the provider and the neurologists. In most cases, nonepileptic movement disorders are best referred directly to a neurologist for diagnosis, after which the primary provider can participate in the management of the child.

ADHD

Primary care physicians play a key role in the diagnosis of ADHD. ADHD and associated conditions are very common with estimates of ADHD frequency of 2 to 10% of all children. ADHD is highly heritable. If a parent has ADHD, the risk to children has been estimated at 57%. In addition, children with epilepsy and tics have a high prevalence of comorbid ADHD. Since these problems are very common, it is clearly not feasible for all to be managed by developmentalists, neurologists, psychiatrists, and other specialists, so the primary care physician must be familiar with the diagnosis and management of such children. Fortunately, there are many sources of information and resources to assist the primary care physician in the management of such children. The AAP has published an evidence-based guideline on the diagnosis and management of ADHD. This guideline is exceptionally useful in managing such children. In the diagnosis of children with these disorders, it emphasizes the use of information from multiple sources, use of specific Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) criteria for diagnosis, and the use of specific ADHD rating scales. There is an extensively developed and tested ADHD Toolkit, produced by the AAP and the National Initiative for Child Health Care. This toolkit is very useful in diagnosis and management. It incorporates one of the standardized rating scales, the Vanderbilt rating scales, for parents and teachers. Administration of this form allows assessment of

behaviors in two settings, with specific ratings in the multiple domains of attention, hyperactivity, opposition defiant behaviors, depression, and school performance. These scales, plus a careful history will usually result in adequate information to determine whether a child meets the DSM-IV criteria for diagnosis.

Once a diagnosis is made for ADD or ADHD, management can be quite effective in improving school performance but must be individualized to the child and must be monitored closely over a long term. These are chronic disorders, and it has been noted that approximately 80% persist into adolescence and 60% into adulthood. While choices of advanced schooling and occupation often will allow adaptation to the symptoms of these disorders in later life, they will often affect persons throughout their lifetime. For instance, adults may choose very active occupations, which do not require prolonged concentration or attention, but will still be hampered in any activities of life that do require such attributes. Management of children with these disorders is logically based on the understanding that the pathophysiology of ADHD is based on neuroregulatory dysfunction primarily related to dopamine, norepinephrine, and serotonin processes. Therefore, it is to be expected that medications that interact with these processes would be the mainstay of therapy. Parents need to be carefully educated that pharmacological therapy is the most effective form of therapy for such children and must be a key element in therapy. Many parents are concerned that pharmacotherapy for these problems are risky, overused, and may lead to later drug abuse in children and adolescents. On the other hand, the impulsivity of ADHD may be only part of the problem with a masked learning disorder that emerges when attention improves on therapy.

Parents should be reassured that medications will only be used when children clearly meet the strict DSM-IV criteria for diagnosis but that many children meet these criteria, as many children suffer from this disorder. They should be reassured about the safety of the medications when used carefully and judiciously with close monitoring by their physician. They should also be made aware that untreated children with ADHD often develop serious behavior problems with high rates of drug abuse. About one-third of all untreated children with ADHD develop problems with drug abuse. However, medicated children with ADHD have rates of drug abuse that are much lower and are not different from children without ADHD. Treatment, therefore, seems to be highly protective against drug abuse, contrary to many parents concern.

When the diagnosis of ADHD is made, pharmacological therapy should be instituted for most children. The mainstay of such therapy is stimulant medication administration. Multiple studies have demonstrated the very high rate of effectiveness of stimulants. At least 60% of children treated in this manner have an excellent response to therapy, placing their scores on evaluation instruments in the normal range. In fact, 80 to 90% of children respond sufficiently to warrant continued therapy with stimulant medication, in the absence of serious side effects. Most studies have suggested that less than 5% of children require discontinuation of stimulant drugs due to side effects. Treatment with amphetamine- or methylphenidate-based medications does require attention to proper institution, titration, and monitoring of the therapy (reviewed in "First-Choice Antiepileptic Drugs" of this book). In general, it is appropriate to begin with the lowest predicted effective dose and titrate to effect or side effects. Immediate release forms of both are more likely to result in side effects without adequate relief of symptoms. This is due to the fact that the pharmacokinetic profile will often show the child in a supratherapeutic range shortly after the dose in order to maintain levels at an appropriate therapeutic range until the next dose. Most children will do better when treated with intermediate or long-acting forms of the stimulant drugs. Their profile allows a much longer period in a therapeutic range without peaks in the toxic range. With either, it is important to monitor children for side effects, particularly with regard to growth in weight and stature and to sleep disturbance. These drugs should be avoided in children with structural heart defects and hypertension or prehypertension. With careful monitoring, many children will adapt to the agents and will have decreased side effects with continued administration. While overall grouped response to amphetamine and methylphenidate medications appear similar, individual children may respond better to one or the other. Therefore, lack of success with one class of medication does not preclude a trial of the other.

In addition to the stimulant medications, newer agents have been developed and marketed for the treatment of ADHD and associated conditions. Atomoxetine has recently been marketed as an alternative to stimulant drugs. It is a norepinephrine depletor and appears to have no addictive potential, simplifying the prescribing process as multiple months may be prescribed at one time. In randomized placebo-controlled trials, it is clearly superior to placebo in the treatment of ADHD. However, though the available data are variable, it appears that a much smaller proportion of children have an excellent response to this agent than to the stimulant medications. In addition, the mode of action requires a slow titration of dose to avoid immediate side effects, and the clinical response is gradual in onset making it quite difficult to judge the effectiveness of this agent in the individual child. For all these reasons, this medication has had much more limited use than the stimulants and is significantly less popular with parents. Another agent that has been used rather extensively as an

adjunct to the stimulant agents is clonidine. It is used primarily as an adjunct to the stimulant agents due to its sedative effects. It has been useful to promote sleep in children with sleep disturbance due to the stimulants and underlying ADHD. Clonidine is far less beneficial in improving attention in children with ADHD and should not be used without concomitant stimulant therapy. However, clonidine may be first-line therapy when managing ADHD and tics concurrently.

In addition to therapy with medications, children with ADD and ADHD should receive behavioral management in their schools and homes to teach them organizational and learning skills. Good counseling and individualized educational support are important adjuncts to the treatment of ADHD. Proper school placement is also essential, as there are marked variations in the ability of individual public and private schools to provide the support and services important to the success of these children. The primary care physician should be familiar with the resources available in the community and be prepared to counsel families as to the best school placement for their child. The primary care physician must interact actively with parents and the schools to see that children are receiving such support and should monitor their progress regularly under the combined medication and behavioral support. However, it is essential to recognize that behavioral support in the absence of medication has a very low rate of success and that medication provides the highest proportion of overall benefit from therapy.

There are children who are not appropriately treated exclusively in the primary care office and require further referral and consultation. Children who do not respond to stimulant medications or atomoxetine are candidates for alternative medications and should be evaluated and managed by individuals with greater expertise in psychotherapeutic medications. Likewise, children with very strong oppositional defiant behaviors or severe depressive symptoms should be managed in consultation with a psychiatrist or clinical psychologists. In these children, psychotherapy and additional medications may be needed for an optimal outcome. Children with moderate to severe developmental delay or associated problems should be managed in consultation with specialists in developmental disability or neurology. The primary care physician plays the key role in the management of ADD and ADHD but should know the limitations of primary care in order to ensure optimal management of children with these problems.

Head Injury

Primary care physicians have a key role in the prevention of head trauma. They have an important responsibility in informing families, children, and adolescents about the prevention of head injuries. Head protection by bike helmets and other protective headgear for sports, such as skateboarding, snow sports, and team athletics, should be repeatedly emphasized by the primary care physician.

Primary care physicians are likewise important participants in decisions regarding the clinical management of children who have suffered acute head injuries. Most severe head injuries are evaluated and managed in emergency departments. Most children and adolescents who reach an emergency department after a head injury receive a thorough evaluation with imaging and often neurological or neurosurgical evaluation and are cleared of serious intracranial damage or hemorrhage by such evaluations. The AAP has published a detailed set of recommendations on the acute management of minor closed head injuries in children. This practice parameter is designed for children who appear normal at the time of initial exam, though they may have had temporary loss of consciousness or other neurobehavioral symptoms. It details specific approaches in various scenarios including periods and methods of observation and evidence-based approaches to cranial imaging.

The primary care physician is often called on to participate in decisions regarding the subsequent activities of the child or adolescent who has suffered a "concussion" as a result of a blow to the head. The American Academy of Neurology has defined a concussion as "a trauma-induced alteration that may or may not involve a loss of consciousness." It has been estimated that > 300,000 sports-related traumatic brain injuries of mild to moderate severity occur in the United States each year, most of these in children and adolescents. It is clear that concussive injuries require time to recover, over days to months. In no case should a child or adolescent who has suffered a concussion be returned immediately to the activity of risk. The prolonged period of recovery has implications for school performance, as well as continued participation in sports. Postconcussive syndromes include alterations in the three domains of somatic, emotional/behavioral, and cognitive disturbance. These syndromes can affect the child or adolescent in all areas of life. Children and adolescents with such symptoms should receive rehabilitative support until these symptoms are relieved. They may require considerable support to function properly in the school setting. It is generally agreed that they should not return to high-risk athletic activities until they have no signs or symptoms at rest or with exercise, have an entirely normal neurological examination and any neuroimaging performed is normal. With regard to competitive athletics, return to competition should be staged and progressive, with careful monitoring for return of symptoms. Strong consideration should be given to discontinuation of competitive sports with high risk of head injury for children who have suffered multiple episodes of symptomatic closed head injury.

Developmental Delay

The primary care physician is key to the early identification of children with developmental problems. The AAP has recently published an extensive algorithm for developmental surveillance and screening. It has been estimated that approximately 16% of children have developmental disabilities and that only approximately 30% are detected prior to school entrance. For this reason, it appears important to improve our screening for developmental disability in children. There is strong evidence that early detection with early intervention is highly effective in improving the outcome for such children. The AAP recommends surveillance for developmental problems at every well-child preventive care. Children suspected of a developmental problem should then be administered a standardized screening tool and, if abnormal, referred to a developmental specialist. Such children also merit evaluation for specific medical causes of their apparent learning problem. It also recommends routine administration of a standardized screening tool at the 9, 18, and 30 month visits. If this tool reveals potential problems, medical evaluation and developmental referral is also indicated. The choice of a screening tool is important. The Denver II Development screen has been shown to have a sensitivity of only 56% and is not an appropriate screening tool since screening tests require high sensitivity to be effective. There are a variety of well-validated screening tests that can be used in the office. In this context, it is important to recognize that parents are skilled observers of development, and screens based on parental reporting of development and development concerns have proven easy and efficient to administer and quite useful in the screening process.

Autism

Autism and broader autism spectrum disorders (ASD) have become very common diagnoses in pediatric practices. A recent policy statement of the AAP regarding the pediatrician's role in the diagnosis and management of ASD states that two or more per 1000 children suffer from ASD. In fact, more recent surveys suggest that this rate may be as high as 6 per 1000 or even higher. It is clear that ASD is being diagnosed more often than in the past and that this increase is a function both of more appropriate diagnosis and actual increases in the rates of this disorder. The reasons for this increase are not clear, but the need to diagnose children early and accurately will assist in our understanding of the disorder and improve the outcome of children diagnosed. The role of the primary care provider is to have a high index of suspicion, to understand the indications for further evaluation, and to be able to assist parents in receiving the proper diagnostic evaluation and therapies for children with ASD. Since there is no specific test for this problem, the diagnosis is made on clinical grounds. It is important to be attuned to parental concerns that may indicate this problem, as parents have been demonstrated to be usually correct in their assessment of problems in the child's development. The hallmark of ASD is aberrant social skill development. Issues of lack of eye contact, aloofness, and lack of interactive play and interest in peers are often observed by parents. Likewise, delayed speech development, which may have many other causes, is a consistent finding in children with ASD. When there is suspicion that a child may qualify for this diagnosis, the primary care provider may either administer one of the well-validated screening tools or refer immediately to an expert in developmental disabilities. The diagnosis should be made as early as possible, as early intervention programs have been proven to be very successful in assisting children with ASD to develop much improved skills. The therapies are broad and are designed to assist these children in all areas of performance.

While ASD diagnosis and therapy has much in common with the management of other developmental disabilities, there are some special challenges for the primary care physician in such cases. This is a diagnosis which is devastating for parents and is increasing in prevalence. For these reasons, there is much speculation as to its causes, and many theories that may be accepted by families are not supported by scientific evidence. This has led to alterations in parental behavior and the aggressive pursuit of alternative therapies. For instance, concerns about various immunizations have led parents to refuse needed protective immunizations for their children. Likewise, parental concerns about the possible relation of autism to metals exposure has led to therapies designed to remove metals from the body. Parents may strongly believe in such actions and be supported by other parents who have pursued such therapies with the belief that they have improved the functioning of their affected child. The primary care physician needs to be familiar with these concerns and therapies and be prepared to discuss them with families in a compassionate fashion. It is very useful, in this context, to use experts in the field as consultants who can guide and counsel parents as to the scientific basis or lack of basis of such approaches and to counsel them as to the risks as well as the potential benefits of various alternative therapies. ASD will continue to be a great challenge for the primary care provider until we have a much better understanding of the causes, including the contribution of environmental agents in its pathogenesis. Likewise, improved understanding of the optimal therapies for this disorder has the potential to provide much improved tools for advising parents of children with ASD.

Suggested Readings

American Academy of Neurology, Quality Standards Subcommittee and Child Neurology Society Practice Committee. Practice parameter: treatment of the child with a first unprovoked seizure. Neurology 2003;60;166–75.

American Academy of Pediatrics, Committee on Children With Disabilities. The pediatrician's role in the diagnosis and management of autism spectrum disorder in children. Pediatrics 2001,107:1221–6.

American Academy of Pediatrics, Provision Committee on Quality Improvement, Subcommittee on Febrile Seizures. Practice parameter: the neurodiagnostic evaluation of the child with a first simple febrile seizure. Pediatrics 1996;97:769–75.

American Academy of Pediatrics, Provision Committee on Quality Improvement, Subcommittee on Febrile Seizures. Practice parameter: long-term treatment of the child with simple febrile seizures. Pediatrics 1999;103;1307–9.

American Academy of Pediatrics, Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. Pediatrics 2001;108:1033–44.

American Academy of Pediatrics, Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement. Clinical practice guideline: diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder. Pediatrics 2000;105:1158–70.

American Academy of Pediatrics; Council on Children With Disabilities, Section on Developmental Behavioral Pediatrics, Bright Futures Steering Committee and Medical Home Initiatives for Children With Special Needs Project Advisory Committee. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. Pediatrics 2006;118;405–20.

Committee on Quality Improvement, American Academy of Pediatrics. Commission on Clinical Policies and Research, American Academy of Family Physicians. The management of minor closed head injury in children. Pediatrics 1999;104:1407–15.

Goadsby PJ, Lipton RB, Ferrari MD. Migraine—current understanding and treatment. N Engl J Med 2002;346:257–70.

Kirkwood MW, Yeates KO, Wilson PE. Pediatric sport-related concussion: a review of the clinical management of an oft-neglected population. Pediatrics 2006;117;1359–71.

Practitioner and Patient Resources

American Academy of Pediatrics
<http://www.aap.org>
The American Academy of Pediatrics site is the portal to extensive information services for practitioners and families. It has both electronic documents and the opportunity to order extensive print materials.

Autism Society of America
<http://www.autism-society.org>
For individuals with autism, parents, family members or friends, professional or other interested advocate, the ASA gets autism information into the hands of those who need it most and supports effort to promote education, awareness, and advocacy on critical issues.

Bright Futures
<http://www.brightfutures.org>
Information on this Web site is based on published guidelines for health supervision of infants, children, and adolescents. One goal of the Bright Futures project is to establish a partnership between health professionals and families. This Web site is designed to be used by both health professionals and families and to help users better understand the diagnostic process and what to expect during health supervision visits. Issues, concerns, and questions are also addressed.

Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD)
8181 Professional Place, Suite 150
Landover, MD 20785
Phone: (800) 233-4050
<http://www.chadd.org>
Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD), is a national nonprofit organization providing education, advocacy, and support for individuals with ADHD.

National Institute of Mental Health
<http://www.nimh.nih.gov>
This Web site provides information to the public, researchers, and clinicians on a range of mental disorders affecting adults and children, including autism spectrum disorders, attention-deficit hyperactivity disorder, and other behavioral conditions that can adversely affect a child's healthy development.

US Department of Education
<http://www.ed.gov>
The US Department of Education promotes educational excellence for all Americans. It provides important online resources for students, parents, and teachers.

Chapter 3

The Neurologic Examination

David Griesemer, MD

This chapter outlines a practical approach to examining children with suspected neurologic disorders, including strategies helpful for infants and young children and for children with cognitive issues. For a detailed video of pediatric neurologic examination at various ages, please see ***http://library.med.utah.edu/pedineurologicexam/index.html*** *by Paul D. Larsen, M.D. and Suzanne S. Stensaas, Ph.D.*

The purpose of neurologic examination of a child is to assess development and integrity of the nervous system and to determine location and cause of suspected dysfunction. Achieving these goals is often complicated by three impediments: (1) the patient's age and willingness to cooperate, (2) the complexity of the complete neurologic examination, and (3) the fluctuating nature of neurologic function. Many patients would prefer to play than be examined and often fear the examiner. To win cooperation, it is important to establish a comfortable rapport with young patients by engaging them in play as they sit on the exam room floor or in a parent's lap. An examiner who feels competent in assessing neurologic function in a child searches first for the most relevant findings while the child is cooperative and begins with the least-threatening maneuvers. Compared with examination of an adult, neurologic examination of a child requires more observation, considerable flexibility, greater patience, and less reliance on instructions that children might easily misunderstand. Not only is repeated examination helpful, because cooperation can change as a function of mood, energy, or familiarity with surroundings, but a complete neurologic examination also may require more than one session. In addition, neurologic function often fluctuates. Children with tic disorders, seizures, complicated migraines, sleep disorders, dystonias, or stereotypies can appear completely normal during examination at one time while manifesting neurologic dysfunction if examined at another. Thoughtful examination, therefore, requires looking for signs associated with presenting symptoms or for subtle abnormalities that suggest an associated or predisposing condition.

Neurologic impairment is not merely the sum of abnormal neurologic findings. A child typically manifests *patterns* of impairment, and the goal of examination is to discern coherent patterns amid abnormal findings. For example, a decrease in the width of one thumbnail, together with slightly greater floppiness of the ipsilateral foot and slight external rotation of that leg, can provide the only evidence of a subtle hemiparesis. Although it is important to be familiar with classic presentations of neurologic dysfunction, a good examiner must also be able to discern subtle presentations of hemiparesis, paraparesis, brainstem abnormality, or autonomic dysfunction. Although the neurologic examination is formally divided into several sections to help us remember the complete exam and to facilitate analysis of our findings, it should be tailored in response to the specific symptoms and needs of the child being evaluated. Highlighted below are approaches that are commonly useful; more detailed examinations are described elsewhere.

Examination of the Older Child

Observation

Valuable information can be obtained when a child feels free of the physician's focused attention. Watching a child come into the exam room, interact with parents, play, or dress and undress provides information about neurologic function that obviates the need for portions of the "adult" neurologic examination. Observation of drooling, respiratory irregularities, pain-related behavior, hyperactivity,

tics, confusion, willful defiance, or unexpected urinary incontinence provides important clues to underlying problems. It is helpful to observe the quality of eye contact and social interaction of a child with parents and with the examiner. It is often possible to observe a child during a nap for the presence of periodic movements, sleep-related seizures, or hypopneic episodes.

Mental Status

In many circumstances, cognitive performance is not central to the reason for neurologic evaluation. It could be sufficient to demonstrate that a child has good language, memory, and intellectual skills through conversation. However, without a methodological approach to thinking about a child's mental status, we lose an opportunity to identify relevant but overlooked cognitive weaknesses. Responses to "who," "what," "when," and "where" questions should be judged for comprehension. Asking a child to tell a story about something that happened provides a friendly way to assess memory, organization, and expressive language skills. Identifying colors or handy objects is helpful to assess naming in young children, whereas spelling the same colors or objects is helpful in assessing older children. Asking a child to read or write age-appropriate information provides an opportunity to assess cognitive and motor function. If needed, a more detailed approach is described below.

Cranial Nerve Testing

Although comprehensive cranial nerve examination is ideal, several aspects of the exam often are more useful than others in children.

Cranial Nerve II

Visual acuity of a child older than 4 years can typically be assessed by asking a child to point in the direction of lines on an E chart. Older children can use a Snellen's chart; each eye should be tested independently. Visual field examination is challenging, but finger counting by confrontation is typically effective. The examiner asks the child to cover one eye and look into the ipsilateral eye of the examiner standing in front of him. With the examiner's hands midway between him and the child and stretched to the limits of his own visual field, the examiner flashes between 0 and 5 fingers in each quadrant. Offering a visual stimulus in a left and right quadrant simultaneously (and asking the child to add up the fingers) keeps the child from turning his gaze away from the examiner's eye.

Funduscopy is also difficult in children without dilation of pupils, but it is commonly possible to ascertain more than the presence of a red reflex. Keeping the room light on or slightly dimmed helps the child maintain focus on a distant visual target, as the examiner explains that the child needs to "look through" his head should it get in the way. Training the light of the ophthalmoscope on the eye while the examiner is still 18 inches away and 10° from the child's midline allows the examiner to descend toward the eye while staying focused on the region of the retina where the optic disk is found. Whiteness of the normally salmon-pink optic disk suggests optic atrophy. Elevation of the disk head, seen best by noting the curvature of distended veins as they drape over the elevated disk onto the retina, suggests early papilledema. An experienced examiner with a cooperative child also can confirm the absence of pulsations in veins that issue from the center of the disk. Before this stage of papilledema, the only findings will be hyperemia of the optic nerve and apparent loss of constricted small vessels as they cross the disk head. Blurring of the temporal boundary between the optic nerve head and the surrounding retina is a later finding. Presence of a crescent of dark pigmentation on the temporal side of the optic disk is not abnormal.

Cranial Nerves III, IV, and VI

Abnormal eye movements at rest or during visual fixation should be noted. Nystagmus is an involuntary rapid jerk of the eyes back to the point of fixation, correcting for the slow drift away from the target. While vertical nystagmus suggests brainstem dysfunction, horizontal or rotary nystagmus reflects congenital abnormality or vestibular or medication effects. Assessment of the symmetry and reactivity of the pupils is important, although 10% of children have subtle baseline asymmetry in pupil size. During migraine, one pupil can be less reactive than the other. There can also be constriction of one pupil with mild eyelid drooping and ipsilateral anhidrosis with Horner's syndrome. In general, however, significant asymmetry of pupil size or reactivity suggests intracranial mass effect, midbrain dysfunction, optic nerve problems, or medication effect.

It is important to assess the width of the palpebral fissures—the vertical opening for the eyes. Decreased palpebral width on one side suggests ptosis, which can be seen with impaired sympathetic innervation, myasthenia gravis, or cranial nerve III dysfunction. Complete loss of cranial nerve III function is characterized by dilation of the pupil, ptosis, and rotation of the eye downward and outward, with impairment of up-gaze and adduction. Increased width of the palpebral fissure on one side suggests facial weakness on that side, caused by either upper motor neuron or cranial nerve VII dysfunction. Cranial nerve VI dysfunction is seen with increased intracranial pressure or focal problems that compromise the transit along this long cranial nerve. It is characterized by in-turning of the eye on the affected side or impairment

of lateral gaze (abduction) beyond the midline. Finally, as a screening test, it is helpful to perform an eye-to-eye cover-uncover test while the child's gaze is fixed on the examiner's nose. This will unmask an eso- or exophoria, which is diagnosed if a "lazy eye" jumps back to fixate on the visual target as it is uncovered while the opposite eye is covered.

Cranial Nerves V and VII

Isolated abnormalities of facial sensation or musculature are uncommon. Nevertheless, perception of light touch of the face in the three distributions of cranial nerve V branches (forehead, maxilla, and jaw) should be symmetric.

Weakness associated with cranial nerve VII can appear as widening of the ipsilateral palpebral fissure, flattening of the nasolabial fold, drooping of facial muscles, or "pulling" of the mouth to the contralateral side with a smile. Facial weakness caused by dysfunction of cranial nerve VII itself involves both lower and upper (forehead) musculature, whereas weakness caused centrally (eg, by a stroke) involves only lower facial muscles. Decreased lacrimation or salivation can suggest a problem with cranial nerve VII rather than with the central nervous system.

Two reflexes are associated with these cranial nerves. The corneal reflex, which is seldom required in ambulatory settings, tests the sensory arc of cranial nerve V and the motor arc (blink) of cranial nerve VII mediated at the level of the pons. The jaw jerk tests the afferent and efferent motor arcs of cranial nerve VII, also mediated at the same level. The reflex is abnormally brisk with upper motor neuron lesions above the pons; with lesions of the lower brainstem or cervical cord, it is normal while reflexes in the arms and legs are abnormally brisk.

Cranial Nerve VIII

Hearing should be assessed behaviorally or in a standardized manner as clinically indicated. Each ear should be tested individually. The examiner should use a low threshold for obtaining audiometry.

Cranial Nerves IX, X, and XII

If there is no abnormality of phonation or articulation, functional assessment of swallowing is often an adequate screen. Liquids are typically more difficult to swallow without choking than are solids for children with upper motor neuron dysfunction, which is generally associated with an exaggerated gag reflex. Quality of speech is important to assess, with attention to nasality, dysarthria, or stuttering. Respiratory function and cough should be assessed, with attention to power and timing.

Motor Function and Strength

General

Identification of handedness or dominance is always important and can be checked by observing with which hand a child writes his name on a piece of paper, with which eye the child looks through a pinhole in the paper, and with which arm or leg the child throws or kicks a wadded piece of paper. Posture should be evaluated, looking especially for a protuberant belly and exaggerated lumbar lordosis suggestive of weak truncal musculature. Abnormal movements, such as chorea, stereotypies, and motor tics should be described. (Tics can include sniffing, throat clearing, or squeaks, as well as complex, ritualistic behaviors.)

Development

Muscle bulk should be observed when the child is undressed, with careful search for muscle atrophy or underdevelopment. Increased muscle bulk, as in the case of Duchenne's muscular dystrophy, does not necessarily indicate good strength. The circumference of asymmetric calf or bicep muscles should be measured. Fasciculation of muscles at rest should be noted, although these are difficult to see in the chubby child. Limitations in range of motion should be noted. Assessment of neck rotation and lateral bending should not be overlooked in children with head or neck pain.

Tone

Passive resistance to movement of a child's muscle by the examiner is a valuable tool in motor assessment. Shaking a leg or arm to evaluate the "floppiness" of the foot or hand easily separates the hypotonic or hypertonic child from the normal child.

Strength

Observing for drift and pronation of one arm while both are outstretched "to catch raindrops" is a helpful screen for mild weakness. Testing against resistance should focus on muscles that are more sensitive indicators of weakness, particularly with the older or stronger child. These muscles include deltoids ("hold your arms out like wings"), wrist extensors ("hold your hands up like a policeman stopping traffic"), hamstrings ("pull your foot back toward your bottom"), and ankle dorsiflexors ("cock your feet up toward your head"). Handgrip, biceps, quadriceps, and gastrocnemius muscles are comparatively stronger, and they are noticeably weak only when symptoms are advanced. (Isolated weakness of the sternomastoid and trapezius muscles, with diminished ability to turn the head away from the involved side and drooping of the ipsilateral shoulder, is caused by cranial nerve XI weakness.)

If weakness is detected, strength should be quantified on a 5-point scale (ie, 1 = visible or palpable muscle contraction, 2 = movement without gravity, 3 = movement against gravity, 4 = movement against resistance, 5 = normal strength). Asking the child to rise from a squatting, sitting, or supine position is a good screen for lower extremity weakness. Gowers' sign is present if the child rises by pushing hands against the legs. Standing or hopping on one foot is a measure of strength and coordination. Observing a child walk or run is an opportunity to identify ataxia or significant asymmetry of posture, arm swing, or foot orientation.

Coordination

Asymmetry of rapid alternating movements reveals abnormal motor function. Comparing rapid left and right pincer movement of thumb and finger ("chomping alligator") or rapid toe-tapping is a good screen, with slowness suggesting upper motor neuron dysfunction and irregularity suggesting cerebellar dysfunction. Finger-to-nose testing can unmask tremor or dysmetria.

Reflexes and Sensory Examination

Muscle stretch reflexes demonstrate the integrity of the reflex arc that occurs at several levels of the spinal cord. An approximate but easy way to remember these is as follows:

- (Sacral) 1, 2 ankle jerk
- (Lumbar) 3, 4 knee jerk
- (Cervical) 5, 6 biceps reflex
- (Cervical) 7 triceps reflex

Significantly *decreased* reflexes suggest a muscle, peripheral nerve, or cerebellar problem. Acutely, an upper motor neuron lesion also causes decreased reflexes. Significantly *increased* reflexes suggest a brain or spinal cord problem. This is typically found in conjunction with absent abdominal reflexes and a positive Babinski's reflex (ie, dorsiflexion of the big toe). Doing this test properly requires stroking the plantar surface of the foot, beginning near the heel and progressing along the lateral side of the sole—not the central region—to the base of the toes and then medially toward the big toe. The *initial* movement, not the greatest movement, of the big toe is recorded. Abdominal reflexes extinguish quickly but are properly done by stroking from lateral to medial in each quadrant above and below the umbilicus.

Sensory examination is more difficult and often less revealing in children than in adults. However, it is essential to identify an early, distal neuropathy. In addition to causing decreased ankle reflexes relative to more proximal reflexes, distal neuropathy is characterized by diminished sharpness to sharp sensation (produced with a splintered, sterile, disposable tongue depressor). Older children with distal neuropathy can also report earlier extinction of vibratory sensation at the nail of the big toe compared with the ankle (medial malleolus) or the knee (patella). Global assessment of proprioceptive pathways is invaluable. The examiner should ask a child to stand with feet together, first with eyes open and then with eyes closed. An abnormal response, *positive* for Romberg's sign, is an inability for the child to maintain balance when eyes are closed. In most circumstances, limited reliability makes detailed assessment of other primary modalities (ie, touch, temperature, and position sense) or cortical modalities (ie, graphesthesia or extinction on double simultaneous stimulation) an unrewarding investment of the examiner's time.

Other Parts of the Examination

Every child should be examined for possible neurocutaneous findings, as both skin and nervous system derive from ectoderm. The examiner should search for hypopigmented spots (seen best with ultraviolet light), café-aulait spots, and angiomas. The dorsal midline from the base of the skull to the sacrum should be examined for defects such as a dimple, angioma, or tuft of hair. The child's nutritional status should be evaluated, including subcutaneous tissue as well as distribution and quality of hair. Autonomic abnormalities, manifest by postural instability of blood pressure and pulse or by changes in skin temperature, color, sweating, capillary refill, or hair loss, should be noted. The head should be examined carefully, with special attention to features of the face, palate, or skull that might suggest a known syndrome. With a child referred for headache or pain, the examiner should search for focal tenderness (eg, temporomandibular joint, gingiva, sinuses, trigger points) and impaired range of motion (eg, scoliosis, contractures, cervical strain, paraspinous muscle spasm). The abdomen should be examined for hepatosplenomegaly when there is concern about metabolic disorders, storage diseases, or human immunodeficiency virus; the heart should be examined carefully as part of evaluation for stroke. The examiner should request old photographs whenever changes in appearance or habitus are reported and home videotapes when there are concerns about paroxysmal events or movement disorders.

Special Considerations for the Infant and Younger Child

Head Growth

Head circumference is a tremendously important measurement to be taken at every visit; it should be double-checked

by the examiner after initially being measured by staff. Up to age 6 years, there is a linear relationship between head circumference and brain volume. Head circumference measurements should be plotted on a standardized growth chart for boys or girls. Head circumference increases approximately 0.5 cm each week in term infants; during the first 2 months it can increase 1.0 cm per week in preterm infants. Average head circumference is about 40 cm at age 3 months, 45 cm at age 9 months, and 50 cm at age 3 years.

Macrocephaly refers to a head circumference above the 98th percentile. It can be familial in origin (underscoring the importance of measuring head circumference in both parents); however, it can reflect abnormal brain growth (eg, megencephaly) or increased cerebrospinal fluid spaces (ie, hydrocephalus). *Microcephaly* refers to a head circumference below the 2nd percentile. It commonly reflects a perinatal insult to the brain, intrauterine growth retardation, or a genetic syndrome; it is rarely caused by fusion of the sutures (ie, craniosynostosis). Special attention should be given to a child whose head circumference crosses percentile lines after serial measurements. Increases can be suggestive of autism or elevated intracranial pressure; decreases can be suggestive of progressive cerebral atrophy or growth problems. Craniosynostosis is most commonly manifest as altered head shape rather than altered head size. The most common form is fusion of the midline sagittal suture; this results in a long, thin (ie, dolichocephalic) head.

Neurodevelopment

Identifying finger-pointing as a preverbal skill is often helpful in distinguishing aberrant development (eg, with autism) from delayed but otherwise normal development. It is necessary to confirm developmental milestones. When lying prone, a 3-month-old should be able to lift his head off the table, a 4-month-old should be able to support his torso on both hands, and a 5-month-old should be able to balance on one hand and reach with the other. A 6-month-old should be able to roll from supine to prone, an 8-month-old should be able to sit unsupported, and a 10-month-old should be able to crawl and to pull up to a standing position. By 12 months a child should be able to walk with support and by 14 months without help.

Developmental reflexes appear at birth and normally disappear at specific ages. Truncal incurvature should disappear by 2 months, the rooting reflex by 3 months, and Moro's reflex by 4 months. Persistence or exaggeration of reflexes is abnormal. The asymmetric tonic neck reflex ("fencer posture"), which typically disappears at 4 to 6 months, must dissipate before the infant can roll over. Side-to-side differences in muscle tone occur with changes in head position because of this reflex, emphasizing the importance of keeping the head midline during assessment of posture and tone. The tonic labyrinthine reflex, which typically disappears around 6 months, accounts for differences in muscle tone depending on the position in which a child is examined. When supine (with head extended), muscle tone is greater than when sitting in the examiner's lap (with head flexed).

Cranial Nerves

Funduscopic examination is possible if the ophthalmoscope can be used in a game of "peek-a-boo." Sometimes toys can be used to help a child fixate, and the child will be more comfortable in a parent's lap than on the examining table. The tongue should be examined carefully for fasciculations, which can be subtle but are a valuable sign of motor neuron disease.

Motor Function

Handedness appears around 1 year of age; earlier manifestations of preference suggest unilateral weakness. The grasp reflex in the hand disappears before normal handedness develops; persistence beyond 6 months of age suggests upper motor neuron dysfunction. A functional grasp in the normal child involves the thumb and two fingers by 8 to 10 months of age and a thumb–index finger pincer movement by 12 months of age. Persistent fisting of the hand, adduction of the thumb against the palm of the hand, and increased flexion of the wrist are signs of upper motor neuron dysfunction.

In the legs, persistent toe walking or shortening of the Achilles tendon are upper motor neuron signs. Plantar grasp reflex is abnormal beyond 10 months of age. Decreased strength with motor neuron disease, peripheral nerve dysfunction, or a muscle problem is suggested by a frog-leg posture when the child is supine; decreased flexion at the hips and knees is abnormal. A child with significant weakness who is suspended upright slides through the examiner's hands because of decreased shoulder muscle strength. In the normal infant, spontaneous movements should be symmetric or reciprocating but equal. In the toddler, functional assessment is helpful; examples are observing the child get up from a supine position on the floor without using the arms, climbing steps if they are available, hopping, or repeatedly stepping up onto a low stool.

Special Considerations in the Newborn

Cranial Nerves

Cranial Nerve II

Full-term infants will typically blink in response to bright light and turn toward and fixate on a light of moderate

intensity. The blink response appears at around 26 weeks of gestation and sustained eye closure appears around 32 weeks; turning toward a light develops at around 37 weeks. The optic disk of a newborn is gray-white in color rather than yellow-pink, particularly in blond, fair-skinned children, so the examiner should be careful in diagnosing optic atrophy. Papilledema is rarely seen in infants because fontanelles and sutures typically remain open and can separate with increased intracranial pressure. (However, the ability to palpate the squamosal suture, which runs in a frontal–occipital direction above the ear, is highly suggestive of increased intracranial pressure.)

In the first few months of life, children are at highest risk for non-accidental trauma, and careful observation for retinal hemorrhages is essential. In the young child, hemorrhages resolve quickly; those that occur in one-third of infants following vaginal delivery usually resolve within 72 hours and essentially all resolve within 1 week. "Shaken baby" hemorrhages of different types typically resolve within a week, depending upon the extent of hemorrhage and the likelihood of multiple insults. Flame hemorrhages, which occur in the transverse nerve fiber layer of the retina, have feathered edges. Dot hemorrhages, which occur in the bipolar layer, are "vertical" hemorrhages. White-centered hemorrhages originate in the bipolar layer but erupt into the nerve fiber layer where they spread out; the volume of blood is such that a fibrin clot forms and appears as the white center.

Cranial Nerves III, IV, and VI

The pupil typically reacts to light by 30 to 32 weeks gestational age, indicating that term infants should demonstrate the same pupillary symmetry and reactivity as older children. Full eye movements can be demonstrated as early as 25 weeks gestational age. At rest, premature infants have slightly disconjugate gaze, with pupils up to 1 mm lateral of their position during fixation. Disconjugate gaze persists in infants with periventricular leukomalacia. In the normal infant, sudden movement of the head horizontally or vertically should be accompanied by a symmetric movement of the eyes in the opposite direction. (This is a *positive* doll's eye maneuver.)

Cranial Nerves IX, X, and XII

Sucking and swallowing, as well as the rooting reflex, develop around 28 weeks gestational age. However, synchronized movements to facilitate feeding occur around 32 to 34 weeks, and coordination of feeding with breathing occurs 4 weeks later. Effective sucking also requires integrity of cranial nerves V and VII. Cough can be triggered by gentle pressure to the trachea at the suprasternal notch.

Motor Function

Observation of tremulousness, exaggerated startle responses, or myoclonus (whether spontaneous or reflexive) suggests central nervous system or metabolic abnormalities. Muscle tone is typically assessed by the range of passive movement around a joint, such as how far the arm can be "stretched" at the shoulder across the chest. In a term infant with normal tone, the elbow does not quite reach the midline chest. This is a function of both gestational age and muscle tone. A normal infant at 28 weeks of gestation has only minimal resistance to movement and the elbow easily stretches beyond midline. Resistance in flexor muscles of the legs increases by 32 weeks and in the arms by 36 weeks.

Another useful measure of tone is the popliteal angle created behind the knee when the foot is stretched toward the abdomen. Contractures from decreased movement in utero can restrict movement and misleadingly simulate increased tone. Central nervous system problems are typically associated with *decreased* tone initially at birth, which evolves to *increased* tone by 4 to 6 months. Increased tone during the first few weeks of life is more likely to represent rigidity than spasticity and suggests metabolic disorder, basal ganglia abnormality, or drug withdrawal.

Assessment of Higher Brain Function

Children are increasingly referred for neurologic evaluation of school failure, hyperactivity, learning disability, and autism, necessitating more detailed assessment of cognition. Prior assessments by school psychologists, speech-language pathologists, or developmental pediatricians can help focus this specialized evaluation. Although several acceptable strategies build upon the traditional mental status examination, the following approach, adapted with permission of the surviving authors (Weinberg and colleagues, 2001), is particularly useful:

- *Attention and vigilance.* The examiner should observe behavior that suggests decreased vigilance or attention, such as yawning, stretching, or napping; daydreaming or distractibility from a current activity; poor cooperation on structured or repetitive activities with complaints of boredom; delayed, slow, or incomplete effort on assigned tasks; fidgetiness, motor restlessness, or akathisia; and poorly focused busyness or talkativeness. It is important to distinguish between the child who remains attentive to the conversation while exploring the room's contents and the child who is not engaged in the process.
- *Language comprehension.* The examiner should also evaluate a child's ability to clearly understand and correctly respond to spoken language. Poor eye contact or inattention to the examiner, irritability or resistance to

listening, and preference for pictures or for a nonverbal environment suggest a problem with language comprehension. Alternatively, a child who maintains an enduring interest in watching the speaker's lips could have difficulty with word reception. Even if hearing has been shown to be normal, this can cause a child to repeatedly say "What?" or "Huh?" when spoken to. A child who provides an inappropriate answer, such as "I'm fine" when asked his name, demonstrates impaired word reception.

- *Language production.* The ability to retrieve and correctly use words also must be assessed. The examiner should meticulously listen to a child's spontaneous speech to make sure that he can effectively communicate his message and that he uses appropriate words to convey his intended meaning. Not only should the normal child be able to correctly name specific objects that are age-appropriate, he also should be able to define the following words:
  - Age 6 to 8 years — baby, name, green, second
  - Age 8 to 10 years — visit, spring, money, thought
  - Age 10 to 12 years — grasp, moist, browse, stride, coward
  - Age 12 to 14 years — freight, obsolete, drought, absorb, occupation
  - Age 14 to 16 years — fortuitous, vaguely, judicious, vocation, absurd

  If the child has difficulty with this task, he should be asked to choose among three definitions, one of which is correct. In addition to knowing words, a child must demonstrate his ability to retrieve them. Asking a child to describe the examining room or his most recent meal offers the examiner an opportunity to evaluate this skill.
- *Speech production.* Closely related to language production is the ability to produce spoken words. By age 18 months, a child should be able to clearly express single words. By 24 to 30 months, a child should be able to make a statement using a short string of words. Repetition of words spoken by someone else (ie, echolalia) is common among toddlers, but is abnormal in the child of preschool age. Consistent stuttering in a young child more likely suggests a problem with word production than does stuttering in an older child during periods of stress.
- *Memory.* By age 6 years, a child should be able to state at least part of his birth date. In the examination setting, a child of this age should also be able to remember a person's name. Introducing a one-syllable name for a 6- to 8-year-old, a two-syllable name for an 8- to 10-year-old, a three-syllable name for a 10- to 12-year-old, and a four-syllable name for an older child, the examiner should ask the child to repeat the name five times and then tell the child that he will have to recall the name in 5 to 10 minutes. If he has difficulty recalling all or part of the name, he should be asked to select correctly from three choices. An older child who has difficulty recalling the names of friends, teachers, or coaches should be carefully evaluated, as should one who has more difficulty with fill-in-the-blank than with multiple-choice tests.
- *Reading and writing.* Effective written communication depends upon recognition of letters and words. By age 5½ years a child should be able to name the capital letters *A, B, C, D,* and *E*. By age 6½ years he should be able to name the lowercase letters *a, b, c, d, h, j, k, m, n, p, u, w, x, y,* and *z*. Listed below are age-appropriate tasks of spelling that build upon the above elements. Also, the ability to spell the target word below both forward and backward, and know what the reversed word means, correlates with the ability to read and understand age-appropriate material. If a child fails these screening tests, they should be supplemented with sample reading passages at grade level.

	Spelling Words	Spell Forward and Backward
Age 6 to 7 years	it, cat, look, stop, spot	dog
Age 7½ to 8 years	work, talk, girl, went	was
Age 8 to 9½ years	should, could, phone, house	tip
Age 9 to 10½ years	monkey, elephant, receive, friend	not
Age 10 to 11½ years	purchase, ethics, delicate, delicious	live, dial

  Like letters and words, numbers and mathematical phrases represent symbolic communication. Similar age-appropriate screens are available to assess skills with numbers and arithmetic (Weinberg and colleagues, 2001). Consideration also should be given to handwriting, which relates to reading and writing as speech articulation relates to receptive and expressive language.
- *Sequencing.* Being able to recognize, learn, and assemble components of a sequence is an important skill for learning. By age 5 years a child should be able to count to 10; by age 6 years he should be able to do it backward. A 6-year-old also should be able to recite the alphabet. A 7-year-old should be able to say the days of the week, and an 8-year-old should be able to say them backward. By 9½ years a child should be able to say the months of the year, and by 11 years he should be able to say them backward. The child's development of sequencing skills with numbers (eg, in simple calculations), with symbols (eg, drawing clocks), and with body parts (eg, in drawing people) also should be evaluated.
- *Prosody.* Although difficult to quantify, the emotional quality of communication is important. This ranges from the pitch, intonation, and musicality of speech,

to the appropriateness of gestures and recognition of personal space. It also includes the concept of empathy and the ability to understand the facial expressions, gestures, and feelings of others. The examiner should ask a child to identify feelings expressed by faces (of the examiner or on face cards) that show happiness, sadness, or anger. The child should then be asked to mimic the facial expression. The examiner can dispassionately make a variety of statements, asking the child which of the three emotions best fits the statement. An older child can be asked to repeat the statement, adding the inflection of happiness, sadness, or anger appropriate to the content of the statement. It is important to observe the repertoire and emotional appropriateness of the child's gestures, as is observing the child's response to the examiner's gestures.

- *Mood.* Depression is often overlooked in children, particularly in those for whom it cycles in minutes or hours to giddiness. The examiner should be alert for signs of sadness, loneliness, frustration, loss of interest, decreased energy, sleep disturbance, or change in appetite. Paroxysms of unprovoked rage or inappropriate hyperactivity should be noted. After winning a child's agreement to answer serious questions, the examiner can inquire whether the child has mostly good or bad days; whether the bad days are accompanied by good or bad feelings about himself; whether the bad feelings cause him to cry, keep him from having fun, or prevent him doing school work; and whether the bad feelings lead to a wish for death, suicidal thoughts, or suicidal behavioral. Depression can significantly interfere with cognitive function. Similarly, obsessive–compulsive or oppositional behavior can compromise performance during examination. Although a better measure of healthy cognition than healthy affect, humor and wit should also be assessed. Like logical thought, humor and wit reflect higher brain processes that help a child to be adaptable, perceptive, and successful in developing social relationships.

Final Notes

The reporting of neurologic examinations is often formulaic or mechanical. However, with children the exam must be descriptive, even if such description implies some lack of sophistication on the part of the examiner. It is more important for the reader to have a vivid mental image of how a child moved, responded, and behaved than to know that the child was "oriented × 3," had a "red reflex present" or that "DTRs were 2+ throughout." During this era in which neurologic disorders are reconsidered and reclassified because of advances in molecular genetics, careful recording of clinical phenomenology is essential.

There is professional pride that derives from mastering the neurologic exam. Even if it is done well, however, there can be circumstances in which deficits remain silent or cannot be localized. For example, strokes can occur in children with sickle cell disease and produce no localizing signs. Focal cortical dysplasia can be the cause of localized seizures but manifest no abnormality on exam. Similarly, it can be impossible to quantify or localize global insults, such as those produced by exposure of newborns to bilirubin or of toddlers to lead. This underscores the importance of coordinating the neurologic exam with thoughtful laboratory evaluation when it is likely to expand understanding of the problem. Diagnostic studies cannot replace meticulous examination, however, because of the expansiveness of the nervous system and potential adverse effects of the tests themselves.

Suggested Readings

Bartholomeusz HH, Courchesne E, Karns CM. Relationship between head circumference and brain volume in healthy normal toddlers, children, and adults. Neuropediatrics 2002;33:239–41.

Haslam RHA. Neurologic evaluation. In: Behrman RE, editor. Nelson textbook of pediatrics. 17th ed. Philadelphia (PA): W.B. Saunders Company; 2004. p. 1973–83.

Maria BL, English W. Do pediatricians independently manage common neurologic problems? J Child Neurol 1993;8:73–7.

Weinberg WA, Harper CR, Brumback RA. Attention, behavior, and learning problems in children: protocols for diagnosis and treatment. Hamilton (ON): BC Decker; 2001.

Practitioner and Patient Resources

PediNeurologic Exam: A Neurodevelopmental Approach
Paul Larsen, MD, and Suzanne Stensaas, PhD
http://library.med.utah.edu/pedineurologicexam
This website demonstrates vignettes of the normal neurologic examination of newborns of children at 3, 6, 12, 18 and 30 months of age. It requires installation of QuickTime.

NeuroLogic Exam: An Anatomic Approach
Paul Larsen, MD, and Suzanne Stensaas, PhD
http://library.med.utah.edu/neurologicexam
This website demonstrates vignettes of the mental status, cranial nerve, coordination, sensory, motor, and gait examinations, with normal and abnormal examples. It requires installation of QuickTime.

Neuroanatomy through Clinical Cases
Hal Blumenfeld, MD, PhD
http://www.neuroexam.com
This is the website for an introductory text of the same name. It provides high-speed and low-speed video examples with excellent teaching for examination of mental status, cranial nerves, motor exam, reflexes, coordination and gait, and sensory exam.

Animated Lessons on the Neurology of Eye Movements and Pupillary Disorders
Howdy R, Calver L. Krumwiede K, Beltran D, Woo D, Frohman E, Galetta S.
This website contains interactive animations for a wide variety of papillary and ocular movement abnormalities. This site requires flash player

Internet Handbook of Neurology
Katalin Hegedüs, MD, PhD
http://www.neuropat.dote.hu/neurology.htm
This page lists neurologic examination guidelines for multiple institutions and includes an online interactive guide with video demonstrations as well as many links to pages containing information on various aspects of neurologic diagnosis and treatment.

NeuroExam.com
www.neuroexam.com
This Web page provides an interactive guide with video demonstrations of all parts of the neurologic examination.

eMedicine: Neurological History and Physical Examination
http://www.emedicine.com/neuro/topic632.htm
eMedicine provides this comprehensive guide to the basic neurologic examination and that aimed at the assessment of more specific problems.

CHAPTER 4

NEURODIAGNOSTIC TESTS: THEIR INDICATION AND SELECTION

JOHN H. MENKES, MD AND W.D. SHIELDS, MD

Children present to the practitioner's office with an array of neurologic complaints, and this chapter reviews indications for the most commonly ordered diagnostic studies. The ability to select appropriate diagnostic studies and interpret the results in clinical context is an essential part of modern medical practice.

At the conclusion of history taking and physical examination (reviewed in Chapter 3), the physician should have a clear understanding of the patients' problems and be able to establish a focused differential diagnosis. Diagnostic tests and procedures are then used to confirm or establish the working diagnosis and plan treatment and management. Before deciding which tests to use in any given patient, the physician must first ask himself what questions need to be answered, and whether the outcome of the test, be it positive, negative, or ambiguous will have an impact on the diagnosis or alter the management of the patient. Many times the decision on whether or not a certain diagnostic test should be ordered is subjective, and whenever the two authors of this chapter are not in agreement, each of their viewpoints will be presented. There are two primary reasons for establishing a specific diagnosis. First, a specific diagnosis will determine management. Second, some disorders have a genetic basis. Even if the diagnosis will not lead to curative treatment, the diagnosis may have a significant impact on the families' decisions regarding future pregnancies and thus may prevent additional affected children.

Examination of Cerebrospinal Fluid

Of the various diagnostic tests discussed in this chapter, the lumbar puncture (LP) and subsequent examination of the cerebrospinal fluid (CSF) has been available the longest, having been introduced by Quincke in 1891 as a means of reducing intracranial pressure in children with hydrocephalus. The need for an LP is often influenced by the age of the patient and the clinical condition. Younger patients with suspected meningitis or degenerative diseases are more likely to need an LP.

CSF examination with a view of isolating and culturing the offending organism and obtaining its antibiotic sensitivities is a mandatory procedure for any child suspected of meningitis. Since the incidence of meningitis in children presenting with an apparent febrile seizure ranges between 2 and 5%, the question whether a LP is required for every infant who has just experienced his or her first febrile seizure is more controversial. In the past, it was recommended that all children with a first febrile seizure undergo an LP. Experienced pediatricians did not find this necessary and believe that an LP is not required unless there is a history of irritability, decreased feeding, or lethargy, when the febrile seizure has been prolonged, when there has been a prolonged postictal depression of consciousness, when the infant has been pretreated with antibiotics, and, of course, when there are physical findings pointing to meningitis or encephalitis. Febrile seizures typically do not occur in children less than 6 months of age, so a very young child with fever and seizures should be

considered more likely to have meningitis or encephalitis and receive an LP. In addition, febrile seizure patients less than 1 to 1 1/2 years of age with meningitis may not show meningismus or other signs of infection and thus are more likely to require an LP to be certain that infection is not missed. In summary, JHM believes that the diagnostic skills required to ascertain whether an infant is more ill than his or her physical signs suggest are so considerable that it is best to err on the side of safety and perform the tap. WDS believes that a decision to defer the LP in a young patient should generally be made only by an experienced physician, not by a physician-in-training. This is particularly so for infants younger than 2 years.

One objection to performing a LP is the possibility of herniation in the presence of increased intracranial pressure. Obtaining a computed tomography (CT) scan prior to a LP in patients with suspected meningitis to determine whether there is increased intracranial pressure is in the opinion of JHM unwarranted, particularly since the CT is generally normal in children with meningitis and increased intracranial pressure. WDS believes that CT is clearly unnecessary in very young children with an open fontanel since the presence of increased intracranial pressure would be manifested by a bulging or tense fontanel. In older children with closed sutures, a CT can be performed if there is reason to believe that there is increased pressure as manifested by abnormalities, such as focal neurologic signs or papilledema. If there is concern for increased pressure and a possibility of infection, antibiotics should be administered prior to the CT or LP.

When a child presents with an afebrile seizure, cerebral palsy, or other manifestations of static developmental delay, examination of the CSF rarely yields additional information and will generally not be necessary. However, we must note that an examination of the CSF and determination of CSF glycine, folate, and biopterin metabolites are required to diagnose some rare and apparently static neurologic disorders, such as hyperglycinemia (which may show increased glycine only in the CSF), the Aicardi-Goutieres syndrome, and the various disorders of cerebral folate metabolism. Measurement of CSF glucose is necessary to arrive at the diagnosis of glucose transporter deficiency, a rare but effectively treatable cause for seizures during infancy and for the diagnosis of various other metabolic disorders (Table 4-1).

Examination of the CSF is an important adjunct to magnetic resonance (MR) imaging (MRI) in the diagnosis of some of the central nervous system (CNS) degenerative disorders, notably the leukodystrophies and the mitochondrial encephalopathies. For example, in Leigh encephalopathy and the mitochondrial depletion syndrome of early infancy, CSF lactate can be elevated despite normal serum lactate.

CSF examination is frequently necessary in infants or children with suspected intracranial bleeding and in subarachnoid hemorrhage. The CSF can be diagnostic when the CT is falsely negative. The various chemical diagnostic tests that can be performed on CSF are summarized in Table 4-1.

Electroencephalography

The importance of electroencephalography in the evaluation of a child with a first afebrile seizure has been stressed by Hirtz and colleagues (2000). In most studies, focal slowing or epileptiform discharges were predictive of recurrent seizures in children who had a normal neurologic examination. In addition, the EEG is informative with respect to the diagnosis of the seizure disorder and identification of a specific epileptic syndrome. The optimal time in relation to the seizure is under dispute. On the basis of work by King and colleagues (1998), JHM suggests that an EEG obtained within 24 hours of a seizure will be more likely to show epileptiform abnormalities that can guide subsequent therapy than one performed later. The value of the EEG in the management of the child with epilepsy is discussed elsewhere in this volume. An alternative consideration, offered by WDS, is that most children who present with a single unprovoked seizure will not have additional seizures and thus should not be treated with anticonvulsant medications. An EEG

TABLE 4-1. Cerebrospinal Fluid Diagnostic Tests

Assay	Conditions
Glucose	Meningitis, glucose transporter defect,
Lymphocytosis	Meningitis, encephalitis, CSF leukemia, malignancies, AGS
Lactate	Mitochondrial disorders, hypoventilation, hepatic disease, pyruvate dehydrogenase defect
14-3-3 Protein	Creutzfeldt-Jakob disease (adults), infantile neuroaxonal dystrophy, MELAS
Asialotransferrin	Vanishing white matter disease
Pterin metabolites	Hyperphenylalaninemias, AGS, sepiapterin reductase deficiency, exercise-induced dystonia
Serotonin, dopamine metabolites	Dopa-responsive dystonia, sepiapterin reductase deficiency
Amino acids	Glycine encephalopathy, 3-phosphoglycerine dehydrogenase deficiency, sulphite oxidase deficiency, molybdenum cofactor deficiency
Hypocretin	Narcolepsy, Niemann-Pick disease C

AGS = Aicardi-Goutieres syndrome; CSF = cerebrospinal fluid; MELAS = mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke.

performed in the immediate postictal period may simply demonstrate abnormalities related to the recent seizure and thus suggest a higher risk for recurrence than is appropriate. Since the EEG will not generally lead to treatment, it is acceptable to perform the EEG two or more weeks after the event. Children who present with frequent seizures should have an EEG performed quickly so that appropriate therapy can be initiated as soon as possible.

The electroencephalogram (EEG) does not guide the treatment of simple febrile convulsions nor does it predict their recurrence. JHM, therefore, defers performing this study unless there is considerable parental pressure for it. Although the role of EEG in guiding the management of complex febrile seizures has not been clarified, JHM generally obtains a tracing within 7 days of the convulsion. WDS obtains an EEG in febrile seizure patients only when there is consideration that this is an epilepsy disorder with seizures precipitated by fever. Generally, an EEG can be obtained after three or more febrile seizures. Only about 10% of febrile seizure patients have three or more seizures so the EEG can be avoided in 90% of the patients.

Although the EEG is abnormal in a significant proportion of children and adolescents with migraine with and without aura, it is rarely of value in guiding treatment, and JHM concurs with the practice parameter advising that EEG's are not indicated in the management of children with migraine or recurrent headaches, and that even should the EEG be paroxysmal the risk for future seizures is negligible. Despite anecdotal evidence to the contrary, treatment of the child with headaches and a paroxysmal EEG with anticonvulsants is usually ineffective.

In the child who presents with clearly documented syncopal attacks, an EEG will not be required even when the syncopal attack triggers an epileptic seizure. In such children, JHM generally orders an electrocardiogram to exclude the long QT syndrome.

An EEG is not required for the evaluation of the child with a static developmental delay or autistic spectrum disorder (ASD) unless there are historical features suggestive of epilepsy or a specific epilepsy syndrome. In the series of 50 children with ASD surveyed by Shevell and colleagues (2001), only one child with a possible Landau-Kleffner variant was identified. Whether a 24-hour sleep tracing with video telemetry would increase the yield has not been ascertained, although in some series, epileptiform EEG abnormalities have been documented in greater than 50% of children with ASD. WDS notes that 30% of patients with ASD have seizures. In some patients, the seizures may contribute to the developmental abnormalities. In such cases, treatment may have a beneficial effect on long-term development. The question of the contribution of continuous spike wave in sleep or Landau-Kleffner syndrome to the developmental abnormalities has not been defined. However, the "Cure Autism Now" consensus statement recommends that autistic children should have an EEG that includes all four stages of sleep. Generally, obtaining all four stages of sleep requires an overnight EEG that can be performed in an outpatient or inpatient setting.

The value of EEG in patients with neuronal storage diseases has been stressed for sometime. In the neuronal ceroid lipofuscinoses, the tracing demonstrates low-amplitude slow wave and spike complexes, with a marked photosensitivity that is diagnostic for CLN3 (juvenile amaurotic idiocy). In all forms of the neuronal ceroid lipofuscinoses, the visual-evoked potentials are abnormal and are abolished early in the course of the disease. This procedure, therefore, provides considerable diagnostic information in the earliest stages of these conditions.

Neuroimaging Studies

Of the two neuroimaging techniques commonly available, CT and MRI, each has its advantages and disadvantages. CT has the advantages of speed, a typical screen takes 5 to 10 minutes, and lower cost, and the fact that it can be used for patients on mechanical respirators. Its major limitations are that bone artifacts often obscure imaging of the posterior fossa and that definition of the cortical architecture is generally insufficient to detect cortical malformations. Nevertheless, CT is useful for the evaluation of the child with acute head trauma and for the detection of suspected brain parenchymal or subarachnoid hemorrhages. Some physicians use CT imaging for the evaluation of every child with a new-onset seizure, and Garvey and colleagues (1998) found that CT scanning found abnormalities in 19.4% of children presenting to the emergency room with a first seizure. Almost all of these abnormalities were not of therapeutic importance with the few exceptions being encountered in children with focal seizures or focal abnormalities on neurologic examination. It should be noted that CT scan typically misses about half of the abnormalities observed on MRI. The most common causes of seizures observed on imaging, mesial temporal sclerosis and cortical dysplasia, are rarely seen on CT. Thus, CT imaging performed in the emergency department in most patients with new onset seizures is noncontributory.

MRI is our favored neuroimaging technique for the delineation of most intracranial and intraspinal abnormalities. It provides better definition of anatomic structures, particularly those in the posterior fossa, and provides more information with respect to pathologic lesions. Combined with MR angiography it provides information on blood flow and the presence of vascular abnormalities. The disadvantages of MRI include the duration of the procedure (20–60 minutes) and the necessity for sedation or

anesthesia in uncooperative youngsters. Open MRI systems are more acceptable to claustrophobic children or adolescents, but image quality of these systems is generally poor, and JHM tries to avoid it. Another disadvantage of MRI is its increased cost and the reluctance of insurance companies to approve the procedure, unless a CT scan has already been performed and has not provided sufficient information.

MRI is also the procedure of choice for the evaluation of infants and children suspected of congenital CNS malformations, degenerative brain disorders, such as the various leukodystrophies, and for the evaluation and management of epileptic patients. When MRI has been used for the evaluation of neurobehavioral disorders, such as ASD, the yield has been too low to justify its use on a screening basis for these types of disorders. MRI has been of considerable assistance in the diagnosis of the leukodystrophies, although the distribution and progression of white matter abnormalities are as a rule not sufficiently specific to arrive at a genetic diagnosis. In addition, there are numerous patients who demonstrate white matter abnormalities compatible with a leukodystrophy but whose clinical picture, progression, and genetic evaluation does not allow them to be placed into any of the previously described categories. The use of diffusion-weighted MR imaging provides further information on the structure of white matter, but its use for genetic diagnosis requires further work.

By providing a detailed anatomic picture of the brain, MRI, sometimes complemented by ^{18}F-fluorodeoxyglucose positron emission tomography, single photon emission computerized tomography, and magnetoencephalography, provides information with respect to the presence of focal cortical dysplasia, tubers, and hippocampal sclerosis. These studies are, therefore, indicated for every patient with recurrent seizures, particularly when surgical management is contemplated.

MR spectroscopy (MRS) has been used extensively in the evaluation of neonates suffering from hypoxic-ischemic encephalopathy, mitochondrial disorders, seizure foci, and in the characterization of cerebral neoplasms. Nevertheless, this procedure plays more of an investigative role than as a guide to patient management. The same can still be said for functional MRI, although it is now used extensively for the mapping of language and motor function prior to surgery, the study of reading disability, and other learning disorders.

Electromyography and Peripheral Nerve Conduction Studies

The principal indication for these studies is in the evaluation of the infant or child with hypotonia or muscle weakness. Of the infants or children who present with hypotonia, the large majority has lesions affecting the upper motor neuron rather than the lower motor neuron, and as a rule, the child who presents with hypotonia and preserved or overactive deep tendon reflexes will not require electromyography or peripheral nerve studies.

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Chapter 5

Child Neurology Education of Medical Students, Pediatricians, and Adult Neurologists

Paul D. Larsen, MD and Roger A. Brumback, MD

Pediatric neurologists, especially in the academic setting, are responsible for the three-fold stewardship of caring for children with neurologic problems, advancing the medical knowledge that promotes such care, and teaching the clinical principles and skills necessary for health care providers to care for childhood neurologic conditions. This stewardship also includes ensuring the future of our discipline by attracting medical students and residents to the subspecialty of child neurology.

Neurologic problems in the pediatric population are frequent, but most primary care physicians feel uncomfortable in evaluating and treating even the most common conditions, such as seizures, headaches, and developmental delay. Children with any possible neurologic condition are often quickly referred to a pediatric neurologist. Unfortunately, there are too many patients that need to be seen for the number of pediatric neurologists practicing in both the United States and Canada. The pediatric neurology workforce analysis published in 2005 concluded that unless more child neurologists are trained in the near future, there will be no growth in the number of pediatric neurologists relative to the projected increase in number of children with neurologic problems, resulting in even greater gaps in care than currently exist. This shortage of pediatric neurologists is much larger than the shortage projected for other pediatric subspecialists. By the year 2022, pediatric neurologists will increase only to 109% of the current workforce while other pediatric subspecialists are projected to increase to 150 to 180% of the current workforce. The solution to this problem is two-fold: first, more students and residents need to be attracted into child neurology, and second, there is a need for better training of pediatricians and neurologists about common pediatric neurologic problems and how to identify those children with more complex problems in need of referral to a pediatric neurologist.

Recruitment to Child Neurology–Obstacles and Opportunities

The structure of American medical education is such that students typically must decide by the end of their third year or beginning of their fourth year of medical school which field of specialization to pursue in order to apply to desired residency training programs. Thus, the first 3 years of medical school are critical formative years in making that decision. Of US medical students who chose to go into child neurology, 70% made that decision before graduating from medical school. Students consider those specialties to which they are exposed, and the mentors in those specialties are important role models. Given time constraints and content limitations of the curriculum, student exposure to child neurology is limited during this

formative period. In a study published in 2004, child neurology residents reported the following percentages as to their first exposure to child neurology: first or second year of medical school-12%, third year-31%, and fourth year-21% (Polsky and Werner, 2004). Because of the limited number of pediatric neurologists and the substantial clinical demands placed on them, pediatric neurologists typically have little contact with medical students during these critical years for career choice.

Given such obstacles, there are also significant opportunities to attract potential trainees. Pediatric neurologists are trained in both pediatrics and neurology, as well as in child neurology, giving pediatric neurologists the background and the expertise to teach in all three of these disciplines. Neurodevelopment is an important aspect of pediatrics. It is essential for a medical student to understand the normal sequence and time frame for the acquisition of neurodevelopmental milestones. These milestones are a reflection of growth and maturation of the central nervous system. Neurodevelopment is the providence of pediatric neurologists who are in the best position to teach this information both in the classroom and in the clinical clerkships. Pediatric neurologists should take the lead in doing so. With expertise in neuroscience and general neurology, pediatric neurologists are also in a position to teach in the basic neuroscience curriculum, particularly with the current curricular emphasis on the application of basic neuroscience to the clinical setting. Pediatric neurologists have a knowledge of neuroanatomy and clinical neurophysiology that can provide this bridge between the basic neurosciences and clinical applications. Pediatric neurologists teaching in the undergraduate setting can provide much more than just information but can also be role models and help students explore the clinical world through this mentoring relationship. Students sensing the enthusiasm and passion that pediatric neurologists have for their discipline are more likely to be attracted to this specialty area. A number of medical schools across the country have seen an increase in the percentage of students choosing child neurology after being mentored by dedicated, enthusiastic pediatric neurology faculty who have increased teaching time in the critical first 2 years of medical school.

The recruiting effect of increased teaching involvement is applicable at a resident level as well. As pediatric residents are introduced to child neurology through educationally well-designed electives, there is an increased potential for recruitment. Of US medical graduates who chose child neurology, 20% did so during their pediatric residency. For international medical graduates who pursued child neurology, 60% made that decision during their pediatric residency (Polsky and Werner, 2004). The importance of teaching involvement for pediatric residents also extends to active participation in morning report, teaching rounds, and formal grand rounds presentations. At the resident level, it is easier for a pediatric resident to pursue the subspecialty of child neurology than it is for neurology residents. Only 7% of child neurology residents chose to pursue child neurology during their neurology residency. The neurology resident would have to go back to a pediatric residency to pick up at least 1 year before being eligible for the American Board of Psychiatry and Neurology Special Qualification in Child Neurology. For pediatric residents, an obstacle to child neurology specialization is that they have to spend a significant amount of their 3 year residency being trained in adult neurology and seeing adult patients. Many pediatric residents simply do not want to return to the setting of adult medical care. Thus, the ideal individual to entice into child neurology is the medical student who enjoys working with children but who also has a love of neurology and sees child neurology as an ideal discipline to combine these two interests. In a survey, child neurology residents strongly recommended more exposure to child neurology during the preclinical years of medical school. It is imperative that pediatric neurologists spend more time teaching in the early years of medical school in order to increase recruitment into child neurology.

The Essential Educational Elements for Child Neurology Problem Solving

What is unique about the discipline of child neurology and what type of thinking do pediatric neurologists use that students and resident need to understand and model? To increase the numbers in child neurology and to train other health care providers to help in caring for neurologic problems in children, pediatric neurologists need to identify the essential elements that are critical for the discipline's problem solving skills. The context that pediatric neurologists practice in is pediatric medicine but the root of their analytical problem solving thinking is neurology. C. Miller Fisher made the statement that the "student learns neurology stroke by stroke." The reasoning behind this statement is that stroke, more than any other disease process, teaches the student anatomical location of neurologic function and the importance of the chronology or temporal profile of the patient's illness. The first principle of neurologic problem solving is "where is the lesion." History directs the focus of localization, and the neurologic examination is the tool used to indirectly examine the brain and confirm that localization. The thought process essential for anatomic localization is viewing the nervous system in terms of systems and levels. These levels are on a vertical axis and consist of the cerebral

cortex (mental status), cranial nerves (cranial nerve testing), cerebellum (coordination testing), spinal cord, and peripheral nerve (motor and sensory examination). The motor and sensory examinations provide a window to view systems within this neuroaxis as they either descend or ascend in connecting the cortex to the peripheral end organ.

Localization is then coupled with the evolution or the temporal profile of the patient's illness to determine "what is the lesion" or what disease process is the most likely etiology for the deficit. Signs and symptoms of the patient's illness usually have one of four temporal profiles: acute (seconds, minutes, hours), subacute (hours, days), chronic (days, months), or paroxysmal (episodes or spells). Most diseases of the nervous system are caused by pathologic processes that have a certain typical temporal profile.

For child neurology, localization and temporal profile are essential but not sufficient. Added to these analytical tools are the contextual framework of neurodevelopment and the expected maturing of the developing nervous system overtime. Delay in obtaining neurodevelopmental milestones and abnormal patterns of development are important indicators of underlying neurologic disease. It is essential that pediatric neurologists teach the concept that the neurologic assessment must be couched in the context of neurodevelopmental expectations. With the emergence of molecular medicine, the pediatric neurologist also assesses the effect of genetic and metabolic pathophysiological processes on the developing brain and identifying the impact and importance of epigenetic influences on development. The pediatric neurologist must interweave genetics and metabolism, as well as psychosocial environmental factors, into the concept of neurodevelopment and combine this with the traditional basic neurologic analytical process of temporal profile and anatomical localization. This process characterizes the thinking and problem solving that defines being a pediatric neurologist.

Child Neurology for Medical Students

The American Academy of Neurology has made recommendations about what all medical students regardless of their ultimate career path should know about neurology. Pediatric neurologists can certainly make a significant contribution to this educational process particularly in the area of development and teaching the neurologic examination of the newborn, infant, toddler, and child. Medical students should be able to perform an age-appropriate neurological and neurodevelopmental examination. Other areas considered important would be paroxysmal syndromes (such as epilepsy and headache) and recognition of the signs and symptoms of increased intracranial pressure and meningeal irritation in the pediatric setting. The medical student should be able to assess a child for developmental delay and recognize the patterns of abnormal development associated with cerebral palsy, mental retardation, autism, and isolated language delay. Congenital brain malformations, dysmorphic and genetic syndromes, and metabolic disease affecting the brain are other areas of importance for the medical student. Obviously, this is not an inclusive list for the medical student, but the point is that there are important aspects of neurologic problems in children that the medical student should be introduced to and pediatric neurologists should be actively involved in developing and teaching the curriculum in these areas.

Child Neurology for Pediatrics

Although a child neurology rotation is not required for pediatric residents, they can select it as one of their elective subspecialty months. Residents gravitate to services that have a well-designed and executed educational structure coupled with enthusiastic teaching and mentoring. If pediatric neurologists create a positive learning environment, pediatric residents will elect the rotation and be appropriately trained to manage basic neurologic problems. Developing a syllabus that includes objectives, required reading, and live or videotaped lectures, along with appropriate assessment of performance will enhance the rotation and ensure that the pediatric resident accomplishes the educational goals. Topics covered should be focused on the common problems that pediatricians will encounter and must be able to recognize and contribute to patient management. Such topics should include loss of consciousness (including syncope, breathing holding, and concussion), new-onset seizures, febrile seizures, status epilepticus, headaches, developmental delay, cerebral palsy and mental retardation, increased intracranial pressure, the weak or floppy child, loss of motor or cognitive milestones, and common behavior problems, such as attention deficit disorder and other school-related problems. Although this is not an exhaustive list, it exemplifies the type of neurologic problems about which pediatricians must receive training in order to contribute to the care of children with neurological problems in conjunction with pediatric neurologists.

Child Neurology for Neurologists

Most adult neurology programs require a minimal 3 months of pediatric neurology. During these months, the neurology residents must still attend their required conferences and outpatient clinics, which further limit their exposure to child neurology. Since neurology residents

usually have had limited experience in examining and caring for children, the major focus of their child neurology experience should be on acquisition of skills related to examining and assessing the developing nervous system. It is essential that neurology residents master the chronology and expectations of normal neurodevelopment as part of their neurologic analysis of the child's problems. They also must learn how to perform the neurologic exam for the newborn through the school-age child and how the exam must be adapted so that it is age appropriate and child directed. Even with this emphasis, most adult neurologists will ultimately not feel comfortable in the newborn intensive care unit or assessing the infant or toddler. However, they can make a valuable contribution in caring for the older child and especially the adolescent whose neurologic problems are often similar to the adult conditions with which they are more familiar. Certainly in those geographic areas that pediatric neurology consultation is limited, the adult neurologist by necessity must have an active role in providing neurologic expertise for children. The adult neurologist can be particularly valuable in helping the pediatrician interrupt neurologic phenomena and neuroanatomical localization. Adult neurologists should also be comfortable in handling pediatric neurologic emergencies, such as status epilepticus, acute weakness, and coma.

Summary

Neurologic problems are a significant part of medicine for children. The need for expertise in treating these problems is not diminishing. In order to meet this need, pediatric neurologists must enthusiastically recruit medical students in their formative years so there is a future for the specialty. Even if they were successful in this recruitment, there would still be more clinical demands than could possibly be met. Therefore, pediatric neurologist must play an active role in the education and training of pediatricians, and adult neurologists who have a valuable contributing role in caring for children with neurologic disease.

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CHAPTER 6

THE INTERNET IN CHILD NEUROLOGY

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The Internet is successfully used in the field of child neurology to facilitate communication among physicians, advance research efforts, aid in patient education, and increase access to medical information. This chapter lists current examples of Internet resources and delineates the future potential of the Internet for child neurology.

The chapter addresses how the Internet can make our jobs easier, more efficient, and more effective. Listed below are examples of how the Internet is of use to neurologists.

Web-based Information

The World Wide Web (WWW) has its own specific jargon. A "home page" is a "virtual" or computer home. Often, a home page contains links to other useful "pages" featuring text or graphics files. These pages are connected by "hypertext," a highlighted word or icon that allows one to switch to a new page, regardless of whether that page is on the same computer, in the same city, or across the world. In this way, the WWW can link a variety of informative Web pages on a single topic from different information sources around the world. The name or location of a page is called a Uniform Resource Locator (URL). Although these generally consist of almost unmanageably long lists of letters, most Web browsers have "bookmark" features that allow one to save URLs of interest for future reference. In addition to its multimedia and hypertext features, the Web allows interactivity: The reader can fill out forms, respond to questions, and run searches for specific information.

Academy Web Sites

The American Academy of Neurology (AAN; http://www.aan.com/), the Child Neurology Society (http://childneurologysociety.org/), and the International Child Neurology Association (http://www.child-neuro.net/) have each formed Web sites that contain information about meetings, fellowship and job opportunities, educational programs, and various academy affairs. The AAN Web site has resources for patients as well.

The Web site of the American Academy of Child and Adolescent Psychiatry (http://www.aacap.org/) is also worth visiting. A most innovative part of this site is its "Facts for Families" (http://www.aacap.org/page.ww?section=Facts+for+Families&name=Facts+for+Families), a series of fact sheets for patients and their families on common clinical problems in the field, such as autism, tics, and depression. The American Academy of Pediatrics (AAP; http:// www.aap.org) has a well-organized, frequently updated site with patient information, current news, and a bookstore for AAP publications. The American Psychiatric Association can be found at http://www.psych.org/. One of the most unique aspects of this site is the availability of continuing medical education (CME) programs through the Internet.

Journal Web Sites

Almost all biomedical journals have online versions. Examples include the *Archives of Neurology* (http:// archneur.ama-assn.org/), the *British Medical Journal* (http:// www.bmj.com/index.shtml), *JAMA* (http://pubs.amaassn.org/), *The Lancet* (http://www.thelancet.com/), The Lancet Neurology (http://www.thelancet.com/journals/laneur), *Neurology* (http://www.neurology.org/), *The New England Journal of Medicine* (http://content.nejm.org/), the Journal of Pediatrics (http://journals.elsevierhealth.com/periodicals/ympd/home), and *Pediatrics* (http://pediatrics.aappublications.org/).

Child neurology subspecialty journals also have recently gone online. Examples include *Brain and Development* (http://www.sciencedirect.com/science/journal/03877604), *Developmental Medicine and Child Neurology* (http://titles.cambridge.org/journals/journal_catalogue.asp?mnemonic=DMC), *European Journal of Paediatric Neurology* (http://www.sciencedirect.com/science/journal/10903798), *Journal of Child Neurology* (http://www.bcdecker.com/productDetails.aspx?BJID=69), and *Pediatric Neurology* (http://www.sciencedirect.com/science/journal/08878994).

The advantages of online journals include the ability to publish quickly, search capabilities, forums for discussions of articles, links to related articles, and the ability to include supplemental resources and data too extensive to include in a print format. Furthermore, audio and video components can be included in publications without difficulty, which should be of tremendous utility to neurologists discussing language or movement disorders, for example.

Journal access is often password-restricted, limited to those who have paid subscriptions. However, there are notable exceptions. *BMC Neurology* (http://www.biomedcentral.com/1471-2377) is an example of a totally electronic effort. All articles are published immediately upon acceptance, and there are no barriers to access. Links to other neurology-related journals can be found at Neuroguide (http://www.neuroguide.com/neurojour_5.html) or at the Stanford University Highwire Press (http://highwire.stanford.edu/).

MEDLINE Access

The MEDLINE database contains bibliographic citations and author abstracts from more than 4,600 current biomedical journals published in the United States and 70 other countries. The file contains in excess of 12 million records dating back to 1966. The OLDMEDLINE database contains 1.5 million citations from 1953 to 1965. These databases can be accessed through various "portals." One such portal, PubMed (http://www.ncbi.nlm.nih.gov/PubMed/), was developed at the National Library of Medicine (NLM) in conjunction with publishers of biomedical literature as a free search tool for accessing literature citations and linking to full-text journals at Web sites of participating publishers. It has the advantage of ease of use and a frequently updated database.

Electronic Texts

Various Web sites feature electronic texts or "books" on neurology-related topics. Online Mendelian Inheritance In Man (OMIM; http://www3.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM) provides information on genetic syndromes. It is based, in part, on Victor McKusik's excellent book and has the advantage of being continually updated. Clinical, historical, and genetic information, with hypertext links to abstracts of cited references, is available. The Web site eMedicine (http://www.emedicine.com/) contains more than 40 peer-reviewed topics in child neurology and many more topics in general neurology and other areas of medicine. The Neuromuscular Disease Center at Washington University (http://www.neuro.wustl.edu/neuromuscular/) catalogs many aspects of neuromuscular disease. Neuropathology and Neuroanatomy on the Internet (http://www.neuropat. dote.hu/) features an online neuropathology atlas, as well as a tutorial on normal brain structures.

Other useful text sites include online versions of the *Physicians' Desk Reference* (http://www.medecinteractive.com/) and of *The Merck Manual of Diagnosis and Therapy* (http://www.merck.com/mrkshared/mmanual/home.jsp).

CME Resources

CME programs are available on the Internet. Some of these programs will charge a modest fee. The American Medical Association (AMA; http://www.ama-assn.org/) maintains a database of AMA-approved CME activities. The National Institutes of Health (NIH) Consensus Development Program "CME Online" (http://consensus.nih.gov/CMELIST.htm) invites physicians to earn CME credits online from the NIH. Participants at this NIH Web site review statements regarding current controversies in clinical medicine. The statements reflect consensus views from panels of experts. The Virtual Lecture Hall Web site (http://www.vlh.com/) offers interactive, online CME courses and gives AMA Category-1 credits to physicians. Medscape (http://www.medscape.com/cmecenterdirectory/ splash?src=hdr) has a listing of free CME courses listed by specialty.

Other Medical Education Resources

The Internet allows access to case presentations that use text, graphics, and hyperlinks to relevant references. An example is the journal *Brain Pathology* (http://www.blackwellpublishing.com/journal.asp?ref=1015-6305&site=1), which gives interesting cases that include magnetic resonance imaging (MRI) images as well as photos of histologic sections. Multiple other sites have MRIs, photos of pathology sections, and even patient videos that are useful tools for teaching. The Visible Human Project (http://www.nlm.nih.gov/ research/visible/visible_human.html) and The Whole Brain Atlas

(http://www.med.harvard.edu/AANLIB/home.html) are excellent examples.

Medical students also may find helpful resources at MedicalStudent.com (http://www.medicalstudent.com) and Stanford University's Medworld (http://www-med.stanford.edu/medworld/home). Another useful set of student Web site come from Paul Larsen at the University of Nebraska and illustrate via text, figures, and movies the adult neurological examination (http://library.med.utah.edu/neurologicexam/html/home_exam.html), the pediatric neurological examination (http://library.med.utah.edu/pedineurologicexam/html/home_exam.html) and the procedure for performing a lumbar puncture (http://webmedia.unmc.edu/larsen/lp/).

Medical Decision-making Tools

Developed by Dr Michael Segal, SimulConsult (http://simulconsult.com/) is a medical decision support application that allows doctors and other medical professionals to combine clinical and laboratory findings and get a "simultaneous consult" about diagnosis. Information about diseases from a large peer-reviewed community of experts is combined to suggest diagnoses and identify additional findings and laboratory tests that will be most useful in reaching a diagnosis. Recently, Dr Segal and his colleagues have also developed Web-based tools to generate and share educational cases over the Web (http://simulconsult.com/neurologicalsyndromes/edu/).

Isabel (http://www.isabel.org.uk/) is an additional online clinical decision information system covering the whole spectrum of pediatrics, including pediatric neurology.

Clinical Testing Information

With the recent explosion of information in molecular biology and proteinomics, it has become difficult to keep up with the data on available specialized laboratory testing. Efforts to consolidate this information include GeneTests (http://www.genetests.org/servlet/access), which contains information about which tests are available for genetic diseases and where to send the specimens, as well as clinical summaries about some conditions.

Research in Child Neurology

A major advantage of the Internet is quick access to up-todate information, including current research studies. Examples of clinical research efforts of interest to child neurologists include the clinical research database from the National Cancer Institute (http://cancer.gov/), the NIH clinical trials database (http://clinicaltrials.gov), and the CenterWatch "Clinical Trials In Neurology" (http://www.centerwatch.com/patient/studies/area10.html).

Finding Other Interesting Sites

The World Wide Web consists of hundreds of millions of documents and resources. Trying to navigate to an area of interest often proves to be a formidable task. One can prompt standard search engines to provide Web site information on topics as diverse as medicine, gardening, space, and art. Some search engines are topic specific. Neil Busis has set up an excellent search engine for neuroscience-related topics at "Neurosciences on The Internet" (http://www.neuroguide.com).

Patient Resources

Patient-related materials are found at the American Academy of Neurology Foundation Web site (http://www.thebrainmatters.org/). The U.S. Department of Health and Human Services also has developed a nice gateway site (http://www.healthfinder.org/) to provide reliable patient-related Internet resources. Similarly, the National Institute of Neurological Disorders and Stroke has a selection of consumer health publications related to neurology (http://www.ninds.nih.gov/health_and_medical/disorder_index.htm). There are now many disease-specific sites, such as the Epilepsy Foundation Web site (http://www.epilepsyfoundation.org/), which serves as a valuable patient resource. The Family Village (http://www.familyvillage.wisc.edu/) has a "library" that provides an excellent link to many neurologic diseases affecting children. Various disease-specific sites are listed in Table 6-1.

E-mail Lists in Child Neurology

In the case of an e-mail list, a member sends his message to a central computer, and then that computer distributes the message to everyone on the e-mail list. Often, daily messages can be consolidated into a digest format, so the total amount of all mail received is limited to one piece of mail per day. For child neurology, e-mail has become a way to interact with busy or geographically dispersed child neurologists in a facile manner.

Currently, the most organized example is the Child-Neuro e-mail list (http://www-personal.umich.edu/~leber/c-n/e-mailUM.html), which we manage. The Child-Neuro e-mail list has more than 1,150 subscribers in 60 countries. This has been supported, in part, by the Child Neurology Society and has shown steady growth since its inception in 1994. The email list has resulted in several positive effects. It has increased communication among

TABLE 6-1. Selected Web Sites of Interest to Child Neurologists

Name	URL (Address)	Description
Academy Web Sites		
American Academy of Neurology	http://www.aan.com/	Academic and administrative publications, AAN News, practice parameters, directory information, neurology rating scales, and clinical trials
American Academy of Child and Adolescent Psychiatry	http://www.aacap.org/	"Facts for Families" gives parent information on various topics; useful for office handouts
American Academy of Pediatrics	http://www.aap.org/	A variety of patient and professional information
American Association of Neurological Surgeons	http://www.aans.org/	A well-designed Web site that features society information
American Psychiatric Association	http://www.psych.org/	CME program via the Internet, as well as publications, news
Child Neurology Education and Research Foundation	http://childneurologyfoundation.org/	Research arm of the Child Neurology Society; information about funding opportunities
Child Neurology Society	http://childneurologysociety.org/	Academy, meeting, and employment information
International Child Neurology Association	http://www.child-neuro.net	Academy and meeting information
Clinical Decision-Making		
Isabel	http://www.isabel.org.uk/	
Simulconsult	http://simulconsult.com/neurologicalsyndromes/edu/	Peer reviewed, frequently updated
Clinical Testing Information		
Gene Tests	http://www.genetests.org/servlet/access	In-depth database of available molecular testing
CME Web Sites		
American Medical Association (AMA)	http://www.ama-assn.org/	Includes database of CME sites
Medscape	http://www.medscape.com/cmecenterdirectory/splash?src=hdr	Listing of free CME courses by specialty
NIH Consensus Program	http://odp.od.nih.gov/consensus/cme/cme.htm	Program based on NIH consensus statements
Virtual Lecture Hall	http://www.vlh.com/	Large listing of online CME courses

child neurologists, particularly among those of different countries. Rapidity of communication is an advantage. The list has been used, for example, at times when pharmaceutical companies were contemplating withdrawal of certain anticonvulsants from the market. The list affords an opportunity to discuss matters of practice that may not be dealt with in journal articles or may have just recently been published. Calls for research subjects also reach the appropriate physicians and appropriate patients can be quickly placed with interested investigators. Practical diagnostic and management issues, both basic and complex, as well as ethical issues in our practice are freely discussed.

The Child-Neuro e-mail list and other pediatric subspecialty e-mail lists have been reviewed (Hernández-Borges and colleagues, 1997). It is of note that the authorship of messages to these e-mail lists is of similar quality (as evaluated in terms of recently authored publications) to that of articles in the respective subspecialty journals. This would argue that contributions to the lists are of similar quality to other venues of communication. Although the messages are not peer-reviewed before posting on a list, the e-mail list typically critiques and discusses the postings after they are sent. Many other regional neurology societies have also started their own e-mail lists.

Although some have commercial sponsorships, e-mail lists intended for dissemination of new publications are also extremely useful and are free. For example, MDLinx (http://www.mdlinx.com/) has daily mailings with summaries of articles related to pediatric neurology, including links to the full articles. Amedeo (http://www.amedeo.com/) has a number of weekly neurology e-mail lists, including epilepsy and migraine. Each mailing lists titles of articles recently published, including links to their PubMed sites.

E-mail Use Between Physician and Patient

Much of current medical care takes place over the telephone. This medium has its disadvantages, including inefficiencies in patients' and medical providers' inability to reach each other (the cursed "telephone tag") and misunderstandings and poor documentation of what is said. Email is being recognized as a solution to these problems, allowing messages to be (1) thought out carefully in advance, (2) posted and read at convenient times and without long-distance telephone charges, and (3) saved for future reference and for the medical record. As advantageous as e-mail may be, it poses risks of

breach of confidentiality (eg, employers have the right to access messages sent over e-mail systems they own) and significant logistical concerns (eg, misuse for communication of emergencies, confirmation of receipt of messages, handling of messages in the clinical office). Patients appear to have a greater interest in using e-mail for these purposes than do physicians, with patients emphasizing the benefits and physicians the risks (Freed, 2003). Specific guidelines have been proposed to maximize e-mail's potential and minimize its risk (Kane and Sands, 1998; Spielberg, 1998).

A potential solution to many of the problems posed by e-mail (eg, confidentiality, triaging of messages) lies in the development of Web-based portals that "triage" patient messages. Patients are given a password, can log into a Web site, and are notified by e-mail that a message waits for them on the Web site. Messages coming in via the Web site are triaged in ways similar to incoming phone calls. A University of Michigan study showed that such a portal increased the amount and, in the eyes of the physicians, the quality of communication between providers and patients but did not reduce the number of telephone calls, office visits, or missed appointments (Katz and colleagues, 2003).

Physician-to-physician phone calls about specific patients are common, but often very disrupting. When the questions are not complex or urgent, e-mail may be a useful solution. Intrainstitutional mail, particularly if an encrypted mail system is used, may present fewer security concerns than would interinstitutional messages. Physicians also must be cautious not to discuss two patients in the same message because descriptions of the discussions may be inserted into the medical record.

Personal Digital Assistants

Personal digital assistants (PDAs) are becoming commonly used in neurology. A recent review showed that 35% of pediatricians use them in clinical practice (Carroll and Christakis, 2004a). The most common uses are for drug references (including drug interactions), personal scheduling, and medical calculations. Other uses may appeal specifically to pediatric neurologists. Many neurology and pediatric texts are being converted to PDA format (see http://www.palmgear.com). The AAN Handheld Computing Center is a resource for neurologists interested in the use of handheld devices within the neurologic setting (http://aan.com/pda.cfm), and Pediatrics on Hand (http://www.pediatricsonhand.com/) is a pediatric-specific site that reviews PDA medical software. Although it is inconvenient to read a full text on a PDA, it is helpful to have databases available, such as for pediatric drug dosing. Growth parameters can be entered and percentiles calculated. In addition, programs currently are available to electronically write prescriptions from a PDA, download patient data, calculate body surface area, and much more.

As more PDAs have wireless capability and more medical records become electronic, it is natural to expect that PDA-based systems will progressively be used for entering orders, writing progress notes, and looking up laboratory results and vital signs. When one study looked at whether such a system would decrease documentation discrepancies in a neonatal intensive care unit setting, however, only a modest benefit was found (Carroll and Christakis, 2004b). In addition, at least some physicians and hospitals have concluded that the screen size is too small on PDAs and are providing their physicians with wireless laptops or tablet-style computers.

Potential Problems

Certainly anyone can post any item of information (or misinformation) on the Internet, and currently there are no safeguards to ensure that information is accurate. Some Web sites, such as the that for the AAN, have high credibility because the postings have gone through some form of review. However, how can we control the quality of a random Web site on "autism" or "headaches"? Certainly, like any journal article that we read, we must be critical and take into account the source for that article or information. As clinicians and scientists, we have been trained to do this, but, unfortunately, most parents have not. The balance between free and easy access to information and the danger of misusing that information once it is obtained is precarious. As time goes on, a few sites may distinguish themselves for their ease of use and accuracy. We are hopeful that labels denoting quality sites (eg, that of the Health on the Net Foundation, http://www.hon.ch/) become more universal. Another category of concern relates to privacy issues. Certainly patient information must be secured in its use in e-mail applications as well as in portable devices.

The Future

The future of the Internet in medicine demands nontraditional, creative ideas. The Internet provides us with unique opportunities to advance our field. We need to reevaluate our ways of publishing, disseminating, and even communicating information among physicians and patients. We are still years away from using the Internet to its full potential. The onus is on us, as users of these protocols and programs, to define our needs and, secondly, to define (or seek computer consultants who can do this for us) solutions to our needs. As neurologists, we should judge the value of the Internet not on what it is now, but on what it will contain in the near future. The best is yet to come.

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Chapter 7

Excelling at the Art of Medicine

Meryl D. Luallin, BA

Excelling at the science of medicine has always been the goal for physicians and other providers. The mark of a well-rounded practitioner is success at the art of medicine as well.

Remember the old days when simply delivering quality medical care ensured a successful practice? Times have certainly changed. Today, the consumer is calling the shots, and patients—and their parents or caregivers—are evaluating physicians on more than their ability to accurately diagnose and prescribe. With the consumer revolution, patients* have redefined quality medicine to include not only clinical excellence but service excellence as well. The qualifications of a physician are assumed; patients now expect skills to include *caring* as well as curing.

This new expectation comes at a time when the practice of medicine is filled with unprecedented challenges.

Challenges Facing Providers

Decreasing reimbursement has affected pediatricians and other specialists nationwide. The result? Widespread disenchantment among clinicians with what has happened to the medical profession. The only way providers today can maintain revenue levels, short of entering alternative careers, is to see more patients in an already crowded day. Patients, meanwhile, want more time and interaction with their doctors. This means that physicians must convey reassurance and caring along with the diagnosis and treatment plan, in less time than ever before.

More sophisticated patients are coming to the office armed with information they have gathered from the Internet and elsewhere. It is not uncommon for patients to tell physicians what they believe their illness is and what drugs should be prescribed. And although this may be an annoyance in the short term, the Internet will be a boon to practice in the long term. Today, there are medical groups whose Web sites enable patients to download registration forms or request prescription refills and appointments!

Increased litigation often encourages providers to practice defensive medicine. Yet malpractice suits are not, as many physicians believe, primarily the result of bad outcomes. Rather, poor communication by the provider is a major cause of patients' annoyance and willingness to sue. In fact, studies show that a patient who perceived that the practitioner was insensitive or uncaring is more likely to file a malpractice suit than one who is dissatisfied with medical outcomes.

Pay for Performance is a phenomenon that has come into its own in the health care field. More group-based physicians than ever are eligible for financial bonuses from health plans based on disease management and patient satisfaction measures. Today, doctors and other providers routinely conduct patient satisfaction surveys to gauge how well they're meeting patient expectations for caring service. Survey results are used to indicate the strengths and limitations of a medical practice, and to point toward improvement opportunities.

These challenges and others often make it difficult to deliver the caring medical service patients have come to expect. Accordingly, this chapter reviews the techniques effective providers use to meet and exceed patient expectations.

*References to patients are made with the assumption that parents or caregivers are the decision-makers.

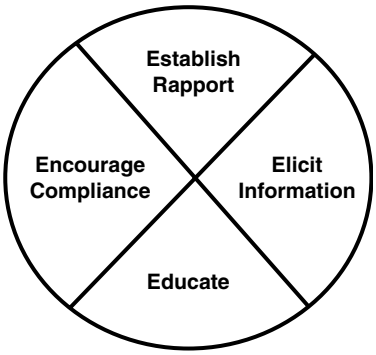

FIGURE 7-1. The four "Es" of the doctor–patient encounter.

Delivering on Patient Expectations

Meeting and exceeding patient expectations and successfully delivering health care services occur during four distinct phases of the doctor–patient encounter: (1) establishing rapport, (2) eliciting information, (3) educating the patient and caregiver, and (4) encouraging compliance (Figure 7-1).

Establishing Rapport

The most important aspect of the relationship with patients and their parents or caregivers is the first impression a physician makes. The following is a list of practical recommendations:

1. *Review the chart outside the examination room.* One practice asks parents for a picture of the child, which is stapled to the inside of the chart cover. It makes it easy to place a face with a name before entering the examination room.
2. *Make a connection to a previous visit.* Write something personal about the child or family that you can refer to in a subsequent visit. Or ask your nurse to keep an ear open while doing the child's work-up. Personal bits of information (Timmy made the soccer team, for example), can be jotted down on a sticky note and placed on the chart so you can comment on it when you greet the child.
3. *Be aware of body language.* Get on eye level with the child. Whereas pediatricians most often discuss the child's health problem with the parents, one very successful provider in Muskegon, Michigan, says he poses all his questions to the child—or infant—well within earshot of the caregiver. According to this popular doctor, the parents always answer for the infant, but they feel that he is interacting in a caring way with their child. Another pediatrician puts the stethoscope on her own chest so the child can listen before she places the instrument on the child's chest.
4. *Maintain a professional appearance.* For years it was commonly accepted that pediatricians did not wear white because it frightened children. That sentiment is changing. With the number of sexual abuse charges coming to light, more and more mothers are requesting that their children's doctor wear something that distinguishes him or her from a stranger. Colored smocks and the ever-present stethoscope denote a health care professional.
5. *Educate parents regarding your philosophy about medication or other treatments.* The first examination with a new patient is the ideal time to share your attitude regarding the appropriate use of medication or other often-requested treatments. Place educational materials in the examination room that describe when medications are called for and when they are not. This will save time later when you need to deny a request for an inappropriate treatment.
6. *Stay on schedule.* Studies have shown that patients are less likely to return to a physician's office or to recommend that provider to a friend or relative if the doctor chronically runs late. Today, it is particularly difficult for the mother when the provider is behind schedule because she may be taking time off from work and paying the price in lost wages. Techniques for staying on schedule include:

   - Schedule appropriately. Leaving one or two open slots in the morning will accommodate unexpected walk-ins. Many providers schedule new patient or annual (school or camp) physicals for the end of the day because these examinations often run longer than anticipated.
   - Ask caregivers to list their questions on a "confidential patient agenda" they can complete while they wait for you in the reception area or examination room. This allows you to see in advance the scope of their issues and avoids the "Oh, by the way," syndrome as you prepare to leave the examination room.
   - Expect patients to play by the rules (but be flexible). Sometimes a doctor's schedule is thrown off because a mother arrives with more children than were scheduled. If a mother sets an appointment for one child but arrives with three children in tow, explain that you were not expecting the others and you cannot see them without their charts. Ask her to return to the reception area while you see other scheduled patients. Tell her that you will try to fit the other children in but it may take some time. Convey that you are making a special accommodation at this visit, but in the future she will need to schedule all three children so you can allot enough time.
   - Delegate as much as possible to your staff, especially return phone calls. Unexpectedly protracted phone

calls can wreak havoc with the schedule. One practice has a list of frequently asked questions (FAQs) that parents call with. The pediatrician created a binder containing the FAQs listed alphabetically by topic and the appropriate answers to each question. Staffers are, thus, empowered to provide the answers (to all nonurgent questions) when caregivers call. This cuts down on the time the doctor spends on the telephone between patients.

- Ask your nurse to keep you posted on your schedule status. A Tulsa, Oklahoma, physician has his nurse alert him to his "lagging" by knocking on the examination room door and announcing, "Doctor, you have a call from Dr. Hind." The doctor quickly ends the encounter and moves on to the next patient.
- Keep waiting patients occupied. One Midwest pediatric department has a carnival mirror in the waiting room, which keeps children and their parents amused for a time. An aquarium is another means of keeping children entertained while they wait. Some practices use videotapes to occupy children, but this strategy has a downside. When it is time to see the physician, a child engrossed in the video might become upset at the interruption and put up a fuss.

Eliciting Information

The second phase of the encounter entails gathering the information needed to determine the treatment plan. One study, reported in the January 1999 issue of the *Journal of the American Medical Association*, showed that the typical primary-care provider allows as little as 23 seconds for the patient to describe the reason for the visit or the symptoms involved before interrupting to ask questions. This study also indicated that, on average, patients take only 90 seconds to tell their story. In most cases where the doctor interrupted before the patient completed the story, that patient stopped the departing doctor with the dreaded words, "Oh, by the way…"

As the parent speaks, the physician should maintain good eye contact and nod. Once the reason for the visit has been described, one should ask, "Is there anything else that's going on that I should be aware of?" The most important technique to employ during this phase of the encounter is to respond with sympathy to the plight of the child or parent. If a new mother with a 5-month-old infant comes to the office saying, "Timmy was awake and crying all night long; I didn't get a wink of sleep. He's been scratching at his ear. I think he has a fever," the immediate response should not be "When did this start?" but rather "You must be exhausted!" That said, it is appropriate to launch into the questions that will guide diagnosis and treatment plan.

Educating the Patient and Caregiver

The third phase of the encounter follows the hands-on examination and describes the course of action that will be recommended. The following are among the more successful techniques used by physicians:

- Using nontechnical terms and, when appropriate, three-dimensional models to explain diagnoses
- Providing written information for even the simplest advice, adding your handwritten notations (this cuts down on phone calls later)
- Explaining why you are recommending the course of treatment
- Establishing the parent's perceptions about their child's illness; correcting any misinformation
- Using the phrase "That's a good question" to build the caregiver's self-esteem
- Before beginning a procedure, asking, "Is there anything I can do to make you more comfortable before we begin?" and during the procedure, explaining what is happening.

Saying No

These days, patients and their caregivers are becoming more educated regarding treatment options. Whether they have read a magazine article, seen a TV program, or surfed the Web, more and more patients are coming to the office with preconceived ideas of what treatment is best for them. As a result, doctors are experiencing the discomfort of saying "no" to requests for inappropriate drugs or procedures. The most successful method for turning down patients' requests without "turning them off" follows a series of steps. Let us look at the best way to handle a parent's demand for a magnetic resonance imaging (MRI) brain scan.

Listen

Let parents (or caregivers) explain why they want the requested scan. It may be that in this case they have misinformation about the treatment they are asking for. ("My neighbor had a headache, and the MRI scan showed she had a brain tumor.") At this point, you have learned the underlying fear contributing to the request, and you can take measures to educate them regarding their child's likely diagnosis.

Allowing parents to say why they want the procedure or drug may identify a common goal. For instance, if your patient's father says, "My boy has a chance at a scholarship to the State University, and if there's something seriously wrong, he'll lose it," your response would be, "I want your boy to get that scholarship, too. And here's how we'll treat his condition to get him back to school as quickly as possible." It is vital that you be seen "on the patient's side" early in the request-denial process.

Empathize

Once you have listened to the parent's request, be sure to respond with a sympathetic statement. The mother who has been sleeping poorly because she is worried her child's headaches are caused by a brain tumor needs to believe you relate to her misery. A response such as, "I bet you're exhausted" will assure the mother that you care.

Describe the Management Plan

At this point, parents or caregivers should believe that you understand their plight and want what they want—what is in their best interests or in the best interests of their child. In describing your management plan, it may be necessary to educate the parent or caregiver using evidence-based examples of why your plan is better.

It is extremely helpful to form the denial of their request in terms of the benefits to the patient. For example, not having an MRI scan means avoiding unnecessary sedation, scheduling hassles, or any delay in beginning treatment for migraine.

Offer Alternatives

To mollify patients who have not received the treatment they requested, some practitioners tell them to call the office for a follow-up if the prescribed regimen is not effective within a specified period of time and reassure them that they will be seen quickly.

Some doctors who do not prescribe daily preventive medication for a migraine do prescribe a stronger abortive agent (eg, sumatriptan) so that parents feel they are receiving something of value from their office visit.

The ultimate alternative is to suggest that the patient solicit a second opinion. Depending on the nature of the patient's request (eg, MRI, computed tomography scan), recommending another consultation also may be necessary.

Reassure Again

A final step is to reassure the patient that the course of management you are prescribing is valid. Many successful physicians end the description of the management plan by saying something reassuring, such as, "If Jason were my son, this is exactly how I would treat him."

Encouraging Compliance

Whether the patient is a child or an adult, compliance is the major factor in determining the successful outcome of a treatment plan. To increase the likelihood that the patient will follow your management plan, consider the following suggestions:

- Solicit the patient's and parents' expectations regarding the child's condition and likely outcome. If their expectations are unreasonable, now is the time to set them straight.
- Educate the patient and caregiver regarding expected outcomes; this will go a long way in avoiding disappointments when results are less than optimal.
- Be candid during the informed consent session and have the caregiver sign an informed refusal form, if appropriate.
- Make follow-up calls to the postprocedure patient at home. This not only shows how much you care (and is a terrific practice builder) but also ensures accountability.

Six Techniques for Encouraging Compliance

Although younger pediatric patients are generally more compliant than their grandparents might be, there are still effective techniques for encouraging patients to follow your management plan:

1. Indicate a reward that will motivate the patient to follow the plan.
2. Find out from the patient or caregiver what could prevent the patient from following the regimen.
3. Keep the plan as simple as possible.
4. Give a date (when possible) when the patient will see results.
5. Put the treatment plan in writing.
6. Identify a third party to assist, if necessary.

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CHAPTER 8

A PRIMER ON PRACTICE MANAGEMENT

BENSON HSU, MD AND MARSHA WENDT, MBA

The field of practice management is expansive. For physicians, a basic understanding of practice management is necessary to critically assess practice function and system breakdowns.

Frequently, physicians shy away from the field of business. Cost-effective care and billing rarely enter the scope of medical education. Instead, physician training focuses on the fundamental structure of medicine: the history, physical exam, laboratory and imaging studies, and assessment and plan. Fortunately, this approach can be applied to understanding practice management. Similar to the history of present illness, understanding the process of how the patient, physician, and payor interact allows physicians to visualize the steps of practice management. In conducting the physical exam, physicians identify variables that can direct additional laboratory and imaging studies. Likewise, in identifying the variables that impact the practice management process, physicians can create evaluative tools and reports to spot breakdowns. In using this structure, physicians can systematically assess each step of practice management.

This chapter takes a high level view of this process. Specifically, this chapter starts by describing the foundation of practice management based on staffing and contracts. Then, we provide a summary of all major points of interaction between patients, payors, and providers. Finally, this chapter assesses funds flow or how and when payment occurs. Each section will apply the structure of understanding the process, identifying the variables, and describing the pertinent evaluative tools.

Overview

The foundation of practice management relies on staff hiring and training, as well as establishing contracts with payors. Subsequently, the interaction between patients, physicians, and payors can be broken down into three distinct time frames. First, the period prior to the patient visit revolves around scheduling. Next, the period during the patient visit involves patient care while ensuring proper documentation and coding. Finally, the period after the patient visit is when documentation and coding will be submitted to the payor and/or the patient for payment (Figure 8-1). At each step, evaluations are vital to assess the integrity of the process.

Staffing

Physicians cannot efficiently operate an office without assistance. Outside of clinical support from nursing and laboratory technicians, staff is also required in the business office. In general, at a minimum, a business manager is needed. For larger offices, additional front-office staff for scheduling and back-office staff for coding and billing may be required.

The business manager must be involved in all aspects of the practice management process from establishing contracts to receiving payment from payors. This person should have educational if not practical background in health care management. An effective business manager will optimize all aspects of practice management. Specific roles include establishing payor contracts, coordinating the reports visible to the physician, identifying and remedying failures in the practice management process, and hiring the rest of the clinical and administrative staffs. Outside of the high-level understanding as

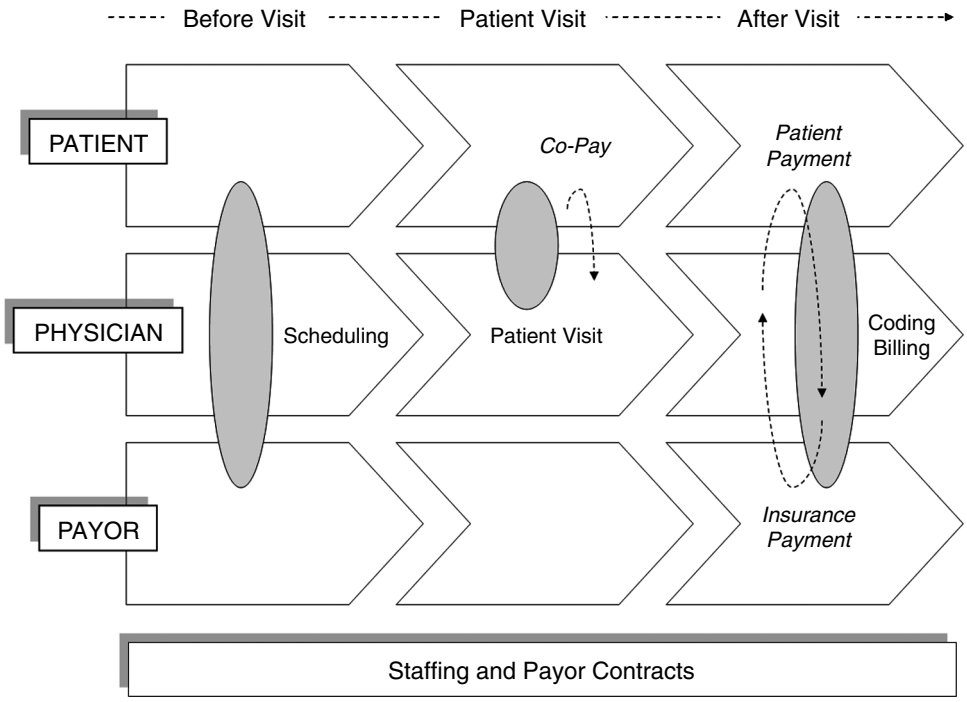

FIGURE 8-1. Depiction of the interactions among patient, provider, and payor separated into three distinct time periods set on a foundation of Staffing and Payor Contracts. During the first time period, scheduling requires interaction between all three parties. During the second time period, the patient visit only involves the patient and physician. At this time, payment (shown by the dotted arrow) may occur in the form of co-pay. During the last time period, the coding and billing process again includes all three parties. Bills can be sent to patient and payor requesting payment from both (shown by the dotted arrows).

proposed in this chapter, physicians should rely on the business manager for the day-to-day activities of running the practice.

The initial contact with patients involves the front-office staff. They schedule visits and, as needed, contact payors prior to the visit. Additional responsibilities involve directing the waiting area and collecting co-pays after the visit. The coding and billing processes involve the back-office staff. This staff codes each visit based on physician documentation and transmits bills to payors. Specific business skills are required, and back-office staff generally have additional training in medical coding and billing.

Retention of staff is often a concern of physicians. As the health care field expands, there is a shortage of qualified health care employees. Retention can be optimized through many pathways. Primarily, a competitive salary is crucial. In addition, benefits, such as membership in professional organizations and continuing education, can also improve retention. Finally, a stable and friendly work environment is fundamental. Staff needs to feel supported in the work environment and should not be given workloads exceeding capabilities. Combined, these conditions can improve staff retention.

Contracts

To have patients, physician offices must establish contracts with payors. Health care is no longer a simple exchange of money as patients see physicians. Now, numerous payor systems exist. The process of establishing a contract involves negotiation with the insurer on an agreement of coverage and payment. Depending on payor type, the payments may be based per patient or per service covered.

The rationale for contracts clarifies the key variables affecting this process. The goal of insurance companies is to find insurable individuals. Subsequently, payors need physicians to care for their clients, as economically competitively as possible. Physicians generally do not actively recruit patients and need insurers, usually on behalf of employers, to direct patients to their practice.

The symbiotic relationship of the two parties is why contracts are established. Thus, the key variables revolve around negotiation power; two main ones are involved: patient coverage and competition (although other less essential variables such as patient preferences exist). In general, more coverage offers more power. The inverse relationship is true for competition; the less the competition, the more the power. For instance, a physician office has the greatest bargaining power if the office serves a large city (greater coverage) and there are few physicians in the city (less competition). In practical application, it is important to note that frequently, especially in large markets with major payors, it may be difficult for a physician office to influence contracting since the office is a small player in comparison.

Nevertheless, evaluation of these variables is vital to establish effective contracts. Continued monitoring of any changes in the landscape can be important for contract renegotiations. Consequently, a valuable report for physicians includes market segment analysis. Creating reports should be delegated to the business manager of the practice. A failure of the physician and business manager to understand market variables can result in a breakdown of the contract process, often resulting in the physician being underpaid for services.

Scheduling

The first contact a patient has with the physician office occurs with scheduling. During this contact, the office coordinates a visit based on mutual availability of the patient and physician. If needed, the front-office staff can capture initial payor information to determine method of payment. For both new and returning patients, depending on type of visit and procedures required, additional communication between the physician office and payor may need to occur for preauthorization and precertification. Failure to do so may result in nonpayment by a patient's insurer, creating financial liability for the patient.

The scheduling process is relatively straightforward. However, recent technologic improvements have increased efficiency. Now, instead of phone interactions, some physician offices use internet-based scheduling linked to patient records. Similarly, some contact with payors now occurs through internet or electronic transmission of data. More than just convenience, these advances have wide repercussions throughout the process of practice management. An electronic scheduling system associated with patient records, coding, and billing can expedite the payment flow and may be required for larger payors. In some instances, payors may guarantee more prompt payment if bills are submitted electronically.

Variables affecting scheduling include technology and balancing schedule with acute visits. Although technology can optimize scheduling and have a significant downstream impact, disadvantages include cost and lost efficiency during initial introduction. The physician office should conduct a cost-benefit analysis prior to implementing new technology. In other words, the advantages of the new technology must be weighed against the disadvantages. Advantages include subsequent increased efficiency in scheduling, documentation, coding, and billing. Disadvantages include cost to buy and implement the system, as well as initial decrease in efficiency. The second variable examines the balance of time available for scheduled visits as opposed to acute visits. Frequently, urgent care visits result in overbooking and increased wait times. However, if urgent care spots occupy too much of the schedule, it can push back the time before the next appointment becomes available. In regards to efficient balancing of open and scheduled spots, an analysis of the population's needs through experience with regular reassessment can identify an appropriate time balance.

Patient Visit

The patient visit is the primary focus of any health care interaction. However, in practice management, documentation is as important as the diagnosis and treatment. In general, the patient arrives at the office, checks in, is seen by the physician, and leaves. As the patient checks in, information about the payor is gathered and confirmed. As the patient is seen by the physician, documentation of the visit through medical records occurs. As the patient leaves, a subsequent visit can be scheduled and co-pay collected.

Appropriate and thorough documentation allows for efficient billing later on in the practice management flow. Specifically, the medical record characterizes the interaction and diagnosis while the billing form captures diagnosis and procedures. In the medical records, chief complaint, history, review of systems, physical exam, assessment, and plan will allow coders to later determine what can be billed. Moreover, any procedures that occurred during the visit should be carefully noted. Payors have fairly standard expectations for what qualifies in each level of billing. This standard is not solely reflective of the visit but also of the documentation. If a review of system was conducted and not documented, it effectively did not occur. Good documentation extends past billing purposes and becomes vital in the treatment of the medical records as a legal record.

The first element of funds flow occurs during the patient visit. With the prevalence of co-pays in many

payor contracts, it is incumbent on the physician office to establish a process in which co-pays are captured. Frequently, this can be integrated into the check-out process. For instance, as the patient leaves the exam room and proceeds to make a follow-up appointment, the co-pay can be collected. The physical structure of the physician office may be instrumental to the success of this process.

Variables in this process include the effectiveness of information capture and co-pay collection. Information is obtained during the check in and the patient visit. Evaluation of this includes spot checks of patient records to ensure all necessary data is current. Denial rates downstream can reflect on how well billing information is obtained and maintained. Finally, an analysis of co-pay capture offers insight on the collection process.

Coding and Billing

Following the patient visit, this interaction will be coded and submitted for billing. The majority of the documentation required occurs during the patient visit. The level of visit can be coded based on duration and complexity using patient medical records. In addition, diagnoses and procedures need to be captured and will often serve as justification for the level of visit billed or procedures performed. This step is the most vital in the whole flow of practice management. Coders ensure all aspects of the visit have been captured and billers ensure that this information is promptly transmitted to the payors.

Variables in this process include efficiency in preparing and transmitting the bill and effectiveness in preventing denials. In general, the faster the process, the quicker the payment will be made. As noted in scheduling, implementation of a seamless electronic system affords rapid transmission. Depending on available technology, the exchange of information can take on several speeds from a paper to an electronic-based system. Billing is a time-dependent practice. Failure to meet time requirements can result in payment denials. Denials can also occur due to incomplete documentation and refusal to pay a certain diagnosis code or a service that is considered noncovered. These claims can usually be easily appealed but a process must be in place to efficiently accomplish this task. Appeals can be an arduous process and may require reassessing documentation and coding. Again, promptness plays an important role in successful appeals.

Evaluation of these variables can be conducted through an analysis of accounts receivable. Accounts receivable captures the amount billed and the time between when a service is rendered and payment is received. This analysis effectively takes into account both the efficiency in documentation, coding, and billing, as well as effectiveness in dealing with denials. Overall, physician office income can be maximized by minimizing both time and amount in accounts receivable.

Funds Flow

The physician office should expect payment in two to three installments. Initially, a patient visit can result in co-pay. During billing, usually a part of the bill is paid by the insurer with the remaining part attributed to the patient. In general, the process involves the payor accepting a claim and sending the physician office a portion of the payment. In cases where the patient has not exceeded the deductible, there will also be an additional portion the patient is responsible for.

The preceding sections have already covered the issues surrounding capturing co-pay and managing accounts receivable from insurers. Payment from patients is more complicated. Patients are often confused by the multiple bills, first from the physician office and then from the insurer. Consequently, payment from patients can be sporadic. In most cases, an additional communication to clarify an outstanding bill resolves any confusion. However, delinquent payments from patients do occur either through failure to pay the co-pay or failure to pay the deductible after the payor has processed the claim.

Delinquency of patient bills can create an awkward situation for physicians. Physicians generally do not like to associate care with compensation so requesting this from patients is a challenging concept to accept. Frequently, a remedy involves the use of collectors to recover part of payment. Bill collectors will pay up the physician office up front for the outstanding accounts receivable. However, the receivables are purchased at a discounted rate so physicians relinquish a part of the payment. Alternatively, some physicians have considered a budget plan for patients financially unable to pay the bill in full. Standards can be set to determine an appropriate budget, and most billing systems are set up to handle regular statements for patients on a budget plan. Thus, the physician would maintain a regular flow of payment and increase the opportunity to collect more for services than would ordinarily occur through the collection agency.

Conclusion

Practice management is not a daunting subject. The foundation for success in managing a practice requires a knowledgeable and well-trained staff. From this, payor contracts can be readily established with understanding of the market environment. The process of practice management involves three distinct time frames; each with a well-defined function. The first is scheduling, followed by the patient

visit, and concluding with coding and billing. During scheduling, patient and payor information is exchanged with time management being paramount. During the patient visit, documentation is vital for downstream activities. Finally, coding and billing allow physicians to be paid for services rendered. Throughout all steps, understanding the funds flow gives insight to the payment process.

This chapter addresses an overview of practice management appropriate for a practicing physician with sufficient business staff. There is no need for physicians to understand every aspect of practice management. With a basic understanding and use of regular reports prepared by a knowledgeable staff, physicians can critically assess for system breakdowns (Table 8-1). This field is extensive and persistently grows with the constantly changing reimbursement landscape. Short of the changes to create a national health system, the basic fund of knowledge addressed in this chapter will continue to be applicable.

Physician Resources

American Academy of Neurology-Patient Care & Practice Management
<http://www.aan.com/professionals/patient/index.cfm>

American Academy of Pediatrics-Practice Management Online
<http://www.practice.aap.org/>

American College of Physicians-Practice Management Center
<http://www.acponline.org/pmc/>

American Academy of Family Physicians- Practice Management
<http://www.aafp.org/online/en/home/practicemgt.html>

Journal of Practice Management Web Log- soundpractice.net
<http://www.soundpractice.net/index.cfm>

TABLE 8-1. Essential Physician Reports

- Analysis of staff turnover
- Analysis of market competition
- Analysis of the cost versus benefit of new technology
- Analysis of open versus acute time slots
- Analysis of payor denials
- Analysis of accounts receivable
- Analysis of collection agency returns
- Analysis of patient budget plans

Section 2

The Office Visit

Chapter 9

Migraine in Children and Adolescents

Nina Felice Schor, MD, PhD

Migraine occurs in approximately 7% of all children and 15% of all people sometime during their lives. This makes migraine among the most prevalent neurologic conditions in any age group. It exacts an enormous toll on the workforce and school-age population vis-à-vis days missed and time taken to complete even routine tasks, costs an estimated $1 billion to $17 billion in lost work productivity, and accounts for 10 million physician visits yearly in the United States alone.

Phenomenology of Migraine

Headache is the most readily identifiable manifestation of migraine, although it is not universally present in all migraine sufferers. Migraine equivalents without headache are, in fact, more common in children than in adults with this disorder. The headache of migraine is frequently, but not always, pulsatile. A subset of children with migraine have headache that is "squeezing" or "vise-like" in character. But, unlike typical muscle contraction headache, migrainous muscle contraction headache is accompanied by features commonly associated with migraine, including nausea, vertigo, and photo- or phonophobia. Although frequently referred to as "hemicrania," migraine is more frequently bilateral in children and, if unilateral, almost always moves from place to place and from side to side from episode to episode, or even within a single episode.

Migraines typically start with mild to moderate pain and build in intensity over minutes to hours. However, in children, they may be very short-lived. They are sometimes persistently mild or initially severe. Both pediatric and adult migraines are often made worse by loud noise, bright lights, fatigue, fasting, or stress or release there from and are made better by rest or sleep.

In some children, migraine is preceded by other phenomena—most commonly, visual aberrations. In fact, compared with adults, children are more likely to develop premonitory symptoms without headache. The most common migraine-associated visual aberration is "scintillating scotoma," often described by children as flashing lights, colored circles or balls, or shiny zigzag lines that start peripherally and over 10 to 20 minutes move centrally, obscuring half the visual world before receding in the reverse direction over the same amount of time, with complete return of normal vision. Closing one eye during this phenomenon does not get rid of it, although only the rare child has spontaneously tried this maneuver, and many children retrospectively report the phenomenon as being in one eye or the other rather than in one visual field.

In adolescents, it is not uncommon for dizziness, tinnitus, nausea, and even fainting to precede or supplant the headache. These so-called basilar migraines are exclusionary diagnoses and often require ruling out other causes of vasovagal or vestibular instability.

Some children experience a hemisensory phenomenon or hemiplegia that evolves over 15 or 20 minutes and subsequently subsides before the headache. Hemiplegic migraine tends to run in families (the calcium channel gene responsible for this disorder has recently been identified, see Chapter 10), and a positive family history for similar episodes helps confirm migraine is the correct diagnosis. Nonetheless, it is prudent to obtain magnetic resonance imaging (MRI) and magnetic resonance angiography studies in patients with episodic hemiplegia or hemisensory changes to be certain there is no structural reason for the events.

Migraines rarely awaken children. If they are present when a child first awakens, they generally worsen rather than improve as the child goes about his or her daily activities. This is in sharp contrast to headaches caused by increased intracranial pressure, which are worst on first awakening but often remit as a patient assumes an upright posture; this type also frequently awaken the patient.

The International Headache Society classification scheme for the clinical nosology of migraine has recently been modified to improve its applicability to migraine in children and adolescents. Table 9-1 gives the current iteration of this scheme, which is likely to evolve.

Hereditary and Genetic Aspects of Migraine

Migraine is a robustly familial phenomenon, so much so that any child with migraine who, on detailed and persistent questioning, does *not* have a positive family history of migraine or migraine equivalents should be referred for MRI of the head. Such children are at risk for having an arteriovenous malformation or other lesion that gives rise to symptomatic, rather than idiopathic, migraine. In obtaining a family history, it is not sufficient to ask if anyone in the family suffers from migraines. It is important to ask if anyone gets headaches periodically, if any of the women get headache associated with their menses, and if anyone gets cold food headache (sometimes called "brain freeze" or "ice cream headache"). A positive response to the first of these questions should trigger questioning as to the nature of these headaches. Many patients call their headaches "sinus headaches," "eyestrain headaches," or "stress headaches," when in fact there is no nasal drainage, fever, or cough, and the headaches are pulsatile, accompanied by nausea, and relieved by sleep.

The genetics of common and classical migraine are almost certainly quite complex, and both have been hypothesized to be polygenic conditions. Recently, however, the gene for familial hemiplegic migraine has been determined, raising hope that the more complex conditions will someday be found to be associated with specific, definable genetic mutations or associations.

Migraine Equivalents

In establishing the diagnosis of migraine in children, it is crucial to be cognizant of symptom complexes that share pathogenetic mechanisms or are genetically linked to migraine. This is so both because these symptoms may occur in the index patient and because these symptoms in family members may be important for the establishment of a positive family history of migraine-related phenomena. A detailed description of headache characteristics and symptoms should be obtained in every patient (See checklist in Table 9-2).

Several migraine equivalents occur primarily in childhood and serve as markers of familial tendency to migraine and not as inevitable harbingers of that particular child ever having more "conventional" migraine. By far and away the most common migraine equivalent in children and adults is motion sickness. Families should be asked specifically if anyone cannot read in the back seat of the car, rather than merely asking if anyone gets motion sick.

Benign paroxysmal torticollis (BPT) of infancy consists of tilting of the head to one side or the other, frequently for periods of 15 to 30 minutes without evidence of discomfort. Children with this symptom have normal head posture between episodes and a completely normal neurologic examination. The head tilt is not accompanied by skew deviation of the eyes or nystagmus and often is not rigid like a fixed torticollis of extrapyramidal or pyramidal origin. BPT remits generally by 1 year of age.

"Alice in Wonderland" syndrome is a much less common but readily identifiable migraine equivalent syndrome characterized by the sensation that objects are getting alternately closer and farther away, bigger and smaller. Each episode of this "oscillatory" phenomenon

TABLE 9-1. International Headache Society Revised Criteria for Migraine in Children

Pediatric Migraine without Aura	Pediatric Migraine with Aura (presumes idiopathic recurring disorder associated with headache lasting 1 to 48 hours)
A. At least 5 attacks fulfilling criteria B–D	A. At least 2 attacks fulfilling criterion B:
B. Headache attack lasting 1–48 h	B. At least 3 of the following characteristics: (1) One or more fully reversible aura symptom indicating focal cortical and/or brainstem dysfunction, (2) At least 1 aura developing gradually over ≥ 4 min or ≥ 2 aura symptoms occurring in succession, (3) No auras lasting > 60 min, (4) Headache following no more than 60 min after aura
C. Headache has at least 2 of the following characteristics: (1) Bilateral (frontal and/or temporal) or unilateral location, (2) Pulsatile quality, (3) Moderate to severe intensity, (4) Aggravation by routine physical activity	
D. During headache, at least 1 of the following occurs: (1) Nausea or vomiting, (2) Photophobia and phonophobia	

usually lasts between 10 and 20 minutes and is followed by complete return to normalcy without headache or other visual symptoms. Although an occasional patient with "Alice in Wonderland" syndrome will have prolonged or atypical episodes, prompting a work-up for partial complex seizures, most can be diagnosed as having a migraine equivalent syndrome on the basis of the phenomenology coupled with a positive family history for migraine and a normal neurologic examination.

Treatment of Migraine in Childhood and Adolescence

Migraine treatment is best aimed at restoration of a normal level of function. For some patients and families, this means rendering the patient virtually or absolutely pain-free. For some, it means ridding the patient of episodes that include vomiting as part of the clinical picture. For occasional patients and families, "treatment" simply means reassurance that the condition is neither dangerous nor inevitably lifelong or progressive. The key in migraine treatment is to tailor therapy to the needs and expectations of the patient and his or her family and to ensure that therapies used are at least as benign as the condition itself.

For children and adolescents whose migraines occur once weekly or less frequently, most physicians would recommend abortive therapy. In children under the age of 10 years, this most often means taking nonsteroidal anti-inflammatory agents or acetaminophen. For older children and adolescents, the triptans (eg, sumatriptan) are often the drug class of choice. For status migrainosus, abortive therapy often involves administration of parenteral therapy with dihydroergotamine, ketorolac, and metoclopramide or with valproic acid in the hospital or office.

When migraine occurs more frequently than once per week, symptomatic therapies can lead to rebound headache. For this reason, prophylactic therapy is recommended in this situation. For infants and toddlers with migraine or its equivalent, cyproheptadine is the most commonly recommended prophylactic agent. For older children younger than 8 years of age, most practitioners would recommend starting with propranolol (10 to 20 mg PO bid) or naproxen (10 mg/kg once daily with food); tricyclic antidepressants (slow escalation of dose to a target range of 1 to 2 mg/kg/d) would be a third choice. In children older than 8 years of age and adolescents, tricyclic antidepressants and anticonvulsants (particularly topiramate for overweight children or valproic acid for nonoverweight boys) are used most frequently. Concerns about appetite suppression and cognitive slowing induced by topiramate and weight gain and ovarian cystic changes induced by valproic acid have shaped the populations according to characteristics of children and adolescents with migraine for whom each is most frequently used.

Alternative therapies are increasingly used for migraine prophylaxis. These include administration of riboflavin, magnesium, or feverfew, individually or in combination; training in biofeedback or relaxation techniques; and performance of acupuncture, acupressure, or chiropractic therapies. However, the long-term effects of these non-pharmacologic therapies are not known, and, in rare instances, chiropractic manipulation has led to cervical root entrapment or arterial dissection.

TABLE 9-2. Headache Checklist

- Does the child have an aura?
- Is there a prodrome, such as change in mood?
- What is the tempo of the headache: sudden or slow in onset?
- Where does the head hurt?
- How severe is the pain?
- Are there any associated symptoms, such as photophobia, phonophobia, nausea, or vomiting?
- Is there pallor?
- Is there periorbital discoloration under the eyes?
- Can the caregiver tell that the child has a headache by their looks or changes in behavior?
- Is nausea present at onset?
- How long does it take for the headache to reach peak intensity?
- How long until the child vomits, and how often?
- Does exercise worsen the headache?
- What, if anything, makes the headache better?
- Are there any headache triggers, such as sleep deprivation, exercise,foods, stress, or school?
- Do headaches occur on the weekends?
- What medication has been used to treat, and at what dose?
- Was the treatment successful in any way, either now or previously?
- Does sleep help?
- What is the average duration of the headache?
- When was the last headache?
- Was there any significant head trauma prior to the onset of these headaches?
- Do headaches awaken the child from sleep in the early morning hours?
- Have you noted any change in your child's personality or school performance since the onset of the headaches?
- Are there any feelings of sadness or depression?
- Are there any visual changes prior to or during the headache?
- Is there any neurologic dysfunction during the headache?
- How disabling are the headaches?
- How much school has been missed in the last 6 months due to headaches?
- What has been done thus far as a work-up?
- Have you seen any other physicians for your headache? If yes, which specialty?
- Is there any family history of migraine?
- Is anyone in your family prone to migraine, even if they have not been diagnosed with a specific disorder?

Natural History of Migraine

Several studies have examined the natural history of migraine diagnosed in childhood. Three years after diagnosis, approximately 20% of children diagnosed with

migraine will be headache-free. Approximately 50% persist in having migraine and 30% convert to tension-type headache. Therapies must therefore take into account the high remission rate among children with migraine, requiring periodic test-withdrawal of prophylactic medication, and the need of many children for prophylactic medications that are safe and effective over the long-term.

Suggested Readings

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Practitioner and Patient Resources

American Headache Society (AHS)
http://ahsnet.org
AHS is a professional society of health care providers dedicated to the study and treatment of headache and face pain. The educational objectives of AHS are to continue to improve the knowledge, skills, and professional performance of physicians, psychologists, and other health professionals in the care of patients with head, neck, and orofacial pain. This information is intended primarily for health care professionals.

American Council for Headache Education (ACHE)
achehg@talley.com
http://achenet.org
ACHE's educational mission reaches out to health career policy makers, employers, and opinion leaders, as well as to headache patients and their families. ACHE's goals are to empower headache sufferers through education and to support them by educating their families, employers, and the public in general. This Web site contains wonderful sections on "kids and headache" and "prevention."

Migraine Awareness Group: A National Understanding for Migraineurs (MAGNUM)
http://www.migraines.org
MAGNUM's mission is to bring public awareness to the fact the migraine is a true biologic neurologic disease, using the electronic, print, and artistic mediums of expression, to assist migraine sufferers, their families, and coworkers, and to help improve the quality of life and lessen the burden of migraine disease and head-pain disorder worldwide.

CHAPTER 10

MIGRAINE VARIANTS AND MIMICS

IAN A. WILKINSON, FRACP

The International Headache Society Classification of Headache Disorders (ICHD), Second Edition, 2004 lists 19 different categories of migraine and probable migraine, with a range of clinical features indicating how heterogeneous migraine is, and by inference, how many variations on etiological mechanisms may exist, involving many different anatomical areas and pathways.

In the last decade, there have been many developments in understanding migraine pathophysiology. The belief that the clinical features of migraine can be explained solely by sequential vasoconstriction and vasodilatation of blood vessels has been challenged. Newer proposed mechanisms place more emphasis on the brainstem playing a complex role as a modulator of a range of inputs and outputs, with major involvement of the trigeminovascular system and with final impact on pain-producing structures of the cranium.

It is not appropriate to go into the detail of these proposed mechanisms, but many of the migraine variants and mimics discussed in this chapter can perhaps be interpreted more easily if we think of primary neurological mechanisms as being at the basis of etiology and clinical manifestations.

The conditions dealt with here have clinical features that are obviously quite different from "classical" or "common" migraine, and at first glance, some may seem to have little connection with the migraine process. However, when careful consideration is given to family history and the natural history of these conditions, with evolution into more recognized migraine types, the case for including them in the broader diagnostic category of migraine is justified.

The specific disorders dealt with here and their ICHD classifications, if allocated, are as follows:

- Familial hemiplegic migraine (1.2.4)
- Sporadic hemiplegic migraine (1.2.5)
- Alternating hemiplegia of childhood
- Basilar-type migraine (1.2.6)
- Childhood periodic syndromes that are commonly precursors of migraine (1.3) with subtypes
    - Cyclical vomiting (1.3.1)
    - Abdominal migraine (1.3.2)
    - Benign paroxysmal vertigo of childhood (BPV) (1.3.3)
    - Paroxysmal torticollis of infancy
    - Acute confusional migraine
    - Alice in Wonderland Syndrome
    - Ophthalmoplegic migraine (13.17)

They will be dealt with in the above order although this does not necessarily reflect the frequency with which they are seen in practice.

Hemiplegic Migraine (Familial and Sporadic)

This condition might better be termed migraine hemisyndromes as the clinical features include sensory changes, visual field losses, and even cognitive dysfunction. The common thread is that the signs and symptoms can be assumed to have origins in one side of the brain. Familial and Sporadic cases are equal in numbers and share clinical features. It is one migraine condition where there have been significant genetic advances, and it has been found that dominant inheritance is often seen.

The clinical features can be dramatic, and when a patient first presents, particularly if there is no family

history, parents and attending clinicians often fear the worst and much laboratory investigation may occur.

The ICHD requires motor weakness, which may be partial or complete, sometimes marching from face to arm and less often to the leg, over a period of 15 or more minutes. The march is slower than that seen with Jacksonian epilepsy. Frequently, there may also be sensory disturbance in a similar distribution, ranging from paresthesias to major sensory loss. There can be an associated visual hemifield loss, which may precede the above. Speech difficulties include dysarthria and sometimes an alarming dysphasia. Confusion and decreased consciousness may be present. During the attack, partial seizures can occur on the affected side. Acute psychosis has been described during episodes in some familial cases.

It is common for these hemi symptoms to be present for an hour or more before the development of headache, which may be contralateral to the somatic symptoms or generalized. Motor or sensory symptoms may persist, and if they outlast, the headache can indicate a more sinister process. There may be interictal cortical excitability demonstrated by magnetic stimulation in familial cases. Electroencephalograms have shown abnormal background rhythms over the contralateral hemisphere during attacks, and cerebral edema has been demonstrated on magnetic resonance imaging (MRI).

Onset can occur throughout childhood and into adulthood, usually after 10 years of age. In one large study, women were affected two and a half times more often than men in the familial group and four and a half times more often in the sporadic group. Although studies suggest up to 30% of all migraineurs may have hemiplegic features, only between 4 and 9% will fulfill more strict criteria.

There has been considerable investigation of the genetic basis of this condition. Among familial cases, approximately 55% have been shown to have defects in the CACNA1A gene on chromosome 19p13 with dysfunction of a voltage-gated calcium channel. Another defect in this large and complex gene has resulted in a very rare condition of "migraine coma," at times induced by head injury, with possible permanent sequelae or death.

Approximately 20% of familial cases are associated with mutations in the ATP1A2 gene on chromosome 1q23, which encodes the α 2 subunit of NaK-ATPase. There is also a report of a family with a mutation on chromosome 2q24 affecting a neuronal voltage-gated sodium channel.

The prognosis in the sporadic form is generally good, and often after a few attacks, the patient may remit or develop migraine with or without aura. Approximately 20% of patients with the CACNA1A mutation will develop a progressive cerebellar ataxia.

Alternating Hemiplegia of Childhood

This is a rare but serious and progressive disorder which was included in the first ICHD in 1988 under "Childhood periodic syndromes that may be precursors to or associated with migraine". It was removed from the 2004 ICHD in the belief that it is not a migraine disorder although recently some patients have been shown to have the ATP1A2 mutation reported in up to 20% of familial cases of hemiplegic migraine.

The clinical features are diverse but include distinct episodes of weakness at times associated with dystonia, athetosis, or chorea. Although classically in a hemiplegic pattern, there are cases with monoparesis, diparesis, or progression to quadriparesis. The tone during the attack varies from reduced to markedly increased. Respiratory irregularities, particularly hyperpnea, occur during the attacks, and in addition, there can be weakness of extraocular muscles and nystagmus, as well as difficulties with bulbar function. Seizures occur in as many as 50% of children.

Onset of the condition is in the first 18 months of age and the frequency of attacks is quite varied, with duration of each ranging from minutes to days. The clinical features remit during sleep but may recur within 20 minutes of awakening. Unfortunately, with recurrent attacks, there is a loss of intellectual function and progressive motor disability with residual dystonia, choreoathetosis, and ataxia.

There are reports of alternating hemiplegia of childhood (AHC) occurring in families, sometimes with apparent dominant transmission, and also in identical twins, but most cases are sporadic.

The etiology is unclear, and it is possible that the condition may be heterogeneous. The evidence for this being an epileptic disorder is poor, but there is some evidence to support channelopathies, mitochondrial cytopathies, or vascular disorders as causes. Although headaches can occur in association, it seems less likely that this is a migraine mimic or variant.

There is a separate condition of benign nocturnal alternating hemiplegia of childhood with a much more favorable outcome and lack of progressive deterioration.

Treatment of AHC has proven difficult. The calcium channel blocker flunarizine has been shown to modify the severity of attacks but does not alter their frequency or the outcome.

Basilar-Type Migraine

Previously known as basilar artery migraine and basilar migraine, this disorder was comprehensively described by Bickerstaff in 1961 when evidence pointed toward a primary vascular mechanism for migraine, but could be seen as consistent with a brain-stem neurological mechanism.

Clinical features include visual field defects, cranial nerve disorders, disturbances of co-ordination, impairment of sensory pathways, headache, nausea and vomiting, altered consciousness, epileptic seizures, and abnormalities on electroencephalogram (EEG).

Patients may have significant variation in the clinical features, and subclassifications have been created dependant upon the number of features present in an individual. The ICHD classification is quite rigid and may be difficult to use in children.

Visual disturbances are often the first symptoms and are usually in both visual fields, with negative effects such as darkening or loss of vision or positive features such as intermittent flashes and spots, but not usually sophisticated images. Double vision occurs as a result of involvement of the oculomotor or abducens nerves. Nystagmus and even internuclear ophthalmoplegia may be present. Dysarthria and dysphagia result from involvement of facial and bulbar nerves, and disturbances of the vestibulo-cochlear nerve can present with dizziness, vertigo, tinnitus, or hyperacusis. Ataxia and altered levels of consciousness may complicate the pattern, and bilateral paresthesias are described. EEGs have shown posterior slowing in attacks. Headache may develop during the aura or may be delayed or even absent and is commonly occipital.

In migraine populations, the proportion with basilar-type can range from 2.3 through to 23% depending upon how rigidly diagnostic criteria are applied. Many children with more typical migraines will have features such as dizziness or double vision.

The onset can be from early childhood through adolescence or into adult life. A family history of migraine is common, but it may not be of basilar type. There is a great variation in the frequency of individual attacks, and the pattern of headache often changes to more typical migraine over time.

The differential diagnosis includes vascular and other structural malformations in the posterior fossa and occipital epilepsy. A cranial MRI is justified. Treatment of attacks and prophylaxis is along conventional lines.

Childhood Periodic Syndromes That Are Commonly Precursors of Migraine

The second edition of the International Headache Society Classification in 2004 now includes three conditions that, although not having headache as a principal presenting symptom, are likely to lead on later to migraines.

The three conditions that have been accepted are
cyclical vomiting (IHS 1.3.1)
abdominal migraine (IHS 1.3.2)
BPV (IHS 1.3.3)

Included in this section is another entity, paroxysmal torticollis, for which there is good evidence of association with migraine headaches, but which is not yet included in the ICHD, and also a list of other conditions where an association has been suggested.

Cyclical Vomiting Syndrome

First described in the French literature 200 years ago, this manifests as recurrent attacks of unexplained pernicious vomiting without concurrent major headache features, but where the patient is likely to develop migraine headaches or where there is a familial history of migraine headaches.

In approximately 12% of children who present with recurrent vomiting, some other specific cause may be found. This includes mechanical obstructions from volvulus, obstructive bands, intussusception, and a range of metabolic disorders including Addison's disease, urea cycle disorders, and fatty acid oxidation defects. Although psychogenic causes are often suspected, this is not usually the case. Patients presenting with this condition are likely to be exposed to much radiological and other investigations.

There is a vomiting center in the lateral reticular formation of the medulla, linked to a chemo-receptor trigger zone in the area postrema. This complex receives afferents from the pharynx, gut, and higher centers as well as the vestibular system.

It sends efferents to the gut, abdominal wall, and sympathetic nervous system. Inputs into the vomiting center interact cumulatively until a critical emetic threshold is exceeded, and vomiting takes place.

There are animal studies that support cyclical vomiting as being a "gut-brain" disorder. In attacks, children with cyclical vomiting manifest a range of hormonal and biochemical disturbances and may have abnormal gut motility studies between attacks.

Attacks in a particular child are often stereotyped. Three quarters will have a trigger such as stress, infection, menses, exhaustion, or particular foodstuffs. In half, there may be a regular cycle of 2 to 4 weeks. Onset is usually at 2 to 7 years with a mean of 5.8 years although a similar condition has been described in adults with onset around 35 years. The frequency of children's attacks ranges from 1 to 70 per year, and the duration of each from 5 hours to several days with a mean of 41 hours. On average, the duration is 3.4 years, and children will often transition into, or after a gap, develop migraine headaches.

Recent literatures describe a condition of cyclical vomiting in association with maternally inherited mitochondrial disease, referred to as "Cyclic Vomiting Syndrome Plus". These children may have associated with developmental delay, poor growth, seizures, and elevated blood lactate. The onset of vomiting is usually earlier, before 1 year, and both

rearrangements of mitochondrial DNA and muscle biopsies showing features of mitochondrial disease have been reported. Although in all children with the cyclical vomiting syndrome (CVS) there is often maternal inheritance, this specific group is quite distinct and should be considered to have a separate condition.

In 1995, international agreement was reached about comprehensive diagnostic criteria for this syndrome. These can be summarized to include requirements that the attacks be discrete, with normal health in between and that there be no specific cause for the vomiting, the attacks be stereotyped and self limited, and that there are sometimes associated features including headache and abdominal pain, diarrhea, fever, and motion sickness.

These children are often much debilitated during attacks, requiring intravenous fluids and electrolyte correction. Many symptomatic reliefs have been offered during attacks, but there is little scientific evidence for benefit. Among these treatments are sumatriptan, ondansetron, lorazepam, aprepitant, as well as more traditional anti-emetics.

Many prophylactic medications have been tried but with little proof of effect. Some children will benefit from regular use of traditional anti-migraine medications such as propranolol, cyproheptadine, or flunarizine, but other drugs including amitriptyline, valproate, erythromycin, pyridoxine, and 5-hydroxytryptophan have been used.

One group of children with CVS was followed to a mean age of 17 years. Thirty-one percent were still experiencing vomiting attacks and forty-six percent had a current or previous history of migraine headaches compared to twelve percent of a control group ($p = .0128$). In another study, 75% developed migraine headaches by age 18 years and others have confirmed an increased personal or family history of migraine. Some patients progress sequentially from vomiting to abdominal migraine and then migraine headaches.

Abdominal Migraine

This disorder, first reported 80 years ago, features recurrent attacks of otherwise unexplained abdominal pain, without concurrent major headache, but where there is a familial association with migraine and in which the patient may subsequently develop migraine headaches as the principal feature. This is different from the common situation where a child with typical migraine headaches may experience abdominal pain during an attack.

There is a long list of differential diagnoses including structural lesions, such as bowel obstruction, obstructive uropathy; inflammatory conditions, such as pancreatitis, peptic ulceration, urinary tract infection; metabolic disorders including lactose intolerance, acute intermittent porphyria, as well as chronic constipation. Again, although frequently attributed to psychogenic disorders, this is so in only about 20% of cases.

Abdominal migraine is a common disorder affecting around 4% of one group of school children aged 5 to 15 years. The mean age of onset is around 7 years, with some evidence for peaks at 5 and 10 years. The frequency of attacks can range from 2 to 100 per year, with a mean of 14 and the duration from 1 to 72 hours with a mean of 17 hours. Essential criteria for diagnosis includes that the pain is severe enough to interfere with normal daily activities, is dull or sore in nature, is periumbilical or poorly localized, and it is associated with some of the features of anorexia, nausea, vomiting, pallor, or flushing. The attacks should last at least an hour, occur at least twice a year, and symptoms must resolve completely between attacks.

In the population study reported above, children with abdominal migraine had an increased risk of suffering migraine headache, whereas those children initially identified with migraine headaches had an increased risk of abdominal migraine. The prevalence of migraine headache in first-degree relatives of children with abdominal migraine was twice that in controls.

Treatment of the acute attack has included many analgesic and other medications, and recently, there have been trials of sumatriptan. A recent Cochrane Review of Recurrent Abdominal Pain in Children found that only pizotifen had established proof of benefit as prophylaxis. Many other drugs including flunarizine, cyproheptadine, propanolol, erythromycin, and phenobarbitone have been tried with anecdotal success.

In a school study, children were followed for a mean duration of 7 years to a mean age of 17 years. Thirty-nine percent still suffered recurrent abdominal pain and 70% had current (52%) or previous (18%) migraine headaches, compared to only 20% of the control group ($p < .001$).

The literature supports the observation that there is cross-over in population of patients with the separate conditions of CVS, abdominal migraine and migraine headaches, that is, being identified as having one of these conditions places the individual at increased risk of developing symptoms of the others.

BPV

This condition is one of the more dramatic of those affecting a child's nervous system, producing much diagnostic uncertainty. It involves recurrent unexplained attacks of sudden disturbance of balance sometimes associated with nystagmus, vomiting, sweating, and pallor. It is critical for this diagnosis that between attacks the patient returns to normal health and is normal to neurological examination. This is a different condition

from that of benign paroxysmal positional vertigo of adults.

In the attack, the child is often extremely distressed and alarmed and will want to be held or cuddled or may go to a wall or ground to seek stability. Onset is usually between 1 and 5 years of age, and the frequency of attacks can be as often as weekly although many children will suffer only a few attacks during the whole course. Each attack tends to be relatively brief, from minutes up to a few hours. Most children will remit by 5 years of age. One study observed that 7% of patients had a previous history of paroxysmal torticollis of infancy. Many children develop migraine headaches subsequently, including basilar type.

Vestibular tests and other laboratory investigations are not usually helpful although a negative structural study is reassuring. Infrequently, this condition can be mimicked by epilepsy. Vestibular neuronitis and more typical migraine headaches are associated with vertigo, but the attacks tend not to be so dramatic. In two separate populations of children seen in clinics for dizziness or vertigo, benign paroxysmal vertigo was the second most common diagnosis after migraine headaches.

Treatment with a range of anti-emetic, antitravel sickness, and other medications has been tried in many patients, but there is a lack of scientific evidence of benefit. Treatment of an acute attack is unlikely to be successful because of the usual brief duration of attacks and the difficulty in administering medication during the attacks.

Paroxysmal Torticollis of Infancy

This uncommon disorder is another which is most dramatic and alarming, and in which sinister alternative etiologies are frequently pursued. It produces recurrent episodes of marked tilting and twisting of the head, usually varying between sides in consecutive attacks. Each event may be preceded or associated with the infant being very distressed, with vomiting and pallor, or at other times appearing apathetic. When it occurs in older articulate children, they may describe disequilibrium. Children remain conscious throughout these episodes, which have duration from 10 minutes up to a few days or even a week.

When a child sleeps during attacks, the tilt or twist may be less striking, only to be exacerbated again upon awakening. Sometimes, the posturing may involve the whole spine and even the pelvis.

The differential diagnosis includes structural lesions of the posterior fossa and spinal cord or vertebrae, and also Sandifer's syndrome. Cranial MRI is a reasonable investigation during the infant's first presentation. Surface EMG studies have shown continuous discharges in attacks, consistent with this being a dystonic process, and muscle enzymes may be temporarily elevated. EEG and vestibular studies are usually noncontributory.

The majority have onset before 9 months of age, occasionally up to 30 months. The frequency of attacks varies widely from every 2 weeks to every few months, and some patients only have a small number of attacks before entering remission, which is usually by 2 years of age, with some reports up to 5 years. Some may later develop benign paroxysmal vertigo, other forms of the childhood periodic syndrome, or suffer migraine headaches. There is a family history of migraine headaches in up to 73% of these infants.

The etiology is not clear but points to a mechanism involving the brain stem and its connections, consistent with recent theories about migraine pathophysiology. The associations with headaches and migraine equivalents, as well as a frequent family history of migraine, make it likely to be one of the childhood periodic syndromes that are commonly precursors of migraine. Although most cases are not familial, this is so in up to 11%. There is a report of one family in which this condition was associated with familial hemiplegic migraine and a CACNA1A gene mutation, suggesting an underlying channelopathy in some cases of paroxysmal torticollis of infancy.

Other conditions in which there is a suggestion of association with migraine headaches.

- Epistaxis (one study showed more migraineurs had epistaxis than controls, $p = .002$, and epistaxis began 3 years before headaches)
- Motion sickness
- Migrating limb pain
- Back pain
- Neck-shoulder pain
- Episodic spontaneous hypothermia
- Fluctuating hearing loss

Acute Confusional Migraine

This condition can create enormous concern when a child presents for the first time, and the diagnosis may only be in retrospect. Five percent of childhood migraine attacks include some elements of confusion, but occasionally it is a dramatic feature without other signs or symptoms to suggest migraine. Children presenting with acute dysphasia, sometimes as part of a migraine attack, may also present as if confused. The attack may be precipitated by head trauma, often trivial, and is sometimes referred to as "footballer's migraine."

The child can be quite agitated and frightened, with acute amnesia. Diagnosis may be made more difficult as headache may be reported in only 50% of cases and can be mild. It often arises as the confusion subsides. The confusion can persist for up to 6 hours or so, rarely more than 24 hours. The whole attack may be terminated by sleep. Clinical features are shared with the state of transient global amnesia,

which is more commonly diagnosed in adults, and there may be overlap between these conditions.

Laboratory investigations are helpful only to exclude more sinister conditions such as intoxications, central nervous system infections, or intracranial bleeds.

EEGs in attacks yield a range of conflicting information sometimes, with slowing seen in dominant, nondominant, or both hemispheres, in anterior or posterior distribution. SPECT studies have shown decreased perfusion in the territory of the dominant posterior cerebral artery.

Similar to other types of complicated migraine, there may be only one or a few attacks of an acute confusional state before the patient proceeds onto more usual forms of migraine.

Treatment during the acute attack is not helpful, and prophylaxis may not be justified due to the infrequent nature of attacks.

Alice in Wonderland Syndrome

It is common for patients in a migraine attack to experience altered sensations and perceptions. Often these symptoms are unsophisticated, such as numbness, paresthesia, darkening or closing of vision or perhaps a little more sophisticated such as seeing flashing spots or jagged edges. Sometimes, the aberrations can be much complex with alterations to what are real and normal sensations, for example, distortion of the objects that are actually in view at the time (metamorphopsia). These can be very distressing for patients particularly when they occur, not infrequently, without a headache being present, although the experience may be engaging and pleasant for some patients. In one overall study of 100 children with any visual symptoms accompanying migraine headaches, 16 described distortions and hallucinations.

The literature often makes reference to these aberrations as the Alice in Wonderland Syndrome. Charles Lutwidge Dodgson, in his 1865 novel "Alice's Adventures in Wonderland", using the pseudonym Lewis Carroll, describes how Alice discovers a bottle marked "Drink me". After doing so she shrinks. Following this, she eats a piece of cake marked "Eat me" and then begins to grow abnormally large. Dodgson was a known migraineur who reported bilious headaches and had disturbances of vision including fortification spectra. It is speculated that he may also have suffered the sensations ascribed to Alice.

Although some definitions of the syndrome include not only disturbances of vision and body perception but also of speech and language, altered perception of time (including a sense of multiple consciousness) and dream-like or delirious states; in the majority of children, the disturbances particularly involve vision, body perception, sound volume, and speed of surrounding events.

Alterations of vision include objects appearing unrealistically small (micropsia) or large (macropsia), perhaps with a sense of zooming; distorted shapes (particularly upper body parts); sometimes, even inversions of images and the texture of objects being disrupted (eg, "ironed out"); and occasionally, a perception of mosaicism. Children may describe how real events taking place may be speeded up or slowed down or how actual sounds and speech are inappropriately loud or soft. The condition can occur at any age but usually appears in children. There is often a family or current personal history of other migraine types, and the condition, which is a variant of migraine with aura, may subsequently progress to more typical migraine headaches.

The differential diagnosis includes various partial epilepsies (including occipital), substance abuse, and various intoxications.

There have been reports of patients who developed this condition in association with EBV infections, before the infection and during the acute phase of the infection, sometimes with evidence of encephalitis. In some such patients, the syndrome has persisted for months. Other infecting agents that have been associated include Coxsackie B1 and Varicella viruses. The features may also occur in association with nonspecific fevers.

As with other migraine mimics and variants, previous vascular theories of etiology have proposed localized disturbances of blood flow in this condition, including the nondominant posterior parietal lobe. Laboratory studies have not been consistent. SPECT studies in patients with the condition in association with EBV infection have shown decreased perfusion near the visual tract and visual cortex, involving temporal areas. MRI and other structural studies of the brain have not contributed.

The symptoms may occur without headache or may precede the headache by hours or even days. Although many patients continue in life with more typical migraine headache, the specific features of the Alice in Wonderland Syndrome tend to remit by adulthood.

Ophthalmoplegic Migraine

This uncommon disorder has recently been moved in the 2nd Edition of the International Classification of Headache Disorders from the category of Migraine (1.3) to that of Cranial Neuralgias and Central Causes of Facial Pain (13.17). This reflects very much the recent information from MRI studies suggesting an inflammatory process.

The differential diagnosis (particularly in adults) includes a number of important conditions, including arterial aneurysms and Tolosa-Hunt Syndrome (idiopathic granulomatous inflammation of the cavernous sinus) both of which are rare in children. Ocular myasthenia can present with

some similar features but not usually with pain. There have been case reports of schwannomas involving the oculomotor nerve.

The attacks commence with unilateral pain in the orbit, periorbital or temporal areas, followed, sometimes days after the pain subsides, by ophthalmoplegia. The most common presentation involves the ipsilateral oculomotor nerve producing an enlarged nonreactive pupil, ptosis, or external ophthalmoplegia, or combinations of these. Lesions of the trochlear, abducens, or sensory trigeminal nerves are less common. The ophthalmoplegia may last days or weeks and occasionally may not remit completely.

Recurrent attacks are common, often on the same side. The literature includes patients with 14 or more attacks.

Classically, the condition has an early onset with one case report at 3 months of age following immunization and most before 12 years of age. There have, however, been cases with initial presentation throughout adult life. A family history of this condition or migraine is not common.

MRI in this condition has been most revealing. The most common finding has been thickening and enhancement of the cisternal portion of the oculomotor nerve, consistent with demyelination. Similar changes have been seen in the cisternal portion of the trochlear nerve. In a case involving the abducens nerve clinically, there was relevant enhancement in the lower pons. Sometimes, Serial MRIs over 2 to 4 years have shown persistent changes despite clinical resolution. Given the positive findings described and the need to exclude other more sinister conditions (although unusual in children), it is appropriate to perform MRI.

Therapeutically, there have been many reports where this condition, similar to Tolosa-Hunt Syndrome (some would argue the two are similar diseases), has responded well to steroids.

Conclusion

These conditions emphasize the huge diversity of the entity of migraine, demonstrating a range of neurological features in addition to headache, in some situations, clinical features that seem remote from the nervous system, and presentations in which headache is not a symptom at that time. Some of these conditions are difficult to reconcile with a vascular pathogenesis but may be more easily understood if we consider them to be neurologically generated, particularly involving the brain stem.

Further, it can be seen how the entity of migraine can evolve through life from one set of clinical features to others that are quite different but more typical of migraine headache.

Although there has long been recognition that migraine headaches are often inherited, there is now evidence that some forms of migraine have specific genetic markers. It is likely that such markers will become available for other types, and although genetic testing is largely a research tool at the moment, it may become more useful for diagnostic purposes. Furthermore, this genetic knowledge may lead to greater elucidation of etiological mechanisms and potentially better treatment strategies.

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Practitioner and Patient Resources

1. American Council for Headache Education (ACHE) http://www.achenet.org.
2. MAGNUM: Migraine Awareness Group: A National Understanding for Migraineurs http://www.migraines.org.

Chapter 11

Abortive Therapy for Migraine

Marcy Yonker, MD

Migraine occurs in 5 to 10% of the pediatric population. Migraine is a severely disabling condition that may cause significant suffering and loss of time from school and social activities for children and adolescents. Accurate diagnosis and early, targeted treatment of attacks may help to alleviate pain and disability.

Appropriate treatment of migraine in children, adolescents, and adults relies on accurate diagnosis of the condition, identification and elimination of triggers, and accurate history-taking regarding specific symptoms experienced by the patient, in order to individualize therapy. Diagnostic criteria for migraine in children and adolescents have been recently revised; however, further refinement is required (see Suggested Readings). Triggers frequently identified in children and adolescents include school stress, difficulties at home, sleep deprivation, poor diet, caffeine, heat, oral contraceptives, and specific odors or foods. Through simple history-taking, these instigating factors may be identified, eliminated, or addressed through nonpharmacologic means. Psychologic evaluation for mood and learning problems should always be initiated in those patients for whom there is concern for these issues. For most migraineurs, trigger avoidance alone may not be sufficient to eliminate all migraines, and pharmacologic therapy may still be required.

At present, most agents typically used by child neurologists to treat migraine in children do not have a pediatric indication from the United States Food and Drug Administration (FDA); however, many are used off-label by practitioners. Some open-label and double-blind studies are available in the literature (see Suggested Readings). At present, convincing evidence for the use of a specific abortive agent exists only for ibuprofen, acetaminophen, and sumatriptan, and zolmitriptan. Table 11-1 summarizes the different abortive agents, dosing, and precautions. After establishing a diagnosis of migraine in a child or adolescent, important issues to clarify to determine which agents may be considered include the following:

- Medical conditions that may be a contraindication to the use of specific preparations (see Chapter 16, "Current Pharmacotherapy for Pediatric Migraine")
- Specific symptoms experienced by the patient:
  - Aura and aura duration
  - Nausea and vomiting
  - Duration
- Prior medications tried
- Effectiveness of specific preparations for the parent's migraine

Important principles in acute migraine treatment for the physician and patient to consider include the following:

- *Early treatment.* Early treatment improves efficacy. Patients should be taught to identify migraine onset so medication can be taken immediately. Patients should be given documentation for proper school administration so migraines that begin in school can be treated as soon as possible. If necessary, teachers and school nurses should be educated that, at migraine onset, the patient may not appear acutely ill, but still should be excused from class for medication to prevent migraine progression. Parents should be instructed to carry medication with them when leaving the house in case a migraine develops while they are away from home.
- *Give patients options.* When recommendations are first made, patients should be given several agents to try so they may determine which is most effective for their migraines. Patients may experience a spectrum of migraines of differing severity and symptoms, which may respond to

different agents. For example, many patients may determine that more mild headaches respond to over-the-counter preparations, whereas headaches that are more severe at onset require prescription medications. Patients should be made aware that a specific abortive agent may not work for every attack, and that a new abortive agent needs to be tried two or three times before it can be deemed ineffective. Patients should understand that increasing the dosage of a specific agent may improve its efficacy and that underdosing may contribute to the development of rebound headaches. Rescue medication should always be prescribed in case of abortive failure. The patient's full understanding of the proper use of the prescribed medications, possible adverse effects, the timing of medication use, and the sequence in which medications may be tried will improve treatment outcome. Written instructions may help eliminate confusion.

- *Dealing with nausea and vomiting.* Patients who have significant nausea with migraines may require coadministration of or pretreatment with antinausea agents to ensure effective absorption of abortive agents. Patients who are unable to keep down oral abortives and antinausea agents should be offered rectal antiemetics or nasal or injectable abortives.
- *Avoid abortive overuse.* Patients and families should be counseled against frequent use (more than two to three times per week on a regular basis) of abortive agents, including over-the-counter products, because of the risk of developing chronic daily headache from analgesic overuse. Families should be advised to call under these circumstances so that preventive medication can be prescribed or adjusted.
- *Keeping track of headaches and treatment.* Practitioners should supply patients with headache calendars to

TABLE 11-1. Abortive Agents for Pediatric Migraine

Generic Name (Trade Name)	Dosage	Precautions	Advantages
NSAIDs			
Acetaminophen	15 mg/kg	Overuse syndrome	Availability, parent familiarity; liquid/rectal preparations
Ibuprofen	10 mg/kg	GI upset, overuse	Availability, parent familiarity; liquid/rectal preparations
Naproxen sodium	125–250 mg/dose	GI upset	Availability, parent familiarity; liquid/rectal preparations
Combination Preparations			
Excedrin	1–2 caps	Contains aspirin and caffeine	Availability, familiarity
Isometheptene/acetaminophen/ dichloralphenazone	1–2 caps	Sedation, need to swallow large pill	May induce sleep, good for rescue
Butalbital Preparations			
	1–2 caps	Contains caffeine and mild barbiturate—risk of dependency	May induce sleep, good for rescue
Antiemetics and Antinausea Agents			
Promethazine	0.5–1 mg/kg	Sedation	Available as liquid and suppository
Metoclopramide	0.1–0.15 mg/kg	Extrapyramidal effects	Available as liquid
Prochlorperazine	0.1 mg/kg	Extrapyramidal effects	Available as liquid and suppository
5HT 1B-1D Agonists (Triptans)*			
Almotriptan (Axert®)	6.25/12.5 mg	Slower onset of action	Longer duration
Eletriptan (Relpax®)	20/40 mg		Less expensive
Frovatriptan (Frova®)	2.5 mg	As above	Longest duration of action
Naratriptan (Amerge®)	1/2.5 mg	As above	
Rizatriptan (Maxalt®)	5/10 mg	Rapid onset of action	Shorter duration
- (Maxalt-MLT®)	5/10 mg	As above, orally disintegrating	Can cut 5 mg in half for younger children
Sumatriptan (Imitrex®)	25/50/100 mg	Slower onset of action	More pills/co-pay
- (Imitrex Nasal®)	5/20 mg	Rapid onset of action	Bad taste
- (Imitrex SC®)	6 mg	Fastest onset of action	Injection/increased side effects
Zolmitriptan (Zomig®)	2.5/5 mg	Slower onset	Longer duration
- (Zomig-ZMT®)	2.5/5 mg	As above	Orally disintegrating, can cut in half for small children
- (Zomig Nasal®)	5 mg	Rapid onset of action	Taste neutral
Ergot Preparations			
Nasal DHE (Migranal®)	1 squirt each nostril, repeat after 15 min	Rapid onset	Nausea, chest pain, cannot use within 24 hours of triptan

* Contraindications: hemiplegic migraine, basilar migraine, migraine with prolonged aura, risk for coronary artery disease, risk for cerebrovascular disease, uncontrolled hypertension. Side effects: chest pain, trismus, paresthesias, sedation, nausea, worse headache.

GI = gastrointestinal; NSAIDs = nonsteroidal antiinflammatory drugs.

keep track of headache frequency, symptomatology, and response to treatment. These calendars should be brought to office visits by the patients to accurately monitor treatment response. Disability tools such as PedMIDAS can also be used (see Suggested Readings).

Nonpharmacologic Treatment

Identification of triggers and trigger elimination may help a number of patients but does not usually eliminate migraines in a typical pediatric migraineur. Often, patients and families cannot identify any provoking factor. In patients whose migraines are triggered by anxiety-producing situations, or for whom the anxiety related to having a migraine worsens the problem, nonpharmacologic modalities such as relaxation training and biofeedback may serve as a primary or adjunctive treatment for acute headaches (see Suggested Readings).

Emergency Room and Inpatient Treatment

For patients with severe migraine unresponsive to outpatient management, emergency room evaluation should be considered. In the emergency department, intravenous medication could be administered in an attempt to "break" the migraine after careful examination to rule out other conditions that may masquerade as prolonged migraine, such as meningitis or subarachnoid hemorrhage. Many emergency department physicians feel comfortable with the use of narcotic agents, intravenous nonsteroidals, such as ketorolac, and antiemetics, such as metoclopramide, promethazine, and prochlorperazine, alone or in combination, and may have already tried these agents before consulting a child neurologist. Although there is a paucity of literature in children, other agents are used successfully in clinical practice. Intravenous dihydroergotamine, per Dr Steve Linder's protocol (see Suggested Readings), can be used in the emergency department and continued for repetitive dosing in those admitted as inpatients who are refractory to other treatments. If triptans have been used in the past 24 hours, dihydroergotamine mesylate would be contraindicated. In this case, intravenous sodium valproate (Depacon®) could be administered (15 to 20 mg/kg at a rate of 3 mg/kg/min). For those with a partial response to sodium valproate, some centers continue treatment of inpatients with 5 mg/kg/dose q8 until the headache is abolished. This also initiates a prophylactic agent for those in whom prophylaxis is indicated.

Conclusion

Effective abortive treatment of migraine in children and adolescents relies on an accurate diagnosis and the collaboration with the practitioner, family, patient, and school personnel to determine the most effective timely treatments for the spectrum of a child's migraine symptoms. Therapy should take into account a patient's specific migraine type, symptomatology, and other medical conditions. Families, patients, schools, and other care providers need to be taught proper principles of medication administration for any therapy to be effective. Although further clinical research needs to be done on the usage of specific agents in the pediatric and adolescent populations, open-label studies and clinical experience with off-label use indicate there are many options likely to be effective for the young migraineur.

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Practitioner and Patient Resources

PedsEducation.org
http://www.pedseducation.org/main/index.html
Free online symposium.

American Headache Society (AHS)
19 Mantua Road
Mt. Royal, NJ 08061
Phone: (856) 423-0043
http://ahsnet.org

AHS is a professional society of health care providers dedicated to the study and treatment of headache and face pain. AHS brings together physicians and other health care providers from various fields and specialties to share concepts and developments about headache and related conditions. The educational objectives of AHS are to continue to improve the knowledge, skills, and professional performance of physicians, psychologists, and other health professionals in the care of patients with head, neck, and orofacial pain.

American Council for Headache Education (ACHE)
http://www.achenet.org
ACHE is a nonprofit patient–health professional partnership dedicated to advancing the treatment and management of headache and to raising the public awareness of headache as a valid, biologically based illness. ACHE's Web site resources include information on children and headache, discussion forums, and support groups.

KidsHealth
http://www.kidshealth.org
Articles written for children and teens on migraine.

Chapter 12

Preventive Therapy for Pediatric Migraine

Donald W. Lewis, MD, FAAP, FAAN

Many therapeutic options exist for patients whose migraines occur with sufficient frequency and severity to produce functional impairment. Treatment options include abortive therapy, prophylactic agents, and behavioral interventions. In this chapter, we review pharmacologic and nonpharmacologic options for migraine prevention.

Once a diagnosis of migraine is established, a comprehensive treatment program may be implemented. Treatment options include biobehavioral interventions, acute or episodic measures, and daily prophylactic agents. The modalities used must be individually tailored to a particular patient's pattern of headaches and flexible enough to accommodate a changing headache frequency.

Establish the Headache Burden

Before instituting any treatment regimen, a patient's degree of disability or headache "burden" must be clearly understood. The headache burden represents an individual patient's headache frequency, duration, and intensity, their functional disability and pain tolerance, and the presence of comorbid conditions. The aggressiveness of medical management is dictated by assessment of the headache burden.

A teenager with one intense headache per month may require only an intermittent triptan agent. Another child with two disabling headaches per week during the school year may warrant daily prophylaxis during the academic year but be taken off medicines during the summer. An "overscheduled" adolescent suffering with daily headache who also is involved with multiple extracurricular activities and driven to maintain a perfect academic record may require lifestyle adjustments, counseling, stress management, and intermittent as well as daily prophylactic medications. Patients with comorbid anxiety disorders or affective disturbances may require psychological intervention coupled with appropriate and judicious use of anxiolytic or antidepressant medication.

Headache calendars help migraine patients document the frequency and severity of their headaches, associated symptoms, triggers, environmental factors, and life stressors. In addition, headache calendars can document seasonal variability and identify analgesic overuse.

Nonpharmacologic Measures

Before initiating daily drug therapy for migraine prevention, it is appropriate to review simple lifestyle issues that may play a part in reducing the headache burden. In addition, a growing number of patients are eager to engage in "alternative or complementary" measures to decrease their headache burden.

For these patients, biobehavioral programs take the forefront.[i] A useful patient-family education sheet outlining these following factors can be downloaded at: *www.achenet.org/kids/children.php.* are crucial.

Sleep

Either too little or too much sleep can be associated with increasing headache frequency, as can chaotic sleep patterns. "Sleep hygiene" is essential. Every effort must be

[i] Baumann RJ. Behavioral treatment of migraine in children and adolescents. Paediatric Drugs 2002;4:555–561.

made to regulate a child's sleep pattern so that he or she goes to bed and arises at about the same time each day. This is particularly an issue during adolescence, when late-night studying or weekend sleeping in until the afternoon may precipitate migraine attacks.

Stress

Adolescents report stress as the most common migraine trigger. Sources of stress during childhood and adolescence include marital or family conflict, peer rejection or harassment, depression, anxiety, sleep disturbances, academic problems, and physical, sexual, or emotional abuse. Chapter 14, "Psychosocial Aspects of Pediatric Headache" and 15, "Biofeedback for Childhood Migraine" describe stress management and biofeedback techniques for migraine prevention and treatment.

Exercise

Although no controlled studies have been conducted to determine whether exercise decreases migraine frequency in children with migraine, a review of patient education Web sites (eg, http://achenet.org) disclosed that regular exercise to limit migraine frequency is a common recommendation.

Diet

The influence of diet on migraine is controversial. Although food triggers can be identified in 10 to 30% of young migraine sufferers, compliance with an elimination diet is poor. Perhaps the most reasonable approach is to acknowledge there may be food triggers and provide families with a list of foods traditionally associated with precipitating migraine. Patients can then be advised to note in their headache calendars whether they can establish a link between their migraine attacks and any of the foods listed. If a consistent association can be found, then logic dictates that the offending food be avoided.

Wholesale elimination of the listed foods is not only unreasonable but also establishes fertile ground for conflicts at home when parents attempt to enforce the diet. One less controversial issue regarding diet is the need to avoid skipping meals. Either because of lack of time or concern about body image, children often omit breakfast or lunch. In the process of regulating lifestyle, it is necessary to encourage a regular eating schedule.

Caffeine

Coffee, tea, and caffeinated sodas warrant special mention. A link between caffeine and migraine has been established. Researchers in Israel studied children aged 6 to 18 years who had daily or near-daily headache and "excessive caffeine intake." Once all were weaned from caffeine, complete cessation of migraine was noted in 33 of the 36 patients evaluated.

Not only does caffeine itself seem to influence headache, it also may disrupt sleep or aggravate mood, both of which may exacerbate migraine. Every effort should be made to moderate caffeine use.

Analgesic Overuse

Well established as a provocative influence in adults, analgesic overuse is increasingly recognized as an issue in children and adolescents. Excessive use of prescription or nonprescription analgesics (eg, acetaminophen, aspirin, ibuprofen) has a demonstrated role in the transformation of episodic migraine to more frequent or even continuous migraine. A simple rule of thumb is to limit use of analgesics to no more than 2 to 3 times per week.

Vitamins and Herbal Treatment

Riboflavin

Although the role of riboflavin (vitamin B2) in children with migraine has not yet been studied, there is a controversial but growing body of literature regarding its use as a prophylactic agent in adult migraine. Doses of 400 mg/d have been shown to be superior to placebo in reducing migraine frequency. Adverse effects were minimal.

Magnesium

Magnesium (Mg) poses as an intriguing, yet incompletely understood, mineral that may influence migraine frequency via an effects on cortical hyper-excitability. Mg binds to the NMDA glutamate receptors which influence calcium metabolism. Low Mg levels reduce the effectiveness of the NMDA gating mechanism, opening calcium channels, increasing intracellular calcium, causing excitatory glutamate release resulting in neuronal cortical spreading depression (CSD) and migraine aura. There is a link between low Mg and aura, which may make magnesium more useful in patients with a history of aura.[ii, iii]

Decreased levels of both serum and intracellular magnesium have been reported in juvenile migraine.[iv] Clinical data to support a role for magnesium is, however, minimal. One randomized, double-blind, placebo-controlled, parallel group trial (n = 86) including

[ii] Welch KMA and Ramadan, NM. Mitochondria, magnesium and migraine. *J Neurol Sci* 1995;134:9–14.

[iii] Mauskop A, Altura BT, Cracco RQ, Altura BM. Deficiency in serum ionized magnesium but not total magnesium in patients with migraines. Possible role of ICa^{2+}/IMg^{2+}ratio. *Headache* 1993;33:135–138.

[iv] Lodi R, Montagna P, Soriani S, et al. Deficit of brain and skeletal muscle bioenergetics and low brain magnesium in juvenile migraine: An in-vivo 31P MR spectroscopy study. Pediatric Research 1997;42:866–871.

children ages 3–17 year with weekly moderate to severe migraine headaches who received either magnesium oxide (9 mg/kg/day) divided orally three times per day versus matching placebo for 4 months showed a statistically significant decrease in headache frequency in the magnesium oxide treated group ($p = 0.004$) vs. the placebo group ($p = 0.09$). Both groups, Mg and placebo, showed improvement in headache frequency and the slopes of the two response curves were not statistically significantly ($p = 0.88$). The authors acknowledged that their study did not "unequivocally determine whether oral magnesium oxide is or is not superior to placebo...the agent did lead to significant reduction in headache days."[v]

Coenzyme Q10 (Co-Q 10)

Another agent with mitochondrial influences is Coenzyme Q 10. Co-Q10 transfers electrons in the respiratory "electron transport" chain in the critical production of ATP.

Unpublished data from University of Cincinnati (Andrew Hershey, MD) found low levels of Co-Q10 in one third of 1478 patients with headache (mean age 13.3 ± 3.5, range 3 to 22 years). Patients with low CoQ10 were treated with 1–3 mg/kg/d of Co-Q10 raising their total Co-Q10 levels to 1.20 ± 0.59 umol/ml ($p < 0.0001$). Headache frequency improved from 17.0 ± 9.8 to 12.4 ± 10.9 and headache disability improved using the PedMIDAS scale from 44.6 ± 48.4 (moderate) to 21.8 ± 29.5 (mild).[vi] The investigators concluded that deficiency of Co-Q10 is very common in recurrent pediatric migraine headaches, but no recommendation can yet be extracted.

ω-3 Polyunsaturated Fatty Acids

Dietary supplementation with fish oils rich in very-long chain ω-3 polyunsaturated fatty acids may be beneficial in some patients.

Other Herbal Remedies

Feverfew and Saint-John's-worth have been recommended for preventing migraine in adults with frequent migraine. However, we are not aware of any published studies of these preparations in children with migraine.

Anecdotal reports indicate that gently rubbing lavender oil or other aromatic oils into the temporal regions during a migraine provides relief.

[v] Wang F, Van Den Eeden S, Ackerson L, et al. Oral magnesium oxide prophylaxis of frequent migrainous headache in children: a randomized, double-blind, placebo-controlled trial. Headache 2003;43:601–610.

[vi] Hershey A; personal communication.

Pharmacologic Measures

A diverse group of medications are used to prevent migraine. Their use, however, should be limited to patients whose headaches occur so frequently or are so severe they warrant daily treatment. Most studies have shown a minimum of three headaches per month is required to justify using a daily agent. A clear sense of functional disability must be established before committing to a course of daily medication.

The duration of treatment is controversial. In recognition of the cyclical nature of migraine, daily agents should be used for a finite period of time. Most practitioners recommend treatment through the school year. Treatment is then gradually eliminated during the summer vacation. In younger children, using a shorter course (eg, 6 to 8 weeks) followed by slow weaning is an option.

Controlled data regarding drug therapies for migraine prophylaxis in children are unfortunately lacking, although some findings are beginning to emerge. Use of many of these agents, listed in Table 12-1, is based upon anecdotal information or extrapolated adult experiences.[1–20]

Cyproheptadine (Periactin®)

This antihistamine with both antiserotonergic and calcium channel blocker activities has not been subjected to rigorous study but has been widely adopted for migraine prevention in young children.

A single uncontrolled, retrospective study of the use of preventative agents for children and adolescents within one child neurology practice found that headache frequency was reduced from a mean baseline of 8.4 headaches/month to 3.7 headaches per month.[vii] A positive response rate, defined as an overall favorable decrease in headache frequency and intensity plus acceptability of the agent, was noted in 83% ($n = 30$). Common side effects included sedation and increased appetite.

Dosing regimens vary widely, from single bedtime schedules to thrice-daily regimens. A dose of 2 to 4 mg orally at bedtime is a rational starting point, with the option to increase to a maximum of 12 to 16 mg/d tid. Cyproheptadine has two major limiting features: sedation and appetite stimulation. These effects make it less acceptable for use in adolescence but may prove advantageous in thin preadolescents.

β-Blockers

The nonselective -blocker propranolol has been studied in three randomized, double-blind studies, but the results have failed to consistently demonstrate its effectiveness.

[vii] Diamond S, Lewis D. Prophylactic treatment of pediatric migraine. Headache 2004:44;230–237.

TABLE 12-1. Pharmacological Options for the Prophylaxis of Childhood Migraine

Drug	Dose	Available	Toxicity
Cyproheptadine	0.25–1.5 mg/kg	Syrup 2 mg/tsp; Tablets 4 mg	Sedation, weight gain
Beta blockers			
Propranolol	2–4 mg/kg/day	10, 20, 40, 60, 80 mg; LA capsules 60, 80, 120, 160 mg	Hypotension, sleep disturbance, reduced stamina, depression
Metoprolol	2–6 mg/kg/day	Tablets 50, 100	Same
Nadolol	0.5–2.5 mg/kg/day	Tablets 20, 40, 80 mg	Same
Antidepressants			
Amitriptyline	10–25 mg qhs	Tablets 10, 25, 50 mg	Sedation
Nortriptyline	10–75 mg qhs	Tablets 10, 25, 50, 75 mg	Weight gain
Fluoxetine	10–40 mg qam	Capsules 10, 20 mg	Insomnia, anxiety, weight gain
Anticonvulsants			
Topiramate	1–10 mg/kg/day	Sprinkles 15, 25 mg; Tablets 25, 100, 200 mg	Sedation, paresthesias, weight loss, glaucoma, kidney stones
Valproic acid	20–40 mg/kg/day (usual 250 mg bid)	Syrup 250 mg/tsp; sprinkles 125 mg; Tablets 250, 500 mg	Weight gain, bruising, hair loss, hepatotoxicity, ovarian cysts
Gabapentin	10–40 mg/kg/day	Syrup 250 mg/tsp; tablets 600, 800 mg; capsules 100, 300, 400 mg	Fatigue, ataxia, tinnitus
Levetiracetam	125–250 mg bid	Tablets 250 mg	Sedation
Non-steroidal anti-inflammatory agents			
Naproxen sodium	250–500 mg bid	Tablets 220 (OTC), 250, 375, 500 mg	Gastric upset
Calcium channel blockers			
Verapamil	4–10 mg/kg/day tid	Tablets 40, 80, 120 mg; SR tablets 120, 180, 240 mg	Hypotension, nausea, AV block, weight gain

Nonetheless, practitioners often view β-blockers as first-line agents in childhood.

The selective β-blockers atenolol, metoprolol, and nadolol may be alternatives, although controlled data to suggest any relative advantage is lacking.

β-Blockers are contraindicated in the presence of reactive airway disease, diabetes mellitus, orthostatic hypotension, and certain cardiac disorders associated with bradyarrhythmias.

Special mention must be made about the use of β-blockers in two other populations: athletes and patients with affective disorders, particularly depression. Athletes may experience a lack of stamina and decreased performance. Children with comorbid affective disorders can experience deterioration of mood and even suicidal depression with propranolol.

The first study was an uncontrolled series of 192 children with headache, of whom 70% had migraine. The average age was 12 years and the patients had more than 3 headaches per month. They were treated in an open-label fashion with *amitriptyline* up to a dose of 1 mg/kg/day. Eighty four per cent reported an overall reduction in headache frequency and severity. Looking specifically at the migraine subset, there was a statistically significant reduction in headache frequency and severity, while the duration of headache attacks was unchanged when compared to initiation of the drug. Side effects were minimal.[viii]

The second study was a retrospective review of the use of preventative agents for children and adolescents within one child neurology practice, and found that amitriptyline produced a "positive response rate" of 89% (n = 73). Positive response rate was defined as an overall decrease in headache frequency and intensity plus acceptability of the agent. Headache frequency was reduced from a mean baseline of 11 to 4.1 headaches per month.[5] The principle side effect was mild sedation.

Antidepressants

Antidepressants have become a mainstay of migraine prophylaxis. Although there is ample data to support their efficacy for adults with migraine, information on their use in children with migraine is limited.

The tricyclic antidepressants amitriptyline, nortriptyline and desipramine are widely used, and selection is generally a matter of personal preference and experience. There are no comparative data.

Amitriptyline is started as a single dose at bedtime of 5 to 10 mg and slowly, every 4 to 6 weeks, titrated upward as necessary toward 25 to 50 mg. Sedation is the primary complication. Advantages of amitriptyline include low cost and its once-daily schedule, which improves compliance. Some practitioners recommend performing an electrocardiogram if higher doses are used.

[viii] Hershey AD, Powers SW, Bentti AL and deGrauw TJ. Effectiveness of amitriptyline in the prophylactic management of childhood headaches. Headache 2000;40:539–549.

Two other antidepressant agents, trazodone, a triazolopyridine derivative, and pizotifen, a serotonin-blocking agent (unavailable in the United States), have been studied in controlled fashion but have not shown benefit in controlled studies.

The selective serotonin reuptake inhibitors (SSRIs) are likewise receiving attention, although again, no controlled studies have been performed in children or adolescents. In children and adolescents with comorbid anxiety or depression, SSRIs may take center stage. A morning dose of 10 to 20 mg of fluoxetine (Prozac®) may be used in this population.

Curiously, the efficacy of antidepressants is reportedly unrelated to their designed antidepressant effect. However, as awareness of the common "comorbidity" of affective disorders and migraine expands, antidepressant properties may play an increasingly important role.

Anti-epileptic Drugs

Older texts have suggested a role for phenobarbital or phenytoin for migraine prevention. Those recommendations should be discarded given current awareness of the cognitive effects of those agents.

Topiramate, valproate, levetiracetam and gabapentin, may have expanding roles for pediatric migraine. In light of the current views of the pathophysiology of migraine with a primary neuronal initiation and propagation through "spreading depression", anti-convulsants pose an intriguing, though yet incompletely defined role.

Topiramate shows the most promise in migraine prevention and is establishing the role as first line therapy in adult migraine. Data and experience in pediatric migraine is growing. Adult trials reported using topiramate at doses of 200 mg/day (divided bid) and demonstrated a 50% reduction in headache frequency and severity (Class II).[ix]

One retrospective study assessing the efficacy of topiramate for pediatric headache included 75 patients of whom 41 were evaluable at a second follow-up visit. Daily doses of 1.4 (+/– 0.74) mg/kg/day were reached and headache frequency was reduced from 16.5 (+/– 10) headaches /month to 11.6 (+/– 10) headaches/month ($p < 0.001$). Mean headache severity, duration, and accompanying disability were also reduced. Side effects included cognitive changes (12.5%), weight loss (5.6%), and sensory symptoms (2.8%).[x] This population was predominantly children with chronic daily headache (≥ 15 headaches per month).

A recently published controlled trial of topiramate for pediatric migraine demonstrated excellent results. One hundred sixty-two children, ages 6–15, received topiramate (2 mg/kg) or placebo (2:1 ratio). Pretreatment headache frequency was 5.5 headaches per month in both groups. The patients in the treatment group experienced a reduction in their headache frequency by 2.6 headaches per month versus 2 per month in the placebo arm. A 75% reduction in headache frequency was experienced in 32% of the topiramate patients versus 14% in the placebo group. The topiramate group had a ≥ 50% reduction in headache severity and frequency.[xi]

Preliminary evidence suggests that topiramate may be an excellent choice for the "complicated migraine" subgroup, basilar-type and hemiplegic migraine, where the "neuro-protective" qualities may be most useful. A recent report of 14 children (ages 6–18 years) with basilar-type randomized to 25 mg/day versus 50 mg bid, found a reduction in both overall migraine frequency (4.7/month to 1.6/month) and a reduction in frequency of basilar migraine attacks from 2.84/month to 0.59/month. In addition, 86% of patients responded with a greater than 50% reduction in migraine frequency.[xii] This data needs to be validated in larger clinical trials.

The doses of topiramate used in migraine prevention are shown in Table 12-1. Generally, the drug is started at a very low dose, 15–25 mg, at bedtime and then, very slowly, at 2–4 week increments, raised toward 50 or 100 mg bid. Many patients will respond at the low starting doses and will not need to be adjusted upward further. Toxicities include parasthesias, mental slowing, and uncommonly, glaucoma and kidney stones.

An uncontrolled, retrospective study of *divalproex sodium* for migraine prophylaxis in children, ages 7–16 years (n = 42) at a dosing range of 15–45 mg/kg/day found 81% were successful in discontinuing all abortive (acute) medications. After 4 months of treatment, 75.8% of the patients reported a 50% reduction in headache frequency, 14.2% had a 75% reduction and 14.2% achieved a headache-free status. Side effects included GI upset, weight gain, somnolence, dizziness, and tremor, similar to those seen for patients with epilepsy.[xiii]

A second study using sodium valproate included children ages 9–17 years (n = 10) who were treated in an open label fashion with doses between 500–1000 mg. Both headache severity and frequency were reduced. Mean

[ix] Storey JR, Calder CS, Hart DE, Potter DL. Topiramate in migraine prevention: A double-blind, placebo-controlled study. Headache 2001;41:968–975.

[x] Hershey AD, Powers SW, Vockell AL, et al. Effectiveness of topiramate in the prevention of childhood headache. Headache 2002;42:810–818.

[xi] Winner P, Perarlman E, Linder S, et al. Topirmate for migraine prevention in children; A randomized, double-blind, placebo controlled trial. Headache 2005;45:1304–1312.

[xii] Lewis D, Paradiso E, Northam R, et al. A double-blind, dose comparison study of topiramate for prophylaxis of basilar type migraine in children. Ann Neurol 2006; 60(Suppl):S154.

[xiii] Caruso JM, Brown WD, Exil G, Gascon GG. The efficacy of divalproex sodium in the prophylactic treatment of children with migraine. Headache 2000;40:672–676.

severity at baseline using a visual analog scale was reduced from 6.8 to 0.7 at the end of treatment (p = 0). Mean headache attacks per month were reduced from 6/month to 0.7/month and mean duration of headache attack was reduced from 5.5 hours to 1.1 hours following treatment. Side effects included dizziness, drowsiness, and increased appetite, but no serious side effects were noted in this small study. The authors conclude that sodium valproate is safe and effective for migraine prophylaxis in children.[xiv]

The doses used for valproate, as shown in Table 12-1, are slightly less than those used for seizure control. A schedule of 10 mg/kg/day or 250 mg po *bid* or a single bedtime dose of the extended release preparation (250 mg, 500 mg), is a reasonable starting point. A similar monitoring schedule to that used for patients taking valproate for epilepsy applies with periodic measurements of blood counts, especially platelets, liver chemistries and amylase.

The acceptability of valproate in adolescent females warrants special mention in view of the appetite stimulation and risk of ovarian dysfunction (eg, polycystic ovary).

Levetiracetam (125–250 mg twice daily) was assessed in a retrospective fashion over a 4 month period (n = 19, mean age 12 years). The average frequency of headache attacks before treatment was 6.3/month and after treatment, fell to 1.7/month ($p < 0.0001$). A striking 52% of patients experienced "elimination" of migraine attacks during treatment. No side effects were reported in 82.4% but 10.5% discontinued treatment because of side effects including somnolence, dizziness, and irritability.[xv]

One retrospective study using gabapentin in children (n = 18) at doses of 15 mg/kg found that over 80% of patients experienced a more than 50% reduction in headache frequency and severity.[xvi] Perhaps the most desirable feature of gabapentin is the low incidence of side effects.

Clearly, more studies are needed in children to assess the efficacy and tolerability of anti-epileptic agents for migraine prevention.

Anti-hypertensive Agents

Two groups of anti-hypertensive agents, the beta-blockers and calcium channel blockers, have, in the past, served as first line agents for migraine prophylaxis. While still worthy of considerations in if the first line treatments fail, support for their role in pediatric migraine is declining.

The exception to this statement is ***flunarizine***. While unavailable in the USA, it has strong supportive (Class I) evidence for its efficacy and, ironically, is the one agent that the American Academy of Neurology has recommended in its most recent practice parameter. European and Canadian physicians may find flunarizine to be the drug of first choice for migraine prevention.

Calcium Channel Blockers

Calcium channel blockers are thought to exert their effects through selective inhibition of vasoactive substances on cerebrovascular smooth muscle.

Nimodipine (10–20 mg tid) was studied in a single controlled, crossover trial including children ages 7–18 years (n = 37), but the results were inconsistent between the two treatment phases. During the first treatment period, there was no difference between active and placebo. Headache frequency per month fell from 3.3 to 2.8 in the active group and from 3.0 to 2.5 in the placebo group (n = NS). During the second treatment phase, there was a significant reduction in headache frequency in the nimodipine group, but there was no effect on headache duration. Side effects were limited to mild abdominal discomfort in > 1%.[xvii]

Although unavailable in the U.S., *flunarizine*, is a calcium channel blocker that has been evaluated in several well controlled trials. Two double-blind, placebo-controlled trials using 5 mg bedtime doses of flunarizine (n = 105) and demonstrated significant reduction in headache frequency in both studies, one also showing decreased headache duration.[xviii, xix] In this first trial, the number of headaches was reduced from a baseline of 8.66 over 3 months to 2.95 attacks during treatment. Of patients taking flunarizine, 76% noted a ≥ 50% improvement, whereas only 19% taking placebo had ≥ 50% improvement. Another open-label trial of 13 patients showed decreased headache frequency.[xx] Other than sedation (9.5%) and weight gain (22.2%), side effects were minimal.

Calcium Channel Blockers

Calcium channel blockers are thought to exert their effects through selective inhibition of vasoactive substances on

[xiv] Serdaroglu G, Erhan E, Tekgul, et al. Sodium valproate prophylaxis in childhood migraine. Headache 2002;42:819–822.

[xv] Miller GS. Efficacy and safety of levetiracetam in pediatric migraine. Headache 2004;44:238–243.

[xvi] Belman AL, Milazo M, Savatic M. Gabapentin for Migraine Prophylaxis in Children. Annals of Neurology 2001;50(Suppl 1):S109.

[xvii] Battistella PA, Ruffilli R, Moro R, Fabiani M, Bertoli S, Antolini A, Zacchello F. A placebo-controlled crossover trial of nimodipine in pediatric migraine. Headache 1990;30:264–8.

[xviii] Sorge F, Marano E. Flunarizine v. placebo in childhood migraine. A double-blind study. Cephalalgia 1985;5 Suppl. 2:145–148.

[xix] Sorge F, DeSimone R, Marano E, et al. Flunarizine in prophylaxis of childhood migraine. A double-blind, placebo-controlled crossover study. Cephalalgia 1988;8:1–6.

[xx] Guidetti V, Moscato D, Ottaviano S, et al. Flunarizine and migraine in childhood an evaluation of endocrine function. Cephalalgia 1987;7:263–266.

cerebrovascular smooth muscle. Such agents are rarely prescribed in children with migraine.

Nonsteroidal Antiinflammatory Agents

Naproxen sodium was shown to be effective in adolescent migraine in one small series using a double-blind, placebo controlled crossover design. Sixty percent of the patients experienced a reduction in headache frequency and severity with naproxen 250 mg bid, whereas only 40% responded favorably to placebo. The rate-limiting effect is gastrointestinal discomfort. For that reason, it should not be used longer than 2 to 3 months.

Conclusion

Findings from uncontrolled studies suggest a beneficial effect with the antihistamine cyproheptadine, the antidepressant amitriptyline, the nonsteroidal antiinflammatory agent naproxen, and the anticonvulsant agents topiramate, valproic acid, gabapentin, and levetiracetam. There is conflicting controlled evidence regarding propranolol and trazodone. Clonidine, pizotifen, nimodipine, and timolol have not been shown to be more effective than placebo. The Cochrane Database review concludes with the statement that there is a "clear and urgent need" for methodologically sound randomized, controlled trials to evaluate the use of prophylactic drugs in pediatric migraine.

Summary

Various therapeutic options exist for patients whose migraines occur with sufficient frequency and severity to produce functional impairment. The first step is to establish the headache frequency and the degree to which migraines affect lifestyle and performance. The next step is to institute nonpharmacologic measures, such as regulation of sleep, diet, and activities, and to identify provocative influences.

Daily preventive drug therapies are warranted in about 20 to 30% of young migraine sufferers. The particular drug selected for an individual patient requires an appreciation of comorbidities, such as affective or anxiety disorders and coexistent medical conditions (eg, asthma or diabetes), and acceptability of potential toxicities, such as weight gain, sedation, or tremor. A diverse group of antidepressants, antihypertensives, and antiepileptic drugs is available and; they are detailed in Table 12-1.

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Practitioner and Patient Resources

National Headache Foundation
http://www.headaches.org
This resource has everything from the latest in headache causes and treatments to self-management tips to minimize the impact of headache on your life.

American Council for Headache Education (ACHE)
http://achenet.org
ACHE's educational mission reaches out to health career policymakers, employers, and opinion leaders, as well as to headache patients and their families. Its goals are to empower headache sufferers through education and to support them by educating their families, employers, and the public in general.

Headache Central™
http://www.headachecentral.net
This site has been sponsored by the Michigan Headache Treatment Network since 1996 as a public service to the millions who are headache sufferers. The purpose of this site is to educate people about the illness and how to get help. Many people are not aware that headache problems can be solved.

Chapter 13

Chronic Daily Headache

Kenneth J. Mack, MD, PhD

Chronic daily headache presents a significant morbidity for as many as 4% of teenagers. For practitioners, patients and their families, it is a challenging and frustrating entity to treat. This chapter outlines a practical approach to these patients.

Introduction

To receive a diagnosis of chronic daily headache, a patient must experience at least 15 headache days in 1 month for 3 consecutive months and show no sign of underlying organic pathology. Chronic daily headache represents 30 to 50% of the cases seen in headache specialty clinics. This headache disorder tends to affect teenagers and adults more so than preteens. It can occur in up to 4% of young women and up to 2% of young men, with similar prevalence rates seen in studies from China, the United States, and Greece. Often the affected patients have a personal past history of migraine or have a strong family history of migraine.

Silberstein and others have defined four categories of chronic daily headache based upon symptoms: (1) transformed or chronic migraine, (2) chronic tension-type headache, (3) new daily persistent headache, and (4) hemicrania continua.

Most teenage patients with chronic daily headache have a past history of episodic migraine. The transformation to chronic migraine may occur over weeks to months, or it may occur abruptly over a matter of hours. Approximately one-quarter of teenagers with chronic daily headache have no significant past headache history. In these patients, an infection such as mononucleosis or a minor head injury may incite a new daily persistent headache. A smaller number of patients have a history of tension-type headaches before developing chronic daily headache. Approximately 1% of patients present with hemicrania continua.

Headache Characteristics

Adolescents with a diagnosis of chronic migraine, new daily persistent headache, or chronic tension-type headache have more similarities in their presentation than differences. Therefore, patients with these types of chronic daily headache will be treated as a single entity in this chapter.

Most commonly, a patient with chronic daily headache will complain of at least two types of headaches: severe intermittent headaches that are migraine-like and continuous headache. They tend to be pancephalic or in the front of the head. The severe headaches are described as pancephalic or frontal, throbbing, severe, crushing, knife-like, or hatchet-like. They are often associated with nausea, photophobia, phonophobia, and osmophobia. For this more severe headache pain, sleep sometimes helps, but patients will still have persistent headache when they awaken. The frequency of these severe headaches varies with the individual. Severe episodes typically occur multiple times a week.

In addition to severe intermittent headaches, a patient with chronic daily headache often complains of a continuous headache that is present 24 hours a day, 7 days a week. This continuous headache may wax and wane in severity, often worsening in the morning or at the end of the school day. The characteristics of the all-the-time headache pain are similar to the episodes of severe headaches, only much less intense.

An occasional patient with chronic daily headache may have allodynia over all or part of their head. A small percentage of patients may have ice-pick headaches, which are severe, intermittent, stabbing headache pains that are often multifocal, occurring for seconds at a time and happening many times during the day.

Headache is not the only symptom in chronic daily headache. Chronic daily headache is really a multiple symptom complex. Frequent comorbid symptoms include dizziness, sleep disturbance, pain at other sites of the body

(including neck pain, back pain, and abdominal pain), fatigue, difficulty in concentration, decreased mood, and increased anxiety. It is important to recognize and treat these symptoms as well.

Diagnostic Considerations

One of the roles of a neurologist treating these patients is to separate out chronic daily headache, which is a primary headache syndrome, from other secondary causes of headache. The evaluation for secondary causes of headaches includes a thorough history and physical exam, and possibly a neuroimaging study, blood tests, and, in the occasional patient, lumbar puncture. In selected patients, tilt-table testing or sleep studies may also be of value.

Perhaps the most useful role of the neuroimaging study in chronic daily headache is to reassure the patient and family. Often, a magnetic resonance imaging (MRI) scan of the head is performed. However, in an overwhelming majority of chronic daily headache patients the MRI will be normal. Occasionally, white matter abnormalities, arachnoid cysts, or pineal cysts that are not related to the chronic daily headache will be seen in migraine patients. If a patient has had a significant history of head or neck trauma, particularly at the onset of the chronic daily headache, then magnetic resonance angiography of the neck should be considered to rule out a possible carotid dissection. When pseudotumor cerebri is a strong consideration, then magnetic resonance venography should also be considered because sinus thrombosis can cause elevated intracranial pressure.

The most informative serum studies are thyroid studies. As many as 4% of adult patients with chronic headache have thyroid abnormalities. A thyroid-stimulating hormone level is a useful screening test. If there is an encephalopathy in addition to the headache, then a thyroid receptor antibody test should also be done. Sedimentation rates could be used to look for signs of an arteritis, although this is a fairly nonspecific test and false positives and false negatives are common. If there are other clinical signs of lupus in addition to headache, then antinuclear antibody (ANA) levels in the blood should be measured. When headache is the only symptom, then measuring ANA levels can add more confusion rather than clarity to the situation. Recent studies have shown some patients with chronic pain have low levels of vitamin D.

Many patients will transition from a headache-free period or from episodic migraines to chronic migraines during an infection. Physicians should consider testing for Epstein-Barr virus, West Nile virus, and Lyme disease. Although for some of the viral etiologies there is no specific treatment, many parents appreciate knowing there was a physiologic underpinning for the transition to a chronic headache.

Idiopathic intracranial hypertension, formally called pseudotumor cerebri, is a constellation of symptoms and signs that include elevated intracranial pressure with a normal MRI scan. Often a patient will complain of headache, diplopia, tinnitus, and eye pain. On exam, the patient will have papilledema and sixth nerve palsies. Although the diagnosis is easy to make when all these signs and symptoms are present, there are rare patients who may have idiopathic intracranial hypertension without showing significant papilledema. It is often difficult to decide whether patients with chronic daily headache and no papilledema should have a lumbar puncture. A lumbar puncture is a relatively simple procedure, but it makes some children very anxious. However, in my experience, patients with chronic daily headache or migraine are almost universally prone to getting a post–lumbar puncture headache. So although a lumbar puncture is a valuable diagnostic tool, one should be cautious about its use, because one can make a patient with a headache significantly worse rather than better. In addition, while measuring the pressure, one should help the child relax as much as possible. Sometimes sedation is necessary, and the pressure should be measured with the child's legs extended and head relaxed.

Seventy percent of our chronic daily headache patients have symptoms of dizziness. The dizziness is associated with feeling weak and unsteady and with changes (ie, blurring or loss) in vision. The dizziness is often positional, and often patients complain of syncope or near syncope several minutes after standing. There is typically no vertigo. The dizziness is particularly prominent in the morning after they first arise. During an office exam, a difference in blood pressure or pulse rate between sitting and standing may be noted. The patient often experiences mild symptoms of dizziness when standing for several minutes. One may see a significant tachycardia with standing (postural orthostatic tachycardia syndrome) or a decrease in the systolic blood pressure (neurocardiogenic presyncope). A tilt-table test will help confirm these impressions, and these orthostatic symptoms can be appropriately addressed and treated.

Sleep is disrupted in at least two-thirds of the patients who have chronic daily headache. The most common sleep disturbance, in my experience, is a delayed onset in sleep, and often these individuals will not be able to fall asleep for 30 minutes to several hours after they go to bed. Patients who have had symptoms for a longer period of time sometimes will wake frequently during the night as well. Occasionally, a patient describes a history of pain in the legs and restless legs during the night. Patients may be referred to a formal sleep study, because lack of sleep may aggravate headache symptoms. Typically the headache syndrome will not resolve until sleep improves.

Other frequent comorbid symptoms include nonspecific abdominal pain, back pain, neck pain, and diffuse muscle and joint pain. Often no additional organic etiology is found to explain these additional pain symptoms. The longer the duration of the chronic daily headache syndrome, the more prominent these symptoms seem to become. In many patients, these additional areas of pain seem to be part of a much more diffuse pain syndrome.

Therapeutic Considerations

Chronic daily headache is difficult to control. There are often no immediate answers or easy answers to the treatment and resolution of the pain. Many of these patients have had a sudden onset to their daily headache, and some can even point to a specific day when they transition from a headache-free life to an all-the-time headache. Unfortunately, it typically takes weeks to months to achieve headache control. The cornerstones of therapy are education, preventive medications, and attention to routine.

It is difficult for many families to comprehend that the head pain can persist for such a long time, that there are no abnormalities showing up on diagnostic testing, and that the medications patients are prescribed are not immediately effective. It is not unusual for patients to see multiple doctors or neurologists because of this frustration. To limit frustration, it is useful to spend adequate time discussing chronic daily headache with the patient and family. The discussion should include describing what chronic daily headache is, how secondary causes of headache have been ruled out, the role of medications, when not to use pain relievers, the role of nonmedicinal approaches (eg, biofeedback or physical therapy), and what the family should expect in the near and long term.

Role of Medications

Preventive medications are traditionally used in episodic migraines to reduce the frequency of the migraine headaches. Occasionally, they may reduce the severity of the chronic daily headaches as well. The term "preventive" may be somewhat of a misnomer for use in chronic daily headache because the headache continues to be there all the time. However, in chronic daily headache, a reasonable therapeutic goal would be to make severe intermittent headaches less frequent, and to make all-the-time headache less intense. Multiple preventives are available for treating episodic migraine, including β-blockers, calcium channel agents, riboflavin, and magnesium. Most published reports describing the use of preventives in chronic migraine or chronic daily headache focus on medicines that work on the serotonergic system or antiepileptic drugs. Unfortunately, few prospective randomized, controlled studies have been conducted in children to guide us as to the most effective or safe medication to use in treating chronic daily headache.

Studies in adults and children suggest that tricyclic antidepressants, such as amitriptyline, are helpful in chronic daily headache. A key to success is to be willing to go up to higher therapeutic levels of these medications than are traditionally used in childhood migraine. Although it is not unusual to treat a child with, for instance, 25 to 50 mg of amitriptyline a day and see significant improvement in their episodic migraines, many patients with chronic daily headache require dosages of 100 mg a day or more. Consideration needs to be given to blood levels as well as electrocardiographic changes. Weight gain is a significant concern in teenage patients taking these medicines, and it affects some children more than others. Amitriptyline can also be helpful for sleep onset. Other tricyclics such as nortriptyline or protriptyline may cause less sedation.

Other serotonergic agents such as the selective serotonin reuptake inhibitors (SSRIs) have also been shown to be effective in some adults with chronic headache. Most of these data come from single-institution, nonblinded studies. The SSRIs seem to be less effective than tricyclics for pain control, although they are more helpful in children for their positive effects on mood. In select patients, the use of an SSRI can be very helpful. Fluoxetine is the only SSRI approved by the United States Food and Drug Administration (FDA) for use in children, and it is metabolized through the same pathway as the tricyclics, so care should be given when using fluoxetine (or paroxetine) with the tricyclics at the same time, because that may cause unexpectedly high levels of both.

Retrospective studies in adult patients have also shown that antiepileptic drugs are useful. Valproate can be easily given, and a starting dose of 500 mg of the extended-release form provides some older teenagers with dramatic results. In the older teenager, gabapentin can be started at 300 mg bid and increased by 300 mg every 5 to 7 days. One prospective randomized, controlled study showed a daily dose of 2,400 mg/d of gabapentin to be useful in treating chronic daily headache. Topiramate can also be an effective drug for some patients. It is unclear what the effective dose range for topiramate is in chronic daily headache. Topiramate may decrease appetite, but one needs to be especially aware that it clouds thinking in some patients.

Other approaches to headache prevention have also been studied. Tizanidine, an α_2-adrenergic agonist, has been shown to be effective prophylaxis for some adults with chronic daily headache. Injection of botulinum toxin has been shown in placebo-controlled studies to reduce the number of headache days and the intensity of headaches. The response rate to botulinum toxin approaches 50% in some studies.

Hemicrania continua, a rare headache syndrome, occurs in approximately 1% of chronic daily headache patients. It is a persistent, unilateral headache pain. The pain may be characterized by a stabbing sensation, and may be associated with autonomic changes. Daily doses of indomethacin may prevent the occurrence of this headache.

It is important to tell patients and their families what to expect from preventive therapy. Preventive therapy may improve headaches, but it will not eliminate them in the short term. After 1 month of effective therapy, one could reasonably expect to have less frequent severe headache episodes and a decrease in the intensity of the continuous headache. It is rare to see complete resolution of headaches after a short time. Once a trend toward improvement is seen, the medication dose is adjusted for optimal control of the headaches, and the patient is continued on the preventive agent for at least 6 months of good (although rarely complete) symptom control.

Controlling headache pain is a very difficult problem for patients. Analgesics that are typically effective for episodic migraine are not very effective for chronic migraine or chronic daily headaches. Most patients report that pain relievers are not effective for the all-the-time headache. It is reasonable to discourage patients from using analgesics to treat an all-the-time headache, because this may result in analgesic overuse and potentially cause analgesic rebound headache. In contrast, for the more severe intermittent headache episodes with migrainous qualities, analgesics should be considered, including indomethacin, triptans, or nonsteroidal antiinflammatory agents. Compounds that contain caffeine, barbiturates, or opiates or that have a high potential for rebound should be used sparingly or avoided. Patients typically find that when preventive medication starts working, pain analgesics also become more effective.

Some headache centers aggressively treat headache pain with intravenous protocols. Several approaches are used alone or in combination. Dihydroergotamine is effective for status migrainous and relieves chronic headache pain in some patients. Valproate also comes in an intravenous formulation and has been used to abort severe headache episodes. Finally, some patients respond to short-term use of oral steroids or intravenous steroids. These approaches seem to be most helpful for patients who have recent onset of daily headaches. Many patients feel better while hospitalized for these treatments but may revert back to their typical headache pattern after leaving the hospital. Hospitalization provides the patient an opportunity for education about headaches, introduction to biofeedback, and, in some cases, physical therapy.

Nonpharmacologic Approaches

Nonpharmacologic approaches to treating headache are also very important. Patients who experience chronic headache pain should consult with a psychologist to at least be introduced to the techniques of relaxation therapy and biofeedback. Anxiety is highly prevalent in migraine populations; some studies have shown that one-half of all adults with migraine have symptoms of anxiety. A psychologist, therefore, also is useful in addressing the issues of mood and anxiety. Many patients have also been ill for months to years and have become physically "deconditioned." Starting a reconditioning exercise program is very important. Patients should be encouraged to start slowly. We have our most severely affected patients do 10 minutes of aerobic exercise a day, increasing that amount by 10% a week. The key is to slowly but persistently increase activity level. A physical therapy consult can be useful in these situations.

Identifying specific trigger factors for chronic daily headache is difficult because the headache is daily, often "24/7." However, important environmental factors do play a role in these headaches. There is an interesting seasonal variability in the degree of chronic daily headache symptoms. Most patients fare better in the summer and frequently have a worsening of their headaches around the start of the school year, in September and October. In some patients, you can observe that the need for preventive medication is greatly reduced in summer but may need to be increased again in the fall. The reason for this variability is unknown, but may relate to such factors such as stress, loss of sleep, bright lights in the school, decreased exercise, decreased time for relaxation, and propensity of some teenagers to skip breakfast in order to make it to school on time.

Other Concerns

School absence is a significant problem. Once patients have been out of school for weeks, it is very difficult for them to return to a regular school schedule. Frequently patients will observe that after returning to 2 or 3 days of a full-day schedule, they come back home with a more severe headache. Some patients do best with gradual reintroduction to the school system. These patients have more success returning to school on an abbreviated schedule, often with one or two class periods that are around the lunch hour. It is difficult for these patients to start off with early morning classes, because many of them have sleep disturbances and lack a full night's sleep.

Sleep disturbance is very common and occurs in approximately two-thirds of patients. The most common complaint is a delay in onset of sleep. The typical child this age will need about 9½ hours of sleep. Often these patients put themselves to bed at 9 pm but may not fall asleep until midnight. Then they have to awaken at 6 am for school the next morning. If they have a 3-hour sleep deficit every day, it usually results in poor concentration and a propensity to get more severe headaches. One of the advantages of using

tricyclic antidepressants is the improvement in sleep. Melatonin may also be helpful in some patients to improve the onset of sleep. A smaller percentage of patients will present with symptoms of restless legs syndrome. They will have an itching or unusual feeling in their legs right before falling asleep, and then during sleep they will be restless and have frequent nocturnal awakenings. Treatment with gabapentin in these patients may help with sleep and the headaches. As patients improve with treatment, the sleep disturbance will often improve before the headaches do.

Patients will frequently complain of dizziness, particularly with standing. The dizziness may persist and worsen during times when they have severe headaches. One can document this in the office by doing supine and standing blood pressures. Typically, the longer the patient is standing, the more robust the documented change. A tilt-table test is another way to document some of these changes. Most patients show some improvement in dizziness by increasing their fluid and salt intake. A percentage of patients with a postural orthostatic tachycardia syndrome may respond positively to β-blockers. Midodrine or Florinef may be needed in other patients. Unfortunately, the tricyclics may worsen dizziness in some patients.

Mood problems and anxiety frequently coexist with chronic daily headache. Mood problems may precede or follow the onset of the headache. It is possible to resolve the problems with mood without affecting the headache, and in other patients it is possible to improve the headaches without improving the mood problem. Chronic daily headache should be considered a primary headache syndrome and not a mood disorder. Both the symptoms of headache and mood need to be addressed.

Follow-up should be scheduled on a routine basis until symptoms come under good control. It is not unusual to make frequent adjustments in management, and it may take months before matching up the right preventive medication or the right therapeutic approach with the individual patient. It is very difficult to work with these patients over the phone. Although the parents can report a score for severity over the phone, it is harder for them to describe the patients' affect, mood, function, and appearance. These target symptoms are just as valuable treatment indicators as their pain scale. In my own practice, I require patients to see me monthly until pain symptoms show a trend toward improvement.

Outcome

No prospective natural history studies have evaluated the outcome of chronic daily headache in children. In adults, chronic daily headache may last months to years. One study indicated the average adult has symptoms for approximately 4 years. The average duration in childhood is unknown, but it is not unusual to see children who have chronic daily headaches persisting for 2 years or more. It is hoped that with successful identification of this syndrome and aggressive pharmacologic and nonpharmacologic management the average duration of chronic daily headache in children could be considerably less.

Patients should be aware these symptoms wax and wane throughout the year. The vast majority of patients do better in the summer, when they tend to sleep more, experience less stress, and have more physical activity in their daily lives. Unfortunately, it is not unusual for many symptoms to recur in September and October, once school is again in session. If patients are aware of this trend and view this as a natural part of the history of chronic daily headache, they will be better prepared to respond.

In my experience with teenagers with chronic migraine, when they do get better, typically their severe migraine episodes become less frequent, and their all-the time headaches start to break up. They gradually experience the onset of headache-free days. When these young people do show significant improvement, often they will return to their premorbid state, which in essence is to become an episodic migraine patient.

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Practitioner and Patient Resources

American Headache Society (AHS)
http://www.ahsnet.org
AHS is a professional society of health care providers dedicated to the study and treatment of headache and face pain. AHS brings together physicians and other health providers from various fields and specialties to share concepts and developments about headache and related conditions. The educational objectives of AHS are to continue to improve the knowledge, skills, and professional performance of physicians, psychologists, and other health professionals in the care of patients with head, neck, and orofacial pain.

International Headache Society (IHS)
http://www.i-h-s.org
This site is open to everyone with an interest in headache. Its aims are to (1) promote IHS's objectives and activities, (2) inform users about relevant forthcoming events, and (3) report on the latest research from key meetings.

American Council for Headache Education (ACHE)
http://www.achenet.org
ACHE is a nonprofit patient–health professional partnership dedicated to advancing the treatment and management of headache and to raising the public awareness of headache as a valid, biologically based illness. ACHE's Web site resources include information on kids and headache, discussion forums, and support groups.

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MayoClinic.Com
http://www.mayoclinic.com
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Chapter 14

Psychosocial Aspects of Pediatric Headache

Jack Gladstein, MD

Because most people get headaches at some point in their life, what distinguishes those who go on with their lives from those who become "headache patients"? In this chapter we briefly review diagnosis, discuss antecedents of headache, and describe the consequences of headache for children. Martin's Model will help us understand the complex interplay of these factors. We then offer an approach to headache treatment from a psychosocial perspective.

Diagnosis

Rothner's Model separates all headaches into four patterns:

1. Acute headache does not recur; a virus or other intercurrent illness usually causes it.
2. Acute recurrent headache can be severe or mild; it goes away but recurs; migraine is a severe version of acute recurrent headache, with accompanying autonomic signs, such as nausea, vomiting, phonophobia, or photophobia; tension-type headache is also acute and recurrent but is not noted for autonomic signs; some call it mild migraine.
3. Chronic progressive headache builds over days to weeks. Brain tumors or benign intracranial hypertension (pseudotumor cerebri) present with this pattern.
4. Chronic nonprogressive headache is also termed chronic daily headache. In childhood, patterns include chronic migraine, where a patient's migrainous symptoms increase in frequency over time. There is a daily headache with few migrainous features, and an occasional migraine with full-blown autonomic symptoms. In chronic tension-type headache, there is daily pain but no autonomic symptoms. In new persistent daily headache, there is no history of any transformation, but a daily headache develops with or without migrainous features. Whether the headache is migraine, tension-type, or chronic daily, the name is not that important. Once secondary headache has been ruled out, the diagnosis is primary headache.

Proper treatment requires proper diagnosis to rule out tumors and the like, but then the art of medicine is in the approach to treatment. Understanding a child and his or her environment will help the practitioner assess disability and steer treatment in the right direction.

Antecedents of Headache

Risk factors for bad headache include the child's general milieu, his or her parents, and intrinsic biological factors. School is a big part of a child's life. Anecdotally, my "no show rate" is high during the summer, when school is out; many patients see me in September. School can increase anxiety and there are heavy social pressures, as some children take on too many after-school activities. A child with undiagnosed learning disabilities may experience even more stress and therefore suffer more headaches. Similarly, if a child is being bullied or picked on, this may manifest in headaches.

A child's headache pain may reflect what is happening at home. Genetic factors play a strong part in migraine. More than 90% of children with migraine have a parent with a history of headache. Second, pain modeling may take place if a child sees a parent's response to stress is translated into pain, and this pain leads to secondary gain. Similarly, a child's pain may reflect a mother or father's depression or anxiety. On another level, how a family reacts to a child's headache may reinforce having the next headache.

Intrinsic factors may put a child at higher risk for recurrent debilitation from headaches. Children with migraine

have a higher frequency of depression and anxiety compared with control subjects. After puberty, gender plays a role. With the rapid drop in estrogen that accompanies the days before menses, teenage girls get more migraines than do boys. A migraine personality has been described, where patients tend to be perfectionistic, internalize stress, and are more sensitive, cautious, and restrained.

Consequences of Pain

In an article in the *Journal of Pediatric Nursing*, Rhee not only discusses the risk factors for debilitation from headache but also beautifully describes the consequences in those afflicted with recurrent headache. She divides consequences into physical and behavioral, social functioning and psychological functioning. Patients with recurrent headache can develop other pains, including recurrent abdominal pain and chest pain. They may develop behavioral difficulties, including hyperactivity and acting out. Sleep disturbance can either be an antecedent or a consequence of headache as well. Social competency can be measured in terms of days of school missed, inability to participate in after-school activities, loss of friendships, and isolation. For the preteen and adolescent, inability to grow up and be independent can be a consequence of headache or other chronic illness. The combination of school absence and the inability to concentrate is a setup for school failure, which may then exacerbate headache. Children and adolescents with recurrent headache are at risk for emotional difficulties. Depression, anxiety, and poor self-esteem often are a result of unchecked headache. Andrasik found chronicity, intensity, and frequency of headaches to be related to higher levels of psychological dysfunction.

Martin's Conceptual Framework

Martin sought to answer how all these pieces fit together to understand the phenotypic presentation of headache. He divides the antecedents of headache into *onset*, *immediate*, and *predisposing* factors. He divides consequences of headache into *immediate reactions* and *long-term effects*. Both the antecedents and consequences influence how a child responds during a headache.

Predisposing factors include family history, gender, and personality type. These alone will not necessarily cause a headache. Onset factors are the events that may precipitate a headache. These include stress at school or in the home, hunger, bright light, change of sleep pattern. Immediate factors relate to the condition the patient is in at the time the onset factor occurs. If a child is depressed or anxious at the time of the precipitating onset factor, headache may be worse. Alternatively, if the patient is doing great, the same precipitant may not cause headache. The relationships of these antecedents influence the phenotypic headache, but so do the consequences. How the child and family copes and whether there are behavioral problems or psychosocial dysfunction are some of the immediate reactions that may affect future headache. Long-term effects related to quality of life and to cognitive and social development also affect phenotypic headache. Using Martin's model, we can understand that intervention in any of these vital areas may positively affect outcome of subsequent headache. Identifying where things have gone wrong helps pinpoint interventions.

Clinical Implications

For the busy practitioner, how can Martin's model help? First and foremost, make the proper diagnosis. Then, if the diagnosis is migraine, use migraine-specific medication to lessen pain. If pain lessens and headaches are eliminated, negative psychosocial consequences may be avoided.

However, it is useful to get a handle on the degree of disability, independent of diagnosis. Two patients may have a migraine three times a month. One patient does well, goes to school, and maintains good family and school functioning. The other patient does not cope well. She is out of school for 5 days per month, her family has become dysfunctional, and her grades drop from As to Cs. These two patients need two completely different approaches. Screens for depression and disability are available and can be used before seeing a patient. This may highlight the presence of depression and or disability. Esposito performed a cross-sectional study of children presenting to his headache clinic with Chronic Daily Headache. He found that 27% of patients endorsed depression, 20% endorsed anxiety, and 31% had lower quality of life scores, so these screens will have high yield in clinical practice. Another take-away message is to ask about exposure to violence. Martin's model was tested in a study examining the role of anxiety in an urban middle school setting. White and Farrell found that 40% of those studied had weekly headaches. This population of urban students exhibited high levels of anxiety, and witnessed a lot of community and family violence. The authors were able to show that pain leads to anxiety, which may lead to increased pain at follow up. When identifying stressors, asking about violence exposure should be routine, especially in the inner city. Using Rothner's model, diagnosis is very easy, so one can focus on identifying both the antecedents and consequences present in Martin's model. For patients who are identified as being debilitated or suffering from a lot of headaches, interventions at various points of Martin's model make sense. Referral to a therapist either at a headache center or someone with an interest in chronic pain in childhood would be indicated.

Once referred, the practitioner may seek to foster healthy coping skills through cognitive restructuring and behavior modification. These methods all enhance youngsters' sense of control and give them a heightened sense of empowerment. Relaxation and biofeedback give children the ability to regain bodily control and take away feelings of helplessness. Assertiveness training helps when children have poor peer or parental relationships. Again, it is a take-control approach. In cognitive coping training, children are taught to overcome unpleasant thoughts during headache episodes using simple problem-solving techniques. In an evidenced-based review of psycho-educational interventions for children with chronic disease, Barlow and Ellard showed that there is evidence of effectiveness for interventions that incorporate self-efficacy, self-management of disease, family functioning, psychosocial well-being, reduced isolation, social competence, knowledge and hope. Further, they were able to show that such interventions improved headache pain, lung function, days of absenteeism, and visits to the ED for asthma, fatigue in patients with Chronic Fatigue Syndrome, and metabolic control in patients with diabetes.

Focusing on how a parent responds to the headache may help avoid reinforcement of headache behaviors. Treating a depressed or anxious youngster with medication also may go a long way in getting the youngster back into school and functioning at a high level again. In essence, treat the youngster with headache, not just the headache itself.

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Practitioner and Patient Resources

American Headache Society (AHS)
http://ahsnet.org
AHS is a professional society of health care providers dedicated to the study and treatment of headache and face pain. The educational objectives of AHS are to continue to improve the knowledge, skills, and professional performance of physicians, psychologists, and other health professionals in the care of patients with head, neck, and orofacial pain. This information is intended primarily for health care professionals.

American Council for Headache Education (ACHE)
achehg@talley.com
http://achenet.org
ACHE's educational mission reaches out to health career policymakers, employers, opinion leaders, as well as to headache patients and their families. ACHE's goals are to empower headache sufferers through education and to support them by educating their families, employers, and the public in general. This Web site contains wonderful sections on "kids and headache" and "prevention."

Migraine Awareness Group: A National Understanding for Migraineurs (MAGNUM)
http://www.migraines.org
MAGNUM's mission is to bring public awareness to the fact the migraine is a true biologic neurologic disease, using the electronic, print, and artistic mediums of expression, to assist migraine sufferers, their families, and coworkers, and to help improve the quality of life and lessen the burden of migraine disease and head-pain disorder worldwide.

Chapter 15

Biofeedback for Childhood Migraine

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Biobehavioral treatments are very useful for children who experience headaches. Indeed, behavioral treatments are central components of all aspects of care for children and adolescents with headaches. In this chapter, we review lifestyle habits, pharmacologic adherence, biofeedback-assisted relaxation training (BART), and the role of disability and quality-of-life assessments as outcome measures.

Changing and maintaining healthy lifestyle habits is a uniform focus within the Headache Center of the Cincinnati Children's Hospital. These lifestyle habits include regular sleep patterns, regular exercise, regular mealtimes, and increased intake of green vegetables and noncaffeinated liquids each day. All children receive these guidelines and, over the course of treatment, are assisted in making these changes and maintaining them as lifelong habits. Specific recommendations are as follows:

- *Regular sleep.* Recommendations call for 8 to 10 hours of sleep each night and scheduling a similar bedtime and wake-up time each day. For this lifestyle habit to be maintained, some flexibility as to weekend sleep and wake-up times is incorporated into the recommendations. One common area of discussion pertains to wake-up time on Sunday mornings, with the goal that the child or adolescent is up at a time that makes going to sleep at the regular bedtime on Sunday night easy for them.
- *Regular exercise.* Children and adolescents are asked to be generally active and to exercise at least three times a week for 30 minutes to the point of perspiring and exertion. Activities and exercises the children find enjoyable and feasible during different seasons of the year and in their home and school environments are discussed as part of the treatment planning process. Having fun with exercise is emphasized.
- *Regular mealtimes and increased intake of green vegetables.* Children and adolescents are encouraged to eat three meals at regular time intervals during the day and often to include one snack period after school. A variety of green vegetables and fruits are discussed with the children, and they are encouraged to increase their intake of those foods they already enjoy and to consider trying some foods they might not have sampled before. Food avoidance is not usually recommended.
- *Adequate hydration.* Increased liquid intake of noncaffeinated beverages is a strong recommendation of our biobehavioral care program. Children and adolescents are encouraged to drink at least 2 L of liquids per day and to strive to intake 3 L of liquids per day during the summer and times of heavy exertion, such as sports activities. These liquids can include water, juice, milk, and sports drinks. In the note that is given to the school about children's headache care, we write that they can carry a water or sports drink bottle with them throughout the day to meet the lifestyle goal of increased liquid intake.

This package of biobehavioral treatments is standard for all children seen in our headache center. During the

course of treatment, we help children make these changes and focus on maintaining them as lifelong headache prevention and treatment strategies.

Pharmacologic Adherence

Biobehavioral care is also central to approaches to abortive treatment for migraine in children. The act of taking the right medication in the right dose at the right time is a behavioral proposition. The child's role in recognizing the initial onset of a migraine and telling a parent, teacher, or other adult is emphasized. This "catch pain early" strategy is central to the success of abortive pharmacologic treatment. In addition, the child's ability to name the abortive medication and the appropriate dose is key to taking an active role in treating the migraine in various settings (eg, home, school, during sports, at a friend's house). Children and adolescents also are encouraged to drink 20 to 32 ounces of sports drink along with their medication at the onset of the migraine. The child and family are given a letter for the school indicating the exact name and dosage of their abortive medication and stating that the prescription includes the intake of sports drink with the medication.

Similarly, the act of taking prophylactic medication is a behavioral proposition. The preventive role of prophylactic medications is emphasized to children and adolescents. This is done so they can appreciate the difference between an abortive medication strategy and a preventive medication strategy. Developmentally and behaviorally, this concept is notable for children and adolescents. Specifically, abortive medication is taken at the moment of onset of pain, whereas preventive medication is taken every day regardless of whether the child feels ill.

Maintaining regular daily adherence to preventive medication is viewed as another central component of biobehavioral care for child and adolescent migraine. Clarifying with children and adolescents the different roles of preventive and abortive medications and rehearsing with them the reasons for taking two different types of medications for their migraines is very beneficial to the long-term effectiveness of a headache treatment program. Finally, with regard to prophylactic medication, children and adolescents are informed early in their treatment that by implementing positive lifestyle habits and active abortive treatment approaches, it is likely they will not need to maintain long-term prescriptions of preventive medications. In our headache center, we find that preventive medications generally are not needed for more than 6 to 12 months for children diagnosed with migraine.

Biofeedback-Assisted Relaxation Training

Biobehavioral treatment also includes training children to use active coping skills. These coping skills include not only the aforementioned positive lifestyle habits and adherence to preventive and abortive medication regimens, but also biofeedback-assisted relaxation training (BART). Relaxation training usually involves one or more of the following techniques: progressive muscle relaxation, diaphragmatic or deep breathing, and guided imagery.

Progressive muscle relaxation training involves alternate tensing and relaxing of various muscle groups throughout the body. Its goal is to teach the child the contrast between tension and relaxation via systematic physical manipulation. Diaphragmatic or deep breathing involves systematic inhalation and exhalation. Again, the child learns the relationship between tension and relaxation by attention to breathing, which produces somatic changes in a systematic fashion. Guided imagery relies on a cognitive means of producing a state of relaxation. In this procedure, the child visualizes a pleasant scene or favored activity, such as playing in the woods or taking a ride on a favorite amusement park attraction, to achieve a state of relaxation.

Relaxation training is used most often with children 7 years of age or older. However, with developmentally appropriate adjustments to the training procedures, relaxation training procedures, especially those emphasizing imagery, have been used successfully with preschool-age children and intellectually challenged children. In practice, because of the cognitive, attentional, social, and emotional demands of the treatment, the use of standard relaxation training protocols is best suited for older children. Children need to be able to understand the rationale of using relaxation to combat feeling such severe pain. They also must be able to concentrate on their bodily sensations for an extended time and have the social and emotional maturity to learn how to both manage stress and sustain the practice necessary to acquire and maintain relaxation. It is quite rare for a child to experience problematic effects from learning relaxation. One exception involves a child becoming emotionally upset because of the novelty of the sensation of relaxation. This sensation might be especially problematic for a child who has experienced a number of traumatic events that are "relived" in a state of relaxation.

Biofeedback is most often used as an adjunct to relaxation training to address migraine. Instrumentation is used to monitor the physiologic effects of relaxation and/or to facilitate the learning of relaxation skills by providing visual and/or audio feedback about actual changes in otherwise invisible bodily processes. When described in this manner, it

is evident that biofeedback itself is not a treatment modality. Rather, biofeedback instrumentation is used to enhance self-control and relaxation training. Therefore, in our biobehavioral approach to care, this technique is referred to as BART.

In typical biofeedback for children and adolescents with headaches, two parameters considered correlates of physiologic arousal are the most commonly assessed. The first is electromyographic (EMG) activity, that is, electrical discharge in the muscle fibers, which is a correlate of skeletal muscle tension. The second parameter is peripheral skin temperature monitoring. Skin temperature is a correlate of vasomotor mechanisms. Feedback is usually given via a visual display. A line graph is a typical display, and displays for children also can be gamelike, with graphics and audio feedback. Biofeedback instrumentation is used in the relaxation treatment process to accomplish three goals: (1) to make the child aware of physical responses, (2) to teach control of these responses, and (3) to transfer or generalize these skills to use in everyday life. Given that improvement in headache symptoms sometimes correlate better to enhancement of self-control and self-efficacy than to actual changes in physiology, these psychological variables may play an especially potent role.

In our headache center, children are introduced to the biofeedback equipment and given the rationale for its use. They are then asked to relax on their own as they normally would while their body's response is monitored. Then the children are taught deep breathing skills and their physiologic responses are subsequently measured. Next, the children are taught progressive muscle relaxation. EMG activity and peripheral temperature are monitored afterward. Third, they are instructed in guided imagery using an individualized approach. Finally, an audiotape of a relaxation procedure combining breathing, muscle relaxation, and imagery exercises is made. The children's response to this complete package of relaxation exercises has been documented in a recent report (see Powers and colleagues, 2001).

Children and adolescents who receive this treatment often exhibit a decrease in muscle tension and an increase in peripheral body temperature after this initial BART session. Such body changes are indications of a relaxation response, and the increase in peripheral body temperature has been associated with the prevention of headaches. We found that children were able to show this response not only at initial training, but also 6 months later when they returned for a follow-up visit. We recently have begun implementing BART on our inpatient pediatric medical/surgical floors using portable biofeedback equipment which is easy to transport and operate. We have found that in the inpatient setting, where children typically do not have much control over their environment, schedule, or interactions with people, biofeedback is often particularly welcomed, with children expressing not only improvement in their physical symptoms but also a return of a sense of control.

Children who receive BART are encouraged to practice with their relaxation tape three to five nights per week before bedtime for the first 2 weeks. Thereafter, they are encouraged to practice either with the tape or on their own three nights per week and at the onset of a migraine.

The relaxation tape is usually between 5 and 10 minutes long. Children and adolescents often find these skills fun and useful. After a couple weeks of practice with the tape, most children find they can do this on their own and change their imagery as needed to keep the process from becoming monotonous. Children and adolescents also are encouraged to use relaxation skills any time they are experiencing stressors or challenges in their day-to-day lives.

Headache Disability and Quality-of-Life Assessments as Outcome Measures

A logical extension of incorporating a biobehavioral approach to the care of children and adolescents with headache is the addition of headache disability and quality-of-life assessments to the traditional outcomes of headache intensity, duration, and frequency. We use a headache disability measure specifically designed for use in pediatrics, the PedMIDAS, and a general quality-of-life measure that is applicable for children age 2 to 18 years, the Pediatric Quality of Life Inventory Version 4.0 (PedsQL). The reliability, validity, and utility of these measures have been demonstrated, and they can be efficiently incorporated into day-to-day clinical care. The measures are complementary, showing a correlation of 0.34, and both add unique information to the determination of the outcome of intervention. Assessments in our headache center occur at initial evaluation and regularly throughout treatment. Results are communicated to the children and their families, as well as described in correspondence with other health care providers, such as the child's pediatrician. Notably, we discuss with children and adolescents that our ultimate goal for their headache care is to achieve a level of disability in the little to none category and a level of quality of life that is comparable with normative values for healthy children. Measurement of these critical outcomes is a key aspect of biobehavioral care.

Summary

In conclusion, biobehavioral treatment is a central feature of the care provided to children and adolescents with headache. Learning new behaviors and using them appropriately is a key aspect in the prevention and immediate

treatment of headaches. From changing poor health habits and maintaining healthy lifestyle habits to recognizing pain at the onset and appropriately using abortive medications to maintaining positive adherence with prophylactic medications, children and adolescents with headaches are asked to behave in ways that optimize their control over their headaches. In addition, coping skills training that includes biofeedback-assisted relaxation skills is an efficacious and enjoyable adjunctive treatment for children and adolescents who experience headache disorders. These biobehavioral treatment approaches and the assessment of disability and quality-of-life outcomes can be included in the interdisciplinary and comprehensive care of children seen for headaches. Treatment programs for childhood headache could profit from incorporating this biobehavioral approach to care.

Suggested Readings

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Practitioner and Patient Resources

Clinical Trials

http://www.centerwatch.com/patient/studies/cat440.html

A Web site that lists ongoing clinical trials for treatment of migraine in children. Listings are by state, study site, and study title.

*Association for Applied Psychophysiology and Biofeedback (AAPB)*10200 W 44th Avenue, Suite 304
Wheat Ridge, CO 80033-2840

http://www.aapb.org

AAPB's mission is to advance the development, dissemination, and use of knowledge about applied psychophysiology and biofeedback to improve health and quality of life through research.

CHAPTER 16

CURRENT PHARMACOTHERAPY FOR PEDIATRIC MIGRAINE

BERNARD L. MARIA, MD, MBA

Headache is the third most common cause of school absenteeism. In pediatric and child neurology practices, headache and migraine consistently rank at the top of the most common neurologic complaints and conditions. However, many children suffer in silence or miss days of school because modern therapies have not been used to control their migraine. It is important for practitioners to intensify their efforts to recognize childhood migraine and treat it more aggressively with ibuprofen or selected antimigraine agents, such as sumatriptan.

Although more than 50% of adult migraineurs seek medical attention for headache, only one in 10 of the estimated 7% of school-age children with migraine has received a diagnosis of migraine. The problem of not recognizing migraine in children is probably multifactorial:
(1) a remarkably high number of caregivers deny their own migraine but when queried give a strong history of "sick headaches," consisting of severe, recurrent headaches that meet all diagnostic criteria for migraine;
(2) in those parents diagnosed with migraine, a remarkably high number deny the presence of similar headaches in their children, though they exhibit similar symptoms;
(3) school personnel and nurses rarely elicit migraine-specific histories (eg, visual aura, bifrontal pulsatile headache, photophobia, phonophobia, nausea) or ask about specific clinical signs (eg, pallor, vomiting); and
(4) many primary-care physicians seem unaware that symptoms and signs of pediatric migraine differ in character and severity from those in adult patients. Because the headache in childhood migraine is of short duration, more often bifrontal, less often associated with nausea *and* vomiting, and less often associated with photophobia *and* phonophobia, children with migraine are regularly misdiagnosed with tension headache or sinus headache even when a strong family history for migraine is apparent.

In addition to the problems of early recognition and proper diagnosis, primary-care gatekeepers who completed medical school more than 10 years ago have had relatively limited exposure to new selective agents for abortive therapy and updated information on proper use of preventive agents. In other words, it is often caregivers who must "ask their doctor about Imitrex®," rather than the other way around. Although practitioners have readily adopted modern pharmacotherapy practices for managing attention-deficit hyperactivity disorder (ADHD) and epilepsy in children, they have only sparingly prescribed selective antimigraine therapies (eg, triptans) for childhood migraine. Although some family physicians have successfully prescribed selective antimigraine drugs for their adult patients, they have been very reluctant to using similar selective drugs in children from the same families with migraine. As a result, many children are suffering in silence and missing school days unnecessarily; by the time such children are seen by neurologists, the headaches have increased in frequency and severity and frequently have transformed themselves into chronic daily headache. Although much less data have been generated on safety and efficacy of new antimigraine drugs in children, we believe the high benefit-risk ratio warrants therapeutic trials in children suffering from migraine who have variable and often ineffective responses to simple analgesics

(eg, ibuprofen). This is especially true when noting that the pain of migraine is but one aspect of the disability and that behavioral changes and academic performance suffer during and after a migraine.

Pharmacologic Abortive Therapy for Pediatric Migraine

Pharmacologic abortive therapy for pediatric migraine is summarized in Table 16-1. In child neurology practice, it is rare that a child meeting diagnostic criteria for migraine has not already been treated with acetaminophen or ibuprofen (10 mg/kg) for episodic headache. Typically, these simple steps have been inadequate as abortive therapy. If headaches are relatively infrequent (1 per month) but moderately severe, 15 mg/kg per dose of ibuprofen in combination with sumatriptan (Imitrex®) is recommended. Most children tolerate tablet and nasal spray forms very well. Occasionally, pressure sensations in the jaw or chest limit the repeated use of sumatriptan; however, many such patients tolerate zolmitriptan (Zomig®) and rizatriptan (Maxalt®) very well. For children and teenagers with poor tolerance for triptans (or when thirdparty payors refuse reimbursement because of age), isometheptene (Midrin®) is an option.

In teenagers seen in the emergency department or hospitalized for severe intractable migraine, rehydration and administration of 10 mg intravenous (IV) metoclopramide hydrochloride in combination with 0.5 to 1.0 mg IV dihydroergotamine (D.H.E.-45®) is recommended. If necessary, the D.H.E.-45® is repeated in 1 hour. A response to D.H.E.-45® is an indication of future responses to Migranal® nasal spray. However, dihydroergotamine should not be used within 24 hours of sumatriptan and propranolol (used as preventive therapy; see below) because it may potentiate the vasoconstrictive action of ergotamine. In children ages 2 to 12 years with severe intractable migraine, or in patients receiving propranolol preventive therapy (D.H.E.-45 relative contraindication), rehydration and administration of prochlorperazine (Compazine®) 2.5 mg by slow IV injection is recommended. If the headache persists, use of dexamethasone (2 to 4 mg IV), diazepam (5 to 10 mg IV), or ketorolac tromethamine (0.5 mg/kg IV, maximum 15 mg) should be considered.

One of the most interesting observations made in using triptans in children with migraine is what powerful effect they have on both the headache and the overall migraine event. Before the advent of triptans, children were frequently challenged by the "washed-out" period that followed the pain, a time when their academic performance was noticeably affected. In addition, and for unexplained reasons, children taking triptans seem to have fewer headaches. That may be because of the psychological aspects of migraine; confidence in the efficacy of one's therapy (ie, triptan) may reduce headache frequency. However, behavioral research to support or refute this hypothesis is lacking. Nevertheless, because of the efficacy of triptans, consideration should be given to staging therapy with selective abortive agents before beginning daily preventive therapy, even if headaches occur at least 2 to 3 times per month.

Pharmacologic Preventive Therapy for Pediatric Migraine

Pharmacologic preventive therapy for pediatric migraine is summarized in Table 16-2. Effective abortive therapy can reduce headache burden, but if moderately severe headaches recur two to three times per month despite best efforts at implementing nonpharmacologic measures (sleep hygiene, stress reduction, exercise, caffeine reduction, regular meals, elimination of triggers), then preventive therapy should be offered. Although antihistamines such as cyproheptadine (Periactin®) reduce migraine headache frequency, duration, and severity, their use should be restricted to thin preadolescents because the drug stimulates appetite; cyproheptadine is also sedating. Propranolol and topiramate (topamax®) are preventive drugs of choice for childhood migraine. Interestingly, the combination approach of propranolol and cyproheptadine can be highly effective (supported by one clinical trial). However, most children do not require combination preventive therapy. Consideration should be given to prescribing propranolol, 1–2 mg/kg/d, and slowly escalating (dosing adjustments every 2 to 3 weeks) to 3 mg/kg/d, as tolerated. In children, the most common limitation to using propranolol is current reactive airway disease. There is no evidence that metoprolol or nadolol are safer or more effective than propranolol in the treatment of childhood migraine. Since topiramate is often effective as once a day therapy, it has become my first choice agent in most children with frequent migraine. In adolescents, migraine is frequently accompanied by depressive or anxiety symptoms that are aggravated by propranolol. In such cases, my first-line preventive therapy is nortriptyline (Pamelor®). Although there are no comparative data between various tricyclic antidepressants in childhood migraine, nortriptyline is somewhat less sedating than amitriptyline. Nortriptyline is started as a single bedtime dose of 10 to 25 mg and then increased every 1 to 2 weeks to effect. Sedation is the primary dose-limiting side effect, and it takes 2 to 3 weeks for patients to adjust to the drug. Blood levels are used sporadically to evaluate adherence or to make decisions on how to proceed when headaches are recurring. I have rarely prescribed carbamazepine, valproate, levetiracetam, gabapentin or calcium channel blockers as first-line therapy in typical childhood migraine, but valproate (as well as topiramate) has received Food and Drug Administration

TABLE 16-1. Migraine Abortive Pharmacotherapy

Generic Name	Trade Name	Web Site	Dosage Forms	Usual Doses	Mechanisms of Action
Almotriptan	Axert®	http://www.axert.com	Tablet: 6.25 mg, 12.5 mg	Adult dose is 6.25–12.5 mg PO at onset of headache, may repeat in 2 h to a maximum of 2 tablets in 24 h; maximum 4 treatments per month	5HT-1B/1D/1F subtype serotonin receptor agonist
Dihydroergotamine	D.H.E.-45®	http://www.migranal.com	1 mg/mL ampoules	Adult dose is 1 mg IM or SQ; may repeat twice at hourly intervals (maximum 3 mg/attack)	5HT-1D subtype serotonin receptor agonist
	Migranal®	http://www.migranal.com	4 mg/mL nasal spray	Adult nasal dose is 1 spray into each nostril after blowing nose, may repeat in 15 min, maximum 2 doses (4 sprays each) per week	
Eletriptan	Relpax®	http://www.pfizer.com/download/uspi_relpax.pdf	Tablet: 20 mg, 40 mg	Adult dose is 20–40 mg PO at onset of headache, may repeat in 2 h to maximum of 80 mg	5HT-1B/1D/1F subtype serotonin receptor agonist
Frovatriptan	Frova®	http://www.elan.com/products/frova/default.asp	Tablet: 2.5 mg	Adult dose is 2.5–5 mg PO at onset of headache, may repeat in 2 h to maximum of 7.5 mg	5HT-1D subtype serotonin receptor agonist
Ibuprofen	Motrin®, Advil®, and others		Suspension: 20 mg/mL, 40 mg/mL; OTC tablets: 200 mg; OTC gel capsules: 100 mg, 200 mg; Rx tablets: 400 mg, 600 mg, 800 mg	Adult dose is 200–400 mg PO, pediatric dose is 10 mg/kg	Antiinflammatory
Isometheptene, dichloralphenazone, acetaminophen	Midrin®		Isometheptene 65 mg and dichloralphenazone 100 mg acetaminophen 325 mg per capsule	Adult dose is 2 capsules at the onset of headache, may repeat 1 capsule each hour until headache relieved or 5 capsules maximum in 24 h (do not exceed 75 mg/kg of acetaminophen)	Isometheptene is a weak vasoconstrictor, dichloralphenazone is a sedative, acetaminophen is an analgesic
Naratriptan	Amerge®	http://us.gsk.com/products/assets/us_amerge.pdf	Tablet: 1 mg, 2.5 mg	1–2.5 mg PO at onset of headache, can be repeated in 4 h (maximum of 5 mg/24 h)	5-HT-1B/1D subtype serotonin receptor agonist
Prochlorperazine	Compazine®	http://us.gsk.com/products/assets/us_compazine.pdf	5 mg/mL injection	Adult dose is 10 mg IV q8h, pediatric dose is 0.15 mg/kg/dose (maximum 10 mg)	Central dopamine antagonist
Rizatriptan	Maxalt®, Maxalt-MLT®	http://www.merck.com/product/usa/pi_circulars/m/maxalt/maxalt-pi.pdf	Tablet: 5 mg, 10 mg; Orally disintegrating tablets: 5 mg, 10 mg	Adult dose is 5–10 mg PO at onset of headache, may repeat in 2 h to maximum of 30 mg/d. Note: patients on propranolol should use the 5 mg tablets to a maximum of 15 mg/d	5-HT-1B/1D subtype serotonin receptor agonist
Sumatriptan	Imitrex®	http://us.gsk.com/products/assets/us_imitrex_tablets.pdf; http://us.gsk.com/products/assets/us_imitrex_nasal_spray.pdf	Autoinjector: 6 mg/mL; Tablets: 25 mg, 50 mg; Nasal spray/6 devices per box: 5 mg, 20 mg	Adult parenteral dose is 6 mg SQ at onset of headache, may repeat dose in 1 h to maximum of 12 mg by injection per 24 h; Adult oral dose is 25 mg PO at the onset of headache, may repeat 25–100 mg PO every 2 h until headache relieved or a maximum of 200 mg by mouth per 24 h; Administer 5–20 mg nasal spray into nostril, may repeat in 2 h (maximum 40 mg/24 h); Package insert does NOT recommend use in children younger than 18 years of age	5-HT-1D subtype serotonin receptor agonist

Continued on next page

TABLE 16-1. Migraine Abortive Pharmacotherapy (continued)

Generic Name	Trade Name	Web Site	Dosage Forms	Usual Doses	Mechanisms of Action
Zolmitriptan	Zomig®, Zomig-ZMT™	http://www.astrazeneca.us.com/pi/zm1108.pdf	2.5 mg, 5 mg tablets; 2.5 mg orally disintegrating tablets	1.25–5 mg PO at onset of headache, can be repeated once in 2 h (maximum of 10 mg/24 h)	5-HT-1B/1D subtype serotonin receptor agonist (10-fold higher affinity for 1B over 1D)

Name	Precautions	Adverse Effects	Drug Interactions
Almotriptan	Avoid in patients with ischemic heart disease, Prinzmetal's angina, history of chest pain, uncontrolled hypertension, peripheral vascular disease, cerebrovascular disease, or hemiplegic and basilar artery migraine; death has been reported in patients with coronary artery disease taking this class of drugs	Usually mild and transient: dizziness, flushing, tingling and pressure sensations of the chest, palpitations, jaw and neck, warm or hot sensation, euphoria, tremor, dyspnea	Do not give within 2 weeks of monoamine oxidase (MAO) inhibitors or within 24 hours of other serotonin receptor agonists or ergot alkaloids; case reports of weakness, hyperreflexia, and incoordination with SSRIs; concentrations may be increased by oral contraceptives.
Dihydroergotamine	Avoid in patients at risk of unrecognized coronary artery disease and in patients with ischemic heart disease, Prinzmetal's angina, history of chest pain, uncontrolled hypertension, peripheral vascular disease, hemiplegic/basilar artery migraine	Numbness or tingling in fingers/toes, muscle pain in arms and legs, weakness in the legs, pain in the chest, speeding or slowing of heart rate, swelling and itching	Do not use within 24 hours of sumatriptan; propranolol may potentiate the vasoconstrictive action of ergotamine, nicotine may provoke vasoconstriction; vasoconstrictors may cause synergistic elevation of blood pressure
Eletriptan	Avoid in patients with ischemic heart disease, Prinzmetal's angina, history of chest pain, uncontrolled hypertension, peripheral vascular disease, cerebrovascular disease, or hemiplegic and basilar artery migraine; death has been reported in patients with coronary artery disease taking this class of drugs	Usually mild and transient: nausea, somnolence, headache, paresthesia, dry mouth, dizziness, flushing, tingling and pressure sensations of the chest, palpitations, jaw and neck, warm or hot sensation, euphoria, tremor, dyspnea	Do not give within 2 weeks of MAO inhibitors or within 24 hours of other serotonin receptor agonists or ergot alkaloids; case reports of weakness, hyperreflexia, and incoordination with SSRIs; concentrations may be increased by oral contraceptives
Frovatriptan	Avoid in patients with ischemic heart disease, Prinzmetal's angina, history of chest pain, uncontrolled hypertension, peripheral vascular disease, cerebrovascular disease, or hemiplegic and basilar artery migraine; death has been reported in patients with coronary artery disease taking this class of drugs	Usually mild and transient: nausea, somnolence, headache, paresthesia, dry mouth, dizziness, flushing, tingling and pressure sensations of the chest, palpitations, jaw and neck, warm or hot sensation, euphoria, tremor, dyspnea	Do not give within 2 weeks of MAO inhibitors or within 24 hours of other serotonin receptor agonists or ergot alkaloids; case reports of weakness, hyperreflexia, and incoordination with SSRIs; concentrations may be increased by oral contraceptives
Ibuprofen	Do not exceed 3,200 mg/d (50 mg/kg/d) or use in patients with hypersensitivity to aspirin; use with caution in patients with asthma, heart disease, liver disease, or renal failure or in those receiving anticoagulation	Fatigue, heartburn, gastrointestinal bleed	Additive gastrointestinal irritation with like agents
Midrin®	Avoid in patients with uncontrolled hypertension, coronary artery disease, peripheral vascular disease, or liver disease	Dizziness, sedation, gastrointestinal upset	Hypertensive crisis in patients on MAO inhibitors
Naratriptan	Avoid in patients with ischemic heart disease, Prinzmetal's angina, history of chest pain, uncontrolled hypertension, peripheral vascular disease, cerebrovascular disease, or hemiplegic and basilar artery migraine; death has been reported in patients taking this class of drugs with coronary artery disease	Usually mild and transient: nausea, somnolence, headache, paresthesia, dry mouth, dizziness, flushing, tingling and pressure sensations of the chest, palpitations, jaw and neck, warm or hot sensation, euphoria, tremor, dyspnea	Do not give within 2 weeks of MAO inhibitors or within 24 hours of other serotonin receptor agonists or ergot alkaloids; case reports of weakness, hyperreflexia and incoordination with SSRIs; concentrations may be increased by oral contraceptives

TABLE 16-1. Migraine Abortive Pharmacotherapy (continued)

Name	Precautions	Adverse Effects	Drug Interactions
Prochlorperazine	Do not use in children younger than 2 years of age or less than 9 kg	Drowsiness, orthostatic hypotension, extrapyramidal side effects, especially in children	Pharmacodynamic interactions with drugs that have the same or opposing pharmacologic activity and potentiation of side effects in drugs with similar side effect profiles
Rizatriptan	Avoid in patients with ischemic heart disease, Prinzmetal's angina, history of chest pain, uncontrolled hypertension, peripheral vascular disease, cerebrovascular disease, or hemiplegic and basilar artery migraine; death has been reported in patients with coronary artery disease taking this class of drugs	Usually mild and transient: nausea, somnolence, headache, paresthesia, dry mouth, dizziness, flushing, tingling and pressure sensations of the chest, palpitations, jaw and neck, warm or hot sensation, euphoria, tremor, dyspnea	Do not give within 2 weeks of MAO inhibitors or within 24 hours of other serotonin receptor agonists or ergot alkaloids; case reports of weakness, hyperreflexia, and incoordination with SSRIs; concentrations may be increased by oral contraceptives
Sumatriptan	Avoid in patients with ischemic heart disease, Prinzmetal's angina, history of chest pain, uncontrolled hypertension, peripheral vascular disease, cerebrovascular disease, or hemiplegic and basilar artery migraine; death has been reported in patients with coronary artery disease taking this class of drugs	Dizziness, flushing, tingling, and pressure sensations of the chest, jaw, and neck, warm or hot sensation, rebound headaches in 35–50% of patients within 24 hours (usually mild for PO and nasal)	Do not give within 2 weeks of MAO inhibitors or within 24 hours of other serotonin receptor agonists or ergot alkaloids; case reports of weakness, hyperreflexia, and incoordination with SSRIs; concentrations may be increased by oral contraceptives
Zolmitriptan	Avoid in patients with ischemic heart disease, Prinzmetal's angina, history of chest pain, uncontrolled hypertension, peripheral vascular disease, cerebrovascular disease, or hemiplegic and basilar artery migraine; death has been reported in patients with coronary artery disease taking this class of drugs	Usually mild and transient: nausea, somnolence, headache, paresthesia, dry mouth, dizziness, flushing, tingling and pressure sensations of the chest, palpitations, jaw and neck, warm or hot sensation, euphoria, tremor, dyspnea	Do not give within 2 weeks of MAO inhibitors or within 24 hours of other serotonin receptor agonists or ergot alkaloids; case reports of weakness, hyperreflexia, and incoordination with SSRIs; concentrations may be increased by oral contraceptives

TABLE 16-2. Migraine Preventive Pharmacotherapy

Generic Name	Trade Name	Web Site	Dosage Forms	Usual Doses	Mechanisms of Action
Amitriptyline	Elavil®, Endep®		Tablet: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg	Initial dose 10–25 mg PO qhs; may increase every 2 weeks to effect, usual dose 50–150 mg/d	Increased availability of serotonin by inhibiting reuptake
Cyproheptadine	Periactin®		Tablet: 4 mg; Syrup: 0.4 mg/mL	Initial adult dose is 4 mg PO tid; initial pediatric dose is 0.25 mg/kg/d PO divided tid; maximum dose is 0.5 mg/kg/d or 32 mg	Serotonin antagonist vs. calcium channel antagonist vs. antiplatelet aggregation effect
Metoprolol	Lopressor®, others, Toprol® XL	http://www.astrazeneca-us.com/cgibin/azpi.asp?product=toprol	Tablet: 25 mg, 50 mg, 100 mg; Extended-release tablet: 25 mg, 50 mg, 100 mg, 200 mg	Initial adult dose 25 mg bid, may increase every week to 250 mg/d divided bid; Extended-release 50 mg PO qd, may increase to 200 mg/d qd	Serotonin receptor blockade, cranial vasodilatation, or decreased platelet aggregation/ adhesiveness
Nadolol	Corgard®, others	http://www.kingpharm.com/uploads/pdf_inserts/Corgard_PI.pdf	Tablets: 20 mg, 40 mg, 80 mg, 120 mg, 160 mg	Adult 40–240 mg PO qd	Serotonin receptor blockade, cranial vasodilation, or decreased platelet aggregation/adhesiveness
Naproxen	Aleve®, Naprosyn®, others	http://www.rocheusa.com/products/naprosyn/pi.pdf	Tablet: 220 mg, 250 mg, 275 mg, 375 mg, 500 mg, 550 mg; Suspension: 125 mg/5 mL	Adults: 250 mg PO 2–3 times a day. Do not exceed 1,100 mg/d	Antiinflammatory
Nortriptyline	Pamelor®, Aventyl®	http://pharmaceuticals.mallinckrodt.com/_attachments/packageinserts/backup/40-pamelor.pdf	Capsule: 10 mg, 25 mg, 50 mg, 75 mg; Solution: 10 mg/5 mL	Initial dose 10–25 mg PO qhs, may increase every week to effect, usual adult maximum dose 150 mg	Increased availability of serotonin by inhibiting reuptake, may down regulate β-adrenergic and serotonin receptors
Propranolol	Inderal®, Inderal LA®, others	http://www.wyeth.com/content/ShowLabeling.asp?id=107	Tablet: 10 mg, 20 mg, 40 mg, 60 mg, 80 mg; Long-acting tablets: 60 mg, 80 mg, 120 mg, 160 mg; Solution: 4 mg/mL, 80 mg/mL; Extended-release capsule: 60 mg, 80 mg, 120 mg, 160 mg	Initial adult dose is 40 mg PO bid, may increase every week to response, usual effective dose is 160–240 mg/d; Initial pediatric dose is 1 mg/kg/d in divided doses, usual effective dose is 3–4 mg/kg/d in divided doses	Serotonin receptor blockade, cranial vasodilatation, or decreased platelet aggregation/adhesiveness, and inhibition of lipolysis, which reduces arachidonic acid production
Topiramate	Topamax®	www.orthomcneil.com/products/pi/pdfs/tpamax.pdf	Sprinkle capsule: 15mg, 25mg tablet: 25mg	Children: 1–3 mg/kg/d divided bid; usual dose is 5–9 mg/kg/d divided bid–tid; Adult: 200–400 mg/d divided bid, initiate slowly with 25–50 mg qhs, increase weekly	Blocks sodium channels, enhances GABA activity, and antagonizes the kainate subtype of the glutamate receptor
Valproic acid	Depakote®, Depakote® ER	http://www.depakote.com/pdf/dep3.pdf	Sprinkle capsule: 125 mg Tablet: 125 mg, 250 mg, 500 mg; Extended-release tablet: 500 mg	Adult dose 250 mg PO bid (immediate release product) or 500 mg PO qd (ER product); pediatric dose is 10–40 mg/kg/d divided bid to tid depending on dosage form used	Increases γ-aminobutyric acid in brain, unknown if this is how it works for migraines
Verapamil	Calan®, Calan SR®, Isoptin®, Isoptin SR®, Verelan®, Verelan PM®	http://www.pfizer.com/download/uspi_calan_sr.pdf	Tablets: 40 mg, 80 mg, 120 mg; Slow-release tablets: 120 mg, 180 mg, 240 mg; Extended-release capsules: 100 mg, 120 mg, 180 mg, 200 mg, 240 mg, 300 mg, 360 mg	Pediatric dose: 4–8 mg/kg/d divided tid; adult dose: 80 mg PO tid initially, titrate to a maximum of 480 mg/d	Inhibits calcium medicated smooth muscle contractions

TABLE 16-2. Migraine Preventive Pharmacotherapy (continued)

Generic Name	Precautions	Adverse Effects	Drug Interactions
Amitriptyline	Avoid in patients with cardiovascular disease, seizure disorders, hyperthyroidism, suicidal risk; do not discontinue abruptly	Dizziness, drowsiness, headache, weight gain, nausea, dry mouth constipation, postural hypotension, tachycardia, seizures, sudden death	May cause hypertensive crisis in patients on monoamine oxidase (MAO) inhibitors; blocks hypotensive effects of clonidine, potentiation of sympathomimetic agents
Cyproheptadine	Because of the anticholinergic effects of cyproheptadine, it should be avoided in asthma, chronic obstructive pulmonary disease, bladder or gastrointestinal obstructions	Sedation, blurred vision, dry mouth, urinary retention, excitation, restlessness, weight gain, nausea, vomiting, jaundice, rash	Pharmacodynamic interactions with drugs that have the same or opposing pharmacologic activity and potentiation of side effects in drugs with similar side effect profiles
Metoprolol	Abrupt withdrawal of medication after prolonged use may cause rebound headaches; avoid in patients with heart failure, reactive airway disease, diabetes, thyrotoxicosis, or general anesthesia	Bradycardia, lightheadedness, weakness, depression, fatigue, nausea, vomiting, diarrhea, and violent dreams; heart failure and bronchospasm in predisposed patients	Pharmacodynamic interactions with drugs that have the same or opposing pharmacologic activity and potentiation of side effects in drugs with similar side effect profiles
Nadolol	Abrupt withdrawal of medication after prolonged use may cause rebound headaches; avoid in patients with heart failure, reactive airway disease, diabetes, thyrotoxicosis, or general anesthesia	Bradycardia, lightheadedness, weakness, depression, fatigue, nausea, vomiting, diarrhea, and violent dreams; heart failure and bronchospasm in predisposed patients	Pharmacodynamic interactions with drugs that have the same or opposing pharmacologic activity and potentiation of side effects in drugs with similar side effect profiles
Naproxen	Do not exceed 1,100 mg/d or use in patients with hypersensitivity to aspirin; use with caution in patients with asthma, heart, liver, or renal failure or those receiving anticoagulation	Fatigue, heartburn, gastrointestinal bleeding	Additive gastrointestinal irritation with like agents
Nortriptyline	Avoid in patients with cardiovascular disease, seizure disorders, hyperthyroidism, suicidal risk; do not discontinue abruptly	Dizziness, drowsiness, headache, weight gain, nausea, dry mouth constipation, postural hypotension, tachycardia, seizures, sudden death	May cause hypertensive crisis in patients on MAO inhibitors; blocks hypotensive effects of clonidine, potentiation of sympathomimetic agents
Propranolol	Abrupt withdrawal of medication after prolonged use may cause rebound headaches; avoid in patients with heart failure, reactive airway disease, diabetes, thyrotoxicosis, or general anesthesia	Bradycardia, lightheadedness, weakness, depression, fatigue, nausea, vomiting, diarrhea, and violent dreams; heart failure and bronchospasm in predisposed patients	Phenytoin, phenobarbital, and rifampin can increase elimination rate of propranolol; cimetidine can decrease elimination rate of propranolol, pharmacodynamic interactions with drugs that have the same or opposing pharmacologic activity and potentiation of side effects in drugs with similar side effect profiles; avoid in patients on monoamine oxidase inhibitors and ergot alkaloids
Topiramate	Avoid in children with psychomotor slowing	Speech and language problems, difficulty in concentration and attention, confusion, fatigue, paresthesias, weight loss	Can decrease efficacy of oral contraceptives in teenage grils; can decrease level of valproate
Valproic acid	Avoid in patients younger than 2 years of age, with urea cycle defects, HIV infection, or bone marrow suppression, and with those who are breast-feeding, pregnant, or have hepatic disease	Gastrointestinal upset, lethargy, changes in menstrual cycle; weight gain, nausea, alopecia, hepatitis, pancreatitis, bruising; risk of hepatotoxicity > 2 yr -1:45,000–117,000	Avoid use with other drugs that induce bleeding, such as heparin, warfarin, nonsteroidal antiinflammatory drugs, and aspirin; valproic acid inhibits the metabolism of lamotrigine, phenobarbital, and zidovudine; phenobarbital, carbamazepine, phenytoin, and isoniazid can all increase the metabolism of valproic acid
Verapamil	Avoid in patients with heart failure, hypotension, increased liver function tests, sinus bradycardia, ventricular tachycardia, and decreased neuromuscular function	Bradycardia, AV block, CHF, hypotension, edema, dizziness, nausea, rash, constipation, weakness	Phenobarbital and rifampin may decrease verapamil concentrations; verapamil may increase concentrations of alcohol, digoxin, carbamazepine, cyclosporine, theophylline; additive pharmacodynamic effects seen with β-blockers, antihypertensive agents, antiarrhythmic agents, lithium, inhalation anesthetics, and neuromuscular blocking agents.

approval for preventive therapy in migraine. In the child with generalized epilepsy and associated migraine, valproate or topiramate therapy may seem like a good approach, but data are lacking in support of the approach (the same principle applies to using nortriptyline in children with ADHD, migraine, depressed mood, and nocturnal enuresis—theoretically brilliant but not evidence-based medicine). There are anecdotal reports of stroke in children with vertebrobasilar migraine treated with β-blockers; for that reason, verapamil has been a preventive drug of choice in rare cases of vertebrobasilar migraine. However, calcium channel blockers are rarely prescribed for any other types of childhood migraine, including migraine with and without aura.

In children with chronic daily headache (CDH), pharmacologic preventive therapy consists of combining daily naproxen as an anti-inflammatory with nortriptyline. In pharmacologically intractable migraine or CDH, or when pharmacologic adherence is a problem, nonpharmacologic measures should take precedence, including these: (1) psychological assessment and management of psychosocial issues, (2) recognition and management of precipitating or aggravating factors, and (3) biofeedback training.

Suggested Readings

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Lewis DW, Ashwal S, Dahl G, et al. Practice parameter: evaluation of children and adolescents with recurrent headaches: report on the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2002;59:490–8.

Olness K, MacDonald JT, Uden DL. Comparison of self-hypnosis and propranolol in the treatment of juvenile classic migraine. Pediatrics 1987;79:593–7.

Eiland LS, Jenkins LS, Durham SH. Pediatric migraine: pharmacologic agents for prophylaxis. Ann pharmacother. 2007 Jul;41(7): 1181–90. Epub 2007 Jun 5. Review.

Practitioner and Patient Resources

See Tables 16-1 and 16-2 for Web sites available regarding each drug.

Chapter 17

What Is Epilepsy?

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Epilepsy is a complex disorder—there are many seizure types, etiologies, and syndromes. The diagnosis is based on the history, an approach that creates many possible pitfalls. This chapter provides an overview on epilepsy for the nonexpert and establishes the context for subsequent, more detailed chapters that address specific types of epilepsy.

How Is Epilepsy Diagnosed?

The diagnosis of epilepsy requires two features: (1) the patient must have recurrent seizures, and (2) the seizures must be unprovoked. Many types of seizures exist, and epilepsy may be caused by a huge array of different brain disorders.

Did a Seizure Occur?

Determining whether a seizure has occurred involves analyzing the history of the event—most seizures have stopped before a child presents to a medical facility and no laboratory evaluation is currently definitive. History from both the child, if possible, and a reliable first-hand witness is key. There are many epilepsy look-alikes, as outlined in Chapter 28, "Paroxysmal, Nonepileptic Disorders of Childhood." The most common differential diagnosis is vasodepressor syncope, which can be very challenging because syncope is often associated with myoclonic jerks. Diagnostic uncertainty after a first seizure is common, and several studies indicate that even epilepsy experts disagree about the nature of a first attack in 15 to 25% of cases. Parents often panic when their child has a convulsive seizure, so it is not surprising they have a hard time describing the event. But studies have shown that even when several neurologists review the same videotaped seizure, they often disagree about the details of what they saw.

The electroencephalogram (EEG) cannot substitute for history. Up to 3% of normal children in one large school based study had spikes (epileptic discharge) on EEG and yet never developed epilepsy. About 70% of children with epilepsy have interictal (between seizures) EEG spikes, which means that about 30% with established epilepsy have a normal EEG between seizures. If the EEG is running during a seizure, then there are nearly always diagnostic changes; however, this approach is of no help with the first seizure or if the child has rare seizures.

To further complicate diagnosis, many types of seizures exist (Table 17-1). The basic distinction is between partial and generalized seizures. Partial (focal) seizures begin in one part of the brain and spread. If they spread to the whole brain, the child may have a generalized convulsion (partial with secondary generalization). If the child is conscious through the attack, the seizure is said to be simple partial. If consciousness is diminished without a convulsion, the seizure is called complex partial. When a child has an aura or warning before a generalized seizure, the aura is actually a simple partial seizure.

Generalized seizures begin everywhere in the brain at once. The first event in the seizure is loss of consciousness. If there is tonic or clonic activity, it is symmetrical. Generalized seizures include absence (previously called "petit mal") and generalized tonic-clonic seizures (previously called "grand mal," but note that partial seizures with secondary generalization still are "grand mal"). Other generalized seizure types include akinetic or atonic drop attacks and myoclonus.

When children present with a first unprovoked seizure, most often it is a convulsion—a dramatic and frightening event that prompts an emergency room visit. Frequently the history indicates there have been numerous previous events, which in retrospect were clearly simple or complex

TABLE 17-1. International Classification of Seizure Type

Partial seizures
- A. Simple partial seizures
  1. With motor signs
  2. With somatosensory or special sensory hallucinations
  3. With autonomic symptoms
  4. With psychic symptoms
- B. Complex partial seizures
  1. Simple partial followed by impairment of consciousness
  2. With impaired consciousness at onset
- C. Partial seizures evolving to secondary generalized seizures
  1. Simple partial seizures evolving to generalized
  2. Complex partial seizures evolving to generalized
  3. Simple partial seizures evolving to complex partial seizures evolving to generalized

Generalized seizures
- A. 1. Absence seizures
  2. Atypical absence seizures
- B. Myoclonic seizures
- C. Clonic seizures
- D. Tonic seizures
- E. Tonic-clonic seizures
- F. Atonic seizures
- G. Unclassifiable epileptic seizures

Adapted from Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981;22:489–501.

partial seizures or absence seizures—these attacks were sufficiently subtle that the family or physician had dismissed them as unimportant. A first unprovoked seizure is often not the first seizure!

Was the Seizure Unprovoked?

Seizures commonly arise from acute brain insults (eg, within 24 hours of a head injury, as the result of fever, with electrolyte disturbance, or from meningitis). The history and physical examination typically settle this issue; however, two issues may require clarification. First, sleep deprivation and severe emotional stress may be associated with seizures but are not considered to be provoking factors from the perspective of diagnosis. Secondly, some seizures are elicited by specific stimuli. For example, some patients have seizures when exposed to flashing lights or video game sequences. These are considered to be epileptic as opposed to provoked.

How much investigation is warranted and has a normal examination, then it is very unusual to try to establish that a first seizure was unprovoked? A practice parameter from the American Academy of Neurology suggests that if the child recovers quickly, is afebrile, to find a provoking factor with further investigation. Blood studies and brain imaging studies are crucial when neurologic deficits persist or a child is slow to recover consciousness. Otherwise, investigations are most appropriately tailored to the specific situation. For example, if a child with diabetes presents with a first seizure, hypoglycemia must be excluded. If the seizure was unprovoked and the child has recovered, an elective EEG and brain MRI are usually valuable.

What Happens after Two Unprovoked Seizures?

When two unprovoked seizures have occurred, is it reasonable to diagnose epilepsy? Many studies have established that the recurrence risk after a first unprovoked seizure is about 40 to 50%. Three large studies have confirmed that after two seizures, the risk of a third is about 80%. This rate seems high enough to reserve the diagnosis of epilepsy to those with two or more unprovoked seizures, provided that the diagnosis of "seizure" is clear. When the nature of the events is not clear-cut, we think that it is better to wait for further events before coming to the diagnosis. It is important for families to know that even if two seizures have occurred, only about 30% will go on to have ≥10 seizures in the next 10 years, so most children with epilepsy do not have very many seizures. In our cohort of 504 children with newly treated epilepsy, there were about 20% with "smooth-sailing epilepsy"—they never had another seizure after medication was started and eventually discontinued.

The Concept of Epilepsy Syndrome

Once two unprovoked, unequivocal seizures have occurred, it is usually possible to assign an epilepsy syndrome (Table 17-2). An epilepsy syndrome diagnosis typically requires the patient's history plus an EEG and brain imaging study. Epilepsy syndromes take into account not only the seizure type but also the etiology, EEG characteristics, the child's neurologic function, and other features. The goals in defining an epilepsy syndrome are to point the way for further investigations and to the best treatment. Many (but not all) epilepsy syndromes have a well-defined prognosis. For example, benign rolandic epilepsy always remits and often does not require medication, whereas juvenile myoclonic epilepsy typically is lifelong and responds well to valproic acid but less reliably to other medications.

There are a growing number of epilepsy syndromes. The classification has two main divisions: (1) localization-related and (2) generalized. Localization-related implies there is dysfunction in one area of the brain that gives rise to the epilepsy. Generalized means that the causative brain process affects wide areas of both hemispheres.

The basic division is then subdivided into idiopathic, cryptogenic, and symptomatic. Idiopathic means the cause is unknown but presumed to be genetic. Children with idiopathic epilepsies are otherwise normal. Cryptogenic means the cause is unknown. Children with symptomatic

TABLE 17-2. International Classification of Epilepsies and Epileptic Syndromes and Related Seizure Disorders

1. Localization-related (local, focal, partial) epilepsies and syndromes
   - 1.1 Idiopathic (with age-related onset)
     - Benign childhood epilepsy with centrotemporal spikes
     - Childhood epilepsy with occipital paroxysms
     - Primary reading epilepsy
   - 1.2 Symptomatic
     - Chronic progressive epilepsia partialis continua
     - Syndromes characterized by seizures with specific modes of precipitation
     - Temporal lobe epilepsies
     - Frontal lobe epilepsies
     - Parietal lobe epilepsies
     - Occipital lobe epilepsies
   - 1.3 Cryptogenic
2. Generalized epilepsies and syndromes
   - 2.1 Idiopathic (with age-related onset)
     - Benign neonatal familial convulsions
     - Benign neonatal convulsions
     - Benign myoclonic epilepsy in infancy
     - Childhood absence epilepsy
     - Juvenile myoclonic epilepsy
     - Epilepsy with generalized tonic-clonic seizures on awakening
     - Other generalized idiopathic epilepsies
     - Epilepsies with seizures precipitated by specific modes of activation
   - 2.2 Cryptogenic or symptomatic
     - West syndrome
     - Lennox-Gastaut syndrome
     - Epilepsy with myoclonic-astatic seizures
     - Epilepsy with myoclonic seizures
   - 2.3 Symptomatic
     - 2.3.1 Nonspecific etiology
       - Early myoclonic encephalopathy
       - Early infantile epileptic encephalopathy with suppression burst
       - Other symptomatic generalized epilepsies
     - 2.3.2 Specific syndromes
       - Epileptic seizures complicating other disease states
3. Epilepsies and syndromes undetermined whether focal or generalized
   - 3.1 With both generalized and focal seizures
     - Neonatal seizures
     - Severe myoclonic epilepsy of infancy
     - Epilepsy with continuous spike waves during slow-wave sleep
     - Acquired epileptic epilepsies
     - Other undetermined epilepsies
   - 3.2 Without unequivocal generalized or focal features
4. Special syndromes
   - 4.1 Situation-related seizures
     - Febrile convulsions
     - Isolated seizures or isolated status epilepticus
     - Seizures occurring only with acute metabolic or toxic events

Adapted from Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389–99.

TABLE 17-3. Epilepsy Syndromes and Related Conditions*

Benign familial neonatal seizures
Early myoclonic encephalopathy
Ohtahara syndrome
Migrating partial seizures of infancy
West syndrome
Benign myoclonic epilepsy in infancy
Benign familial infantile seizures
Benign infantile seizures (nonfamilial)
Dravet's syndrome
HH syndrome
Myoclonic status in nonprogressive encephalopathies
Benign childhood epilepsy with centrotemporal spikes
Early-onset benign childhood occipital epilepsy (Panayiotopoulos type)
Late-onset childhood occipital epilepsy (Gastaut type)
Epilepsy with myoclonic absences
Epilepsy with myoclonic-astatic seizures
Lennox-Gastaut syndrome
Landau-Kleffner syndrome (LKS)
Epilepsy with continuous spike-and-waves during slow-wave sleep (other than LKS)
Childhood absence epilepsy
Progressive myoclonus epilepsies
Idiopathic generalized epilepsies with variable phenotypes
Juvenile absence epilepsy
Juvenile myoclonic epilepsy
Epilepsy with generalized tonic-clonic seizures only
Reflex epilepsies
Idiopathic photosensitive occipital lobe epilepsy
Other visual sensitive epilepsies
Primary reading epilepsy
Startle epilepsy
Autosomal dominant nocturnal frontal lobe epilepsy
Familial temporal lobe epilepsies
Generalized epilepsies with febrile seizures plus
Familial focal epilepsy with variable foci
Symptomatic (or probably symptomatic) focal epilepsies
Limbic epilepsies
Mesial temporal lobe epilepsy with hippocampal sclerosis
Mesial temporal lobe epilepsy defined by specific etiologies
Other types defined by location and etiology
Neocortical epilepsies
Rasmussen syndrome
Other types defined by location and etiology
Conditions with epileptic seizures that do not require a diagnosis of epilepsy
Benign neonatal seizures
Febrile seizures
Reflex seizures
Alcohol-withdrawal seizures
Drug or other chemically induced seizures
Immediate and early posttraumatic seizures
Single seizures or isolated clusters of seizures
Rarely repeated seizures (oligoepilepsy)
Syndromes in development.

Adapted from Engel J Jr. A proposed diagnostic scheme for people with epileptic seizures and epilepsy: report of the ILAE Task Force on Classification and Terminology. Epilepsia 2001;42:796–803.

epilepsies have something wrong in their brain that is presumed to cause the epilepsy. For example, a child with global mental handicap, generalized tonic-clonic seizures, and a generalized epileptic discharge on interictal EEG has a form of symptomatic generalized epilepsy. A child with a localized brain malformation on magnetic resonance imaging and partial seizures has a form of symptomatic partial epilepsy.

Some epilepsy syndromes now have a specific genetic *abnormality* identified. The syndrome of generalized epilepsy with febrile seizures plus (GEFS+) is caused in most families by an autosomal dominant defect in cerebral voltage-gated sodium channels. This genetic discovery has made epilepsy syndrome diagnosis more complicated because in large kindreds with GEFS+, different family members may have different classic epilepsy syndromes, apparently caused by the same basic genetic defect. We expect the classification of epilepsy syndromes to continue to evolve. Table 17-3 outlines a current published proposal from the International League Against Epilepsy for a new classification.

The number of epilepsy syndromes continues to grow. An expert assessment may be needed in the course of epilepsy to be sure that the epilepsy syndrome has been correctly defined.

A confusing concept is that of an epilepsy syndrome in a child with a single seizure. For example, consider a normal 6 year old child presenting after a single seizure arising from sleep with onset with a sensory disturbance in the face and then a secondarily generalized seizure. The EEG shows the typical centro-temporal spikes of Benign Rolandic Epilepsy. This child has had only a single seizure but otherwise fills all the criteria for the specific epilepsy syndrome of Benign Rolandic Epilepsy. It seems inconsistent but nonetheless compelling that many children with a first unprovoked seizure can be assigned to an epilepsy syndrome. A better definition of epilepsy than two unprovoked seizures has not been forthcoming; however, the physician can gain a great deal of useful information in terms of cause and prognosis by attempting an epilepsy syndrome diagnosis after a first unprovoked seizure. We find that families can cope with the ambiguity that their child with a first seizure does not yet have epilepsy and yet has an epilepsy syndrome.

Summary

In summary, the number of epilepsy syndromes continues to grow. An expert assessment may be needed in the course of epilepsy to ensure the epilepsy syndrome has been correctly defined.

Suggested Readings

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Practitioner and Patient Resources

The Epilepsy Project
http://www.epilepsy.com
Epilepsy.com is an online resource provided by The Epilepsy Project. Its mission is to inform and empower two groups of patients and their families: those facing newly diagnosed epilepsy and those struggling with epilepsy that has resisted the usual treatments.

Epilepsy Foundation
http://www.epilepsyfoundation.org
The Epilepsy Foundation (also known as the Epilepsy Foundation of America) is the national organization that works for people affected by seizures through research, education, advocacy, and service. This organization of volunteers is committed to the prevention and cure of epilepsy and a positive quality of life for everyone who lives with seizure disorders. Its current strategic goals include broadening and strengthening of research, providing individuals and families with easy access to reliable information, and ensuring access to appropriate medical care for those affected by seizures.

CHAPTER 18

FEBRILE SEIZURES

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Febrile seizures are a common and mostly benign type of seizure. Daily antiepileptic drugs are not recommended for children with simple febrile seizures and are often unnecessary for those with complex febrile seizures. Understanding the natural history and prognosis of febrile seizures helps the physician counsel families and choose the appropriate management, while avoiding unnecessary diagnostic procedures and therapies.

Febrile seizures are the most common form of childhood seizures, occurring in 2 to 5% of the population. In 1993, the International League Against Epilepsy (ILAE) defined a febrile seizure as a "seizure occurring in childhood after the age of 1 month, associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other symptomatic seizures," including those secondary to acute electrolyte imbalance. This is similar to the definition adopted by the National Institutes of Health Consensus Conference in 1980, except that the lower age limit was shifted from 3 months to 1 month. It is generally accepted that the febrile illness must include a temperature of at least 38.4°C, though not necessarily at the time of the seizure.

Simple febrile seizures are relatively brief (< 10 to 15 minutes) generalized seizures that do not recur during the same febrile illness. Complex febrile seizures are characterized by one of the following features: prolonged duration (> 10 to 15 minutes), partial onset, or multiple recurrences within 24 hours. If a careful history is taken, approximately one-third of all febrile seizures presenting to the emergency room have complex features. Seizures in the context of a febrile illness occurring in a neurologically abnormal child are still considered simple or complex according to the above criteria. Although children who have preexisting neurologic abnormalities are more likely to present with complex febrile seizures and are more likely to develop subsequent epilepsy, they can still have simple febrile seizures.

If the febrile seizure lasts longer than 30 minutes (whether as a single seizure or as a series of seizures) without full recovery between seizures, it is classified as febrile status epilepticus. Febrile status epilepticus accounts for approximately 5% of all febrile seizures. However, because of the frequency with which febrile seizures occur, it accounts for approximately one-quarter of all cases of status epilepticus in childhood and for two-thirds of cases of status epilepticus in the second year of life.

Epidemiology

The U.S. National Collaborative Perinatal Project (NCPP) tracked 54,000 children and determined the prevalence of febrile seizures at 7 years of age to be 3.5% in Caucasian children and 4.2% in African American children. Studies in Western Europe reported a similar prevalence. Febrile seizures occur more frequently in Japanese children, 9 to 10% of whom experience at least one episode, which may indicate a genetic predisposition in this population. The onset of febrile seizures peaks between 18 and 22 months of age, and most cases occur between 6 months and 3 years of age. Onset of febrile seizures after age 5 years is uncommon, but seizures can occur up to 10 years of age. Some studies have reported a slightly higher incidence among boys than girls.

A case-controlled, population-based study identified the risk factors associated with first febrile seizure as follows:

- History of febrile seizures in a first- or second-degree relative
- Neonatal nursery stay of more than 30 days

- Developmental delay
- Day-care attendance

Children with two of these risk factors have an almost 30% chance of developing febrile seizures. A case-controlled study to identify which children with a febrile illness were likely to develop seizures found that family history of febrile seizures and peak temperature were important risk factors. The specific type of illness also was relevant. Children with gastroenteritis and fever were less likely to have a febrile seizure than were children with other types of febrile illnesses.

In the past, febrile seizures were thought to usually occur as the first sign of a febrile illness. A study by Berg and colleagues in 1997 found that only 21% of children experienced febrile seizures before or within an hour of recognized fever onset. Most (57%) had a seizure after 1 to 24 hours of recognized fever, and 22% had seizures more than 24 hours after the onset of fever.

Initial Evaluation

To make the diagnosis of febrile seizures, meningitis, encephalitis, accidental poisoning, trauma or abuse, electrolyte imbalances, and other causes of acute symptomatic seizures must be excluded. Of these, the one of most concern to the clinician is meningitis. The incidence of meningitis in children with first seizures associated with fever is 2 to 5%. The following risk factors for meningitis have been identified:

- A visit for medical care within the previous 48 hours
- Focal or prolonged seizures
- Suspicious findings on physical or neurologic examination

The American Academy of Pediatrics (AAP) has issued guidelines for evaluating children aged 6 months to 5 years who have simple febrile seizures. A spinal tap should be strongly considered in an infant less than 12 months of age. Because signs of meningitis may be subtle in the 12- to 18-month age group, careful assessment is mandatory. A spinal tap is not necessary in a child older than 18 months if the history and physical examination are not suspicious for meningitis. A spinal tap is still recommended in children with first complex febrile seizures or with any other risk factors listed, as well as in those with persistent lethargy or prior antibiotic therapy.

Many studies have found that in the absence of suspicious history (eg, vomiting or diarrhea) or abnormal physical examination findings, routine measurement of serum electrolytes, calcium, phosphorus, magnesium, complete blood count, and serum glucose is of limited value in the evaluation of a child with febrile seizures who is older than 6 months. In younger children, more detailed laboratory investigations may be helpful in select cases.

Neuroimaging studies are not helpful in the evaluation of simple febrile seizures. The role of neuroimaging in the evaluation of complex febrile seizures is more controversial. Neuroimaging may be useful in evaluating a child with a prolonged focal seizure, particularly when the etiology of the seizure is not clear. Magnetic resonance imaging (MRI) may be of use in assessing whether hippocampal damage has occurred after febrile status epilepticus, though the clinical utility of this finding is not yet fully established. Data show that prolonged febrile seizures can result in acute hippocampal injury and subsequent mesial temporal sclerosis, but imaging cannot be used to predict who will develop intractable temporal lobe epilepsy. Other studies have shown that MRI abnormalities in the hippocampus after febrile status epilepticus may be transient and, therefore, not detected, unless the study is performed shortly after the prolonged seizure occurs.

Electroencephalogram (EEG) is of limited value in evaluating a child with febrile seizures. The clinical relevance of EEG abnormalities in this setting is unclear, because they do not predict febrile seizure recurrence or development of epilepsy. Evidence does not support the previously held belief that performing an EEG 2 weeks after the febrile seizure helps distinguish benign febrile seizures from other types.

Pathophysiology

The pathophysiology of febrile seizure remains elusive. It is clearly an age-specific phenomenon. Animal models of febrile seizures demonstrate an age-specific susceptibility to seizures induced by fever. Induction of epileptiform activity by temperature elevation has been demonstrated in hippocampal slices of rat pups. In animal models, febrile seizures begin in the hippocampus or amygdala. There is little evidence of neuronal death in the normal immature rat, even after very prolonged febrile seizures. More recently, long-term functional changes in the hippocampal circuit after febrile seizures lasting 20 minutes have been described in a rat model. However, whether these changes lead to epilepsy remains unclear. Interestingly, seizures lasting less than 10 minutes are not associated with any anatomic or functional changes. Young rats with induced neuronal migration disorders are more susceptible to seizures induced by fever as well as to hippocampal damage. These results suggest that preexisting central nervous system (CNS) anomalies may make the brain more susceptible to prolonged seizures and to seizure-induced injury.

Clinically, febrile seizures are associated with febrile illnesses but do not necessarily occur at the peak temperature or on the rising phase of the fever. The most commonly

associated illnesses are upper respiratory infections, otitis media, and herpesvirus infections, including roseola. Up to 50% of febrile seizures in children younger than 3 are associated with human herpes virus (HHV 6 and 7) infections. Whether this occurs because these viruses are neurotropic or because these infections are typically associated with high fevers remains unclear. Of note, gastroenteritis seems to protect against febrile seizures, with the notable exception of *Shigella* infection.

Morbidity and Mortality

The morbidity and mortality associated with febrile seizures is extremely low, even in the case of febrile status epilepticus. No deaths were reported from the NCPP or the British Cohort Study. No deaths and no cases of new motor or cognitive impairment occurred in a recent series of 180 cases of febrile status epilepticus.

Cognitive and behavioral outcomes after febrile seizures also are favorable. The NCPP found no difference in intelligence quotient (IQ) scores or performance on the Wide Range Achievement Test between children with febrile seizures and their siblings. Similarly, the British Cohort study found no differences in measure of IQ, academic achievement, or behavior between children with febrile seizures and children without febrile seizures in the same birth cohort. The favorable cognitive and behavioral outcomes in these two large, well-designed prospective studies apply to children with both simple and complex febrile seizures, including febrile status epilepticus.

Recurrent Febrile Seizures

Approximately one-third of children who have a febrile seizure will have at least one recurrence. Multiple studies have identified the following as the most consistent risk factors for recurrent febrile seizures:

- Family history of febrile seizures
- First febrile seizure before age 18 months
- Temperature (the lower the fever, the higher the risk of recurrence)
- Brief duration (< 1 hour) between onset of recognized fever and seizure

Children with two or more risk factors have a 30% recurrence risk at 2 years; those with three or more risk factors have a 60% recurrence rate. One-half of all recurrences are within the first 6 months, and 90% occur within 2 years. A complex febrile seizure is not associated with an increased risk of recurrence in most studies. However, complex features tend to persist if recurrences occur. In particular, children who have a prolonged initial febrile seizure and have a recurrence are likely to have a prolonged recurrent seizure as well.

Febrile Seizures and Subsequent Epilepsy

Data from large epidemiologic and prospective studies indicate that 2 to 10% of children with febrile seizures will develop epilepsy. In most studies, the risk of developing epilepsy after a single febrile seizure is not substantially different than that of the general population. Even in populations with a high incidence of febrile seizures, such as the Japanese, the incidence of epilepsy is not significantly different from that in populations with a lower incidence. The pessimistic view that febrile seizures cause brain damage, which prevailed in the older literature, was based on a select population and has been refuted by prospective studies.

Risk factors for epilepsy after febrile seizures are as follows:

- Preexisting neurodevelopmental abnormality
- Complex febrile seizures
- Family history of epilepsy
- Short duration of recognized fever before seizure

Note that contrary to prior views, a short duration of recognized fever prior to seizure onset is not only associated with higher risk of subsequent febrile seizures, but also with increased risk for subsequent epilepsy. This is the only risk factor that recurrent febrile seizures and subsequent epilepsy share. In the case of complex febrile seizures, multiple complex features may be additive and may increase the risk. Children with prolonged and focal febrile seizures are particularly at high risk for developing subsequent epilepsy. Two of the most important risk factors for epilepsy are neurodevelopmental abnormality and a family history of epilepsy, whether or not there is a history of febrile seizures. Family history of febrile seizures, age at first febrile seizure, temperature, gender, and ethnicity have not been shown to increase the risk for developing subsequent epilepsy.

Do Febrile Seizures Cause Mesial Temporal Sclerosis?

Retrospective clinical studies from epilepsy surgery centers, where many patients with mesial temporal sclerosis had a history of focal or prolonged febrile seizures, have suggested a causal relationship between prolonged febrile seizures and subsequent temporal lobe epilepsy. However, large population-based studies and prospective studies have failed to find this association. Recent imaging data suggest that very prolonged febrile seizures lasting more than 60 minutes may cause hippocampal damage, particularly in brains that already have some preexisting abnormalities. This is so rare that even large prospective series may not have enough cases to detect its occurrence. The frequency with which this occurs remains an unanswered question.

Genetics

Genetic factors clearly play a role in febrile seizures but are not the whole story. Children with a family history of seizures are at increased risk for both febrile seizures and recurrent febrile seizures. However, it would appear that given the appropriate febrile illness in the age-specific period of vulnerability, most children would be at risk for febrile seizures. What proportion of the risk is attributable to genetic causes is somewhat unclear. Studies have shown a concordance rate of 56% in monozygotic twins and 14% in dizygotic twins. Analysis of the Rochester, Minnesota registry points to a multifactorial mode of inheritance for febrile seizures. Recently, a generalized epilepsy with febrile seizures plus syndrome (GEFS+) has been described in families in whom seizures are inherited in an autosomal-dominant pattern, with high penetrance. Affected children tend to have febrile seizures that persist beyond the expected age and may develop generalized tonic-clonic seizures in adolescence (with eventual remission). One-third of abnormal gene carriers have other epileptic syndromes, including absence, myoclonus, and akinetic seizures. The gene codes for a neuronal voltage-gated sodium channel and at least three different mutations have been described so far. The role of specific genetic mutations in febrile seizures is a rapidly evolving field and it will take at least a few more years before sufficient data become available to be of practical use to the pediatrician.

Available Treatment Modalities

Antipyretic Agents

As febrile seizures, by definition, occur in the context of febrile illness, one would assume that aggressive treatment with antipyretic medication would reduce the risk of febrile seizure. However, controlled clinical trials provide little evidence to suggest antipyretics reduce the risk of recurrent febrile seizure. It should be noted that children in whom febrile seizures occur at the onset of fever have the highest risk of recurrent febrile seizures. Recommendations for antipyretic therapy should recognize its limitations and avoid creating feelings of undue anxiety and guilt in parents.

Continuous Anticonvulsant Therapy

Phenobarbital given in doses that achieve serum levels of 15 μg/mL or sodium valproate effectively reduce recurrence risk. However, the morbidity of therapy, including cognitive and behavioral side effects in the case of phenobarbital and the potential for hepatic failure in young children treated with valproate, is such that this therapy is indicated only in rare cases. Even for children with recurrent febrile status epilepticus, or multiple episodes of complex febrile seizures, daily therapy is rarely recommended. Instead, these children are treated with oral diazepam when febrile to reduce their risk for seizure recurrence. Additional treatment includes abortive therapy with rectal diazepam at the time of seizure.

Carbamazepine and phenytoin have not been shown to effectively prevent simple febrile seizure recurrence. There are insufficient data on the newer antiepileptic drugs, including gabapentin, lamotrigine, topiramate, tiagabine, and vigabatrin, to justify their use in the treatment of febrile seizures.

Intermittent Antiepileptic Drug Therapy

Diazepam, given orally or rectally at the onset of illness, can reduce the risk of recurrent febrile seizures by up to 44%. Sedation is the most significant adverse effect. Drawbacks are the number of times therapy may be needed, considering the frequency of febrile illnesses in early childhood. There is also the theoretical concern that sedation could mask signs of a more serious illness, such as meningitis. There is less experience with other benzodiazepines, though presumably some of them would be effective.

Intermittent therapy with phenobarbital at the onset of a febrile episode has been shown to be ineffective in reducing the risk of seizure recurrence, most likely because of the long time needed to achieve meaningful serum levels. Intermittent therapy with valproate is also ineffective.

Intermittent Benzodiazepines for Stopping a Febrile Seizure Episode

Interrupting a prolonged seizure is desirable. Most febrile seizures are brief, lasting less than 10 minutes, and no intervention is necessary. Rectal diazepam has been shown to be effective in terminating febrile seizures. It is widely used in Europe, Canada, and Japan, and increasingly in the United States. It would seem a rational therapy for abortive therapy when needed. Candidates for this treatment include children at high risk for prolonged or multiple febrile seizures and those who live far from medical care. This approach has the obvious advantage of minimizing drug exposure. However, it should be used only with reliable caregivers who have been trained in its use. Other benzodiazepines also have been used, including rectal lorazepam and buccal midazolam, though there is far less experience with them than with rectal diazepam.

Emergency Department Treatment of Febrile Seizures

A child who arrives in the emergency department seizing should be treated using the department's pediatric status epilepticus protocol. Usually this calls for intravenous benzodiazepines, either diazepam or lorazepam. If no

intravenous access is available, rectal diazepam can be used. In general, once a febrile seizure stops, it stops completely, so there is usually no need to load the patient with fosphenytoin. Loading can be done if the child continues to seize. A full discussion of the treatment of status epilepticus is beyond the scope of this chapter and is covered elsewhere in this volume. The child who has a febrile seizure in the emergency department can be treated more conservatively with rectal diazepam if the seizure does not stop within a few minutes, and the full status protocol is not usually needed.

Treatment of Children with Febrile Seizures

Treatment of febrile seizures is a controversial subject. There are two major rationales for treatment, each leading to different approaches. The first approach is based on the old idea that febrile seizures are harmful and may lead to the development of epilepsy and is aimed at preventing febrile seizures using either intermittent or chronic treatment with medications. However, several studies have shown that although these therapies reduce the risk of recurrent febrile seizures, they have no effect on the rate of development of subsequent epilepsy. The second approach is based on epidemiologic data that indicate febrile seizures are generally benign. Therefore, the only concern is very prolonged febrile seizures. These considerations lead to a therapeutic approach that focuses on aborting febrile seizures when they occur to prevent status epilepticus.

Treatment of Simple Febrile Seizures

The AAP has issued practice guidelines stating that most children with simple febrile seizures do not require treatment. Antipyretics are ineffective and the morbidity of chronic or intermittent antiepileptic drug therapy makes them unsuitable for the treatment of an essentially benign condition, despite their efficacy. We fully agree with this position. In patients who live far from medical care or whose parents or caretakers are particularly concerned, a prescription for rectal diazepam may be appropriate.

Treatment of Complex Febrile Seizures

There is no consensus on the treatment of complex febrile seizures. However, few practitioners would recommend chronic prophylactic therapy, except in exceptional cases. Recommended therapies for these patients include intermittent diazepam at the time of fever and rectal diazepam if a seizure should occur and last longer than 5 minutes. We prefer rectal diazepam for the reasons discussed above. If intermittent diazepam is used at time of fever and a seizure does occur, rectal diazepam can still be given as an abortive agent with good safety and efficacy.

Conclusion

In summary, febrile seizures are common and mostly benign form of seizure. Daily antiepileptic drugs are not recommended for children with simple febrile seizures and often are unnecessary, even for those with complex febrile seizures. The rationale for treatment is prevention of prolonged or repetitive febrile seizures.

The clinician needs to recognize that seizures are frightening events for those who witness them. Parents need to be reassured that the child will not die during a seizure, a widespread fear. Keeping the child safe during a seizure usually is the only measure needed. Parents should be offered information about febrile seizures, prognosis, and management. If rectal diazepam gel is prescribed, explicit information regarding its correct administration needs to be provided. Proper education about when to contact their clinician for evaluation of the source of fever is key to proper management, even if medications are not prescribed. Understanding the natural history and prognosis of febrile seizures helps the physician counsel families and choose appropriate management, while avoiding unnecessary diagnostic procedures and therapies.

Acknowledgment

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Practitioner and Patient Resources

Epilepsy Foundation
4351 Garden City Dr., Suite 406
Landover, MD 20785-2267
Phone: (301) 459-3700 or (800) EFA-1000
E-mail: postmaster@efa.org
www.epilepsyfoundation.org
An excellent and reliable resource for all consumers and clinicians who want to find out more about seizures of all kinds including febrile seizures. Catalog of available materials can also be obtained.
Freeman J, Vining E, Pillas D, editors. Seizures and epilepsy in child-hood: a guide for parents 3rd edition. Baltimore (MD): The Johns Hopkins University Press; 2002.

American Academy of Pediatrics (AAP)
141 North West Point Boulevard
Elk Grove Village, IL 60007-1098
Phone: (847) 434-4000
Fax: (847) 434-8000
www.aap.org
Practice guidelines on evaluation and treatment, an information fact sheet about febrile seizures (also available directly from AAP), and regularly updated information.

National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)
Bethesda, MD 20892-2540
www.ninds.nih.gov
Printed publications: National Institutes of Health Publication No. 95-3930 (1995). Fact Sheet: *Febrile Seizures.* Office of Scientific and Health Reports, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892-2540.

Chapter 19

First Unprovoked Seizure

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Most children who experience a first unprovoked seizure, even status epilepticus, do not have recurrent unprovoked seizures. Thus, a single unprovoked seizure does not necessarily justify use of daily antiepileptic drugs.

A seizure is defined as an abnormal paroxysmal neuronal discharge associated with motor, sensory, autonomic, or behavioral alterations. It is thought to arise from an imbalance between excitatory and inhibitory activity in the brain. Seizures can be provoked or unprovoked. A provoked seizure is linked to a specific trigger. Common examples are a contact seizure after head trauma or a seizure associated with intoxication, fever, or central nervous system infection. In these cases, it is clearly indicated to treat the seizure acutely, while addressing the precipitating cause. An unprovoked seizure does not have an obvious precipitating cause and may be related to epilepsy. The overall recurrence risk for another seizure after a first unprovoked episode is 45% (22% at 6 months, 29% at 12 months, 37% at 24 months, 43% at 60 months, and 46% at 120 months).

Recognition of different settings in which an unprovoked seizure occurs and identification of risk factors for recurrence help define management options. After a first unprovoked seizure, the decision regarding initiation of antiepileptic drugs should be made on the basis of weighing the relative risks of potential adverse effects of the different drugs versus further seizure episodes. Rigid practice parameters should be avoided. In this chapter, we review the evaluation and management of a first unprovoked seizure. Neonatal convulsions are not considered part of this discussion. A rational, individualized approach, based on scientific data, is recommended.

To define the goals of treating a child after a first unprovoked seizure episode, two questions should be addressed:

- Do seizures injure the brain?
- Can we prevent the development of epilepsy?

To answer the first question, we should consider what is known about the impact of seizures on the developing brain. Most of the available information pertains to seizure-induced hippocampal damage. Factors such as age, neurologic status, and seizure duration, as well as genetic predisposition, may affect the extent (if any) of seizure induced hippocampal injury.

Epidemiologic data suggest that most seizures are brief, and that one prolonged seizure episode rarely causes permanent brain damage, unless there is an associated acute neurologic insult or the presence of preexisting injury. Data obtained in experimental studies suggest that early in life, one episode of motor status epilepticus appears to be of little consequence in an otherwise normal brain. However, both human and animal models indicate that in the presence of prior neurologic anomalies, seizures early in life are likely to produce some degree of hippocampal injury, including selective cell loss and synaptic reorganization in the hippocampus and age-specific alterations in neuronal communication. In current experimental models, these changes occur more frequently with increasing age; the older the rat, the greater the likelihood of developing seizure related hippocampal injury. Experimental evidence also indicates that although prolonged seizures early in life may not produce hippocampal damage in a normal brain, these seizures may influence learning and behavior, although to a lesser extent than in older rats. For these reasons, effective treatment to stop prolonged seizures, especially motor status epilepticus, should be promptly initiated.

The second question implies a clear differentiation between treatment of the first seizure in the acute setting and subsequent treatment to prevent the development of

recurrent seizures (ie, epilepsy). Epilepsy can be defined as the occurrence of two or more unprovoked seizures. The risk of subsequent seizures increases to 70% or more after two unprovoked episodes and does not change significantly after a third episode. Antiepileptic drugs can be used to stop acute seizures and to prevent recurrent seizures. However, there is no evidence that antiepileptic drugs alter the natural history of a seizure disorder.

Evaluation

Was the Event a Seizure?

Paroxysmal events may be subtle or quite frightening for patients, family members, or other incidental witnesses. On many occasions, the first challenge is differentiating between a true seizure and another type of event. Many disorders mimic epileptic seizures. Syncope, breath-holding attacks, tics, and night terror episodes are some examples. Careful description of events by a reliable person is of great value. Precipitating events, "warning" symptoms (auras), duration, semiology of seizure, and description of postictal period are fundamental aids in the characterization of an event. Considering the possibility this is not the first event is as important as identifying a true seizure from another paroxysmal event. With careful questioning, retrospective recognition of previous nonconvulsive or convulsive seizures is possible. Obtaining this information may change the approach because a child who has had at least two unprovoked seizures is considered epileptic. If this is the case, and depending on successful classification of the epilepsy syndrome, the decision to treat or not to treat may be less controversial. The risk of further seizures may outweigh the adverse effects of anticonvulsants.

Was the Seizure Provoked or Unprovoked?

Once diagnosis of a seizure is established, the next step is to determine the etiology. Intercurrent infections, trauma, intoxications, and febrile state, if present, preclude the diagnosis of an unprovoked episode. A detailed birth, neonatal, and general medical history should be obtained to assess a child's neurologic status. The neurologic examination may provide important clues in regard to the etiology of the seizure, especially when focal signs are discovered, suggesting a symptomatic cause.

What Tests Should Be Obtained?

A "laundry list" of laboratory studies should be avoided. Instead, thoughtful use of ancillary testing oriented toward each particular case is recommended. Serum or urine toxicology studies, are indicated in the event of a prolonged postictal state or when clinical symptoms or signs suggest intoxication. Complete blood cell count and basic chemistry panel should be obtained only under specific clinical circumstances. For example, a glucose level should be obtained in diabetic patients, and blood urea nitrogen/creatinine and basic electrolytes are of significance in patients with history of renal disease, vomiting, or diarrhea. A complete blood cell count should be obtained whenever an infectious process is suspected.

A lumbar puncture is indicated whenever meningeal signs are present or in very young children, in whom signs of meningeal irritation may be absent. This procedure also is recommended in the event of prolonged alteration of mental status not attributed to postictal state. Many physicians routinely perform computed tomographic (CT) scans before proceeding with a lumbar puncture, especially if there is suspicion of increased intracranial pressure. In the acute setting (ie, emergency rooms), a head CT scan is usually obtained. The current practice parameter recommends emergent neuroimaging in any child with postictal focal deficit not quickly resolving, or who has not returned to baseline within several hours after the seizure. Although CT scan abnormalities are associated with a higher recurrence risk, this study is not necessarily the best way to assess a patient with seizures.

Magnetic resonance imaging (MRI) of the brain provides the most detailed and helpful anatomic information. This test is strongly recommended after certain electroencephalogram (EEG) findings, such as focal slowing or abscence of electrographic patterns consistent with a benign epilepsy or primary generalized epilepsy. If a temporal lobe pathology is suspected, it is important to obtain thin imaging cuts through the temporal lobes. Thus, the MRI should not be obtained in the emergency room but as part of an outpatient comprehensive evaluation.

The EEG is extremely useful for identifying seizure type, aiding in proper classification, and assisting in predicting long-term prognosis. It is also helpful in recognizing encephalopathy, subclinical seizures, and toxic or abnormal metabolic states. In most cases, there is no reason to obtain an EEG in the emergency room, but it should be performed soon after the event. Indeed, postictal abnormalities have predictive value. This test, preferentially obtained within 7 to 10 days after a seizure, may reveal focal or lateralized abnormalities, including focal slowing and focal epileptiform discharges that may be absent later. If possible, EEGs should be obtained while the patient is awake and asleep, although we do not routinely sedate children. Hyperventilation and photic stimulation are also recommended, as they may increase the yield for abnormalities.

Risk Factors for Recurrence

Most children will not experience recurrence after a first unprovoked seizure. When seizures recur, they do so

within 6 months in one-half the cases. Still, identifying those at highest risk is fundamental. The approach to a child who is at high risk for recurrence should not be the same as for one with no risk factors. The information disclosed to anxious parents differs accordingly, monitoring visits are scheduled differently, and medical management may vary. The individualized approach is ideal.

Epidemiologic studies have revealed several factors that may predict seizure recurrence (Table 19-1). Etiology is the most important factor influencing long-term prognosis. The risk for recurrent seizures increases significantly when a patient has a prior neurologic abnormality such as a history of central nervous system infection, severe head trauma, or static encephalopathy. Being asleep at the time of the first seizure raises risk of recurrence by 50% or more. Also, recurrences tend to occur in the same sleep state as the initial event. An abnormal or epileptiform EEG and a history of prior complex febrile seizure are important determinants. The presence of Todd's paresis may be of marginal significance. A combination of risk factors may increase the chance for a seizure recurrence.

There is no conclusive evidence to show that the risk of recurrence is increased by the following factors: age of onset, seizure type, history of prior provoked seizure, duration of seizure, multiple seizures within 24 hours, family history of epilepsy, and gender.

Treatment

Treating a child who has had several seizures may not be as challenging as deciding how to best treat a patient who suffered a single episode, but then again this is one of the situations in which it is obvious that practicing medicine is an art.

There are no current therapeutic agents with a true antiepileptic effect. As a general rule, the decision regarding medical therapy should consider the risks of future seizure episodes versus the complications and potential adverse effects associated with chronic use of antiepileptic drugs.

TABLE 19-1. Risk Factors for Seizure Recurrences

At Risk	No Risk or Inconclusive
Remote symptomatic seizures	Age at onset
Mental retardation, cerebral palsy, Head trauma, CNS infection	History of prior provoked seizure
	Seizure type
Epileptiform EEG	Duration of seizure
Sleep state	Family history of epilepsy
Prior complex febrile seizures	Gender
More than one risk factor	

CNS = central nervous system; EEG = electroencephalogram.

Study findings support the fact that anticonvulsant therapy reduces the risk of seizure recurrence by approximately 50%. However, early treatment does not affect the development of epilepsy in the future. The epileptogenic process appears to continue, independently of the use of current antiepileptic drugs. Remission of seizures appears to be related more to the etiology of the seizures, the underlying syndrome, and other risk factors than to early therapeutic intervention. Specific benign self-limiting epilepsy syndromes of childhood (ie, Benign Rolandic Epilepsy) may not need chronic treatment unless seizures occur at frequent intervals.

Because of potential adverse effects associated with antiepileptic drugs, practitioners recommend deferring treatment until it is clear seizures will be recurrent. Because of the potential side effects of the current anticonvulsants, it is advisable to defer treatment until a second episode occurs If therapy is not initiated after the first episode, it is important to thoroughly discuss the decision with parents and the patient, when appropriate. Information should be provided to the patient and the family (Table 19-2) with tips that certainly will produce less day to day anxiety, avoid common precipitating factors, and offer immediate help to the person that may undergo another seizure Parents and the patient should receive all the information available regarding risks and benefits of recommended management options. Restrictions in activity and the possibility of physical injury in the event of recurrence also should be discussed. Despite the current lack of preventive antiepileptic drugs, it is important to recognize recurrence risk factors that would help distinguish different patient populations and their chances of developing epilepsy. In such patients, it may be appropriate to consider treating with antiepileptics. It is very useful and to instruct parents on the use of abortive anticonvulsants (rectal or sublingual as they are available in different countries) with direction on what to do if a seizure recurs.

TABLE 19-2. A Patient's Guide (Precaution and Prevention of Injuries)

No bathtub baths
No upper bunk bed sleeping
No scuba diving
No swimming unattended
No sleep deprivation (take naps before pajama parties, no waking up for breakfast, etc.)
Helmet (for horse riding, roller-skating, skateboarding, using bicycle, etc.)
No removable orthodontic devices
No oral piercing (tongue, lips)
Keep lights on when watching TV or using the computer
No alcohol
No energy drinks (ginseng and derivatives)

Adolescents: keep a card with name, telephone contacts and emergency medication (whenever sublingual meds are available) inside wallet

Future Research Goals

Based on animal research studies there is evidence that provide the family with instructions on use of rectal benzodiazepines to abort seizures produce changes in many brain functions. However, the significance of these changes is not clear and there is no proof that these alterations are always necessarily detrimental to the brain. Understanding the spectra of the induced changes as a function of age, sex and etiology is the necessary step to design effective treatments. Neuroprotection may be the answer to the controversy of the management of the first unprovoked seizure.

The ideal therapeutic agent should be one that could prevent the development of epilepsy, by protecting the brain tissue from the consequences of the epileptogenic process. There is limited evidence suggesting that some anticonvulsants may have a neuroprotective action. A neuroprotective agent should be capable of preventing neuronal injury or induce recovery of injured neurons, without any or only minimal side effects. If such an agent was available, there would be no doubt that every case of seizure should be treated. However, it is still unclear how to administer these drugs, at which doses, and for how long, to achieve a prophylactic effect. Although anticonvulsant drugs are extremely useful in stopping acute seizures and in many cases, in preventing recurrences, to date, their side effects profile as well as their yet unproven true antiepileptic effect, argue against their indiscriminate long term use after a first seizure. Future studies may identify new specific agents that can prevent the consequences of seizures in an age- and sex- specific fashion they recur.

Summary

Most children who experience a first unprovoked seizure, even status epilepticus, do not suffer recurrent unprovoked seizures. Thus, a single unprovoked seizure does not justify the use of daily antiepileptic drugs. Such agents reduce the incidence of seizure recurrence, but there is no evidence they alter the natural history of the seizure disorder. As the etiology of the seizure is the most important risk factor for recurrence, we do consider treating children with symptomatic seizures, especially if they have multiple risk factors for recurrence. Perhaps in the future, the approach will be simpler, when effective antiepileptic drugs with limited side effects become available.

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Practitioner and Patient Resources

Epilepsy Foundation of America (EFA)
Phone: 1-800-EFA-1000
http://www.epilepsyfoundation.org
The Epilepsy Foundation is a national organization that works for people affected by seizures through research, education, advocacy, and service. This volunteer organization is committed to the prevention and cure of epilepsy and a positive quality of life for everyone who lives with seizure disorders. The foundation's current strategic goals include broadening and strengthening of research, providing individuals and families with easy access to reliable information, and assuring access to appropriate medical care for those affected by seizures.

CHAPTER 20

STARING SPELLS

JOSEPH M. DOOLEY, MD

Staring spells are a frequent reason for referral to pediatricians and pediatric neurologists. Teachers often fear the presence of seizures and encourage parents to seek specialist advice for their child's episodes of inattention. As discussed in this chapter, these children seldom have epilepsy.

Differential Diagnosis

The differential diagnosis of staring spells is usually limited to the following conditions:

- Non-epileptic events
- Absence seizures
- Complex partial seizures

The initial goal is to distinguish epileptic from non-epileptic spells. This distinction can usually be established by determining the characteristics of a child's events. Children who respond to touch or tickle during an episode, do not have spells during play activities, and whose events are initially recognized by a teacher or health professional, are highly likely to have non-epileptic staring spells. In contrast children who have associated limb twitches, upward eye rolling or urinary incontinence are much more likely to have seizures. Overall about 20% of children who are referred to an epilepsy clinic do not have epilepsy. Among those referred for isolated staring spells, the number with non-epileptic events will be much higher. In a review of children who underwent video-EEG monitoring, Bye et al. found that more than one third of those with non-epileptic events had staring spells.

Staring owing to non-epileptic events is usually either due to inattention or distraction. The differential diagnosis should also include: ritualistic behavior, infantile gratification behavior (masturbation) and cognitive slowing caused by overtiredness or as an adverse effect of medication. Hindley et al. have shown that some episodes may also reflect parental anxiety or even fabrication of the events (Münchausen syndrome by proxy).

Non-epileptic Spells

Inattentive Staring Spells (Distraction/Daydreaming):

All children daydream. Daydreaming almost never occurs when a child is physically active, but is much more prevalent during periods of inactivity, while watching television or when a child finds activities boring. In contrast, seizures occur at any time and may interrupt play. Children who are daydreaming may "ignore" verbal stimulation, such as calling their names, or arm waving, but usually quickly respond to tactile stimulation, such as touching or tickling ("the tickle test"). Children with absence seizures or complex partial seizures almost never respond to the tickle test. When the history establishes that the staring spells never occur during play activities and that the events can be interrupted, no further investigations are necessary. If there is uncertainty regarding the response to these criteria, video-EEG recordings, which capture a spell, are usually diagnostic.

Those whose daydreaming leads to concern among their parents or educators are more likely to have confounding comorbid difficulties. Children with attention-deficit hyperactivity disorder-inattentive type (ADHD) spend more time off task and are therefore more likely to be referred. The DSM-IV-TR criteria for ADHD-inattentive type require at least a 6 month history of six or more of the following symptoms of inattention to a level that is disruptive and inappropriate for the child's developmental level:

1. Often does not give close attention to details or makes careless mistakes in schoolwork, work, or other activities.

2. Often has trouble keeping attention on tasks or play activities.
3. Often does not seem to listen when spoken to directly.
4. Often does not follow instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions).
5. Often has trouble organizing activities.
6. Often avoids, dislikes, or doesn't want to do things that take a lot of mental effort for a long period of time (such as schoolwork or homework).
7. Often loses things needed for tasks and activities (eg, toys, school assignments, pencils, books, or tools).
8. Is often easily distracted.
9. Is often forgetful in daily activities.

Many teachers and parents are skeptical about the presence of attention difficulties, without coexisting hyperactivity, and these patients may therefore be older when referred. It is important to rule out learning difficulties (LD), which may occur in conjunction with ADHD or independently and can also lead to difficulties maintaining attention during tasks that are particularly challenging.

Inattention may also be part of the spectrum of symptoms associated with fatigue or sleep disorders. For those whose parents report difficulty with sleep, it is valuable to keep a sleep diary to accurately establish the sleep pattern of children who present with staring.

Many children who have neither ADHD nor learning difficulties have staring spells, especially when they are bored. Not all teachers are blessed with an engaging style. Children may find the classroom tedious and therefore retreat into their own thoughts. As with all of the non-epileptic events, tactile stimulation will terminate these spells. Similar spells are seen in children who are worried or depressed. Traumatic events within the child's life, such as turmoil within the home or among friends, can lead to preoccupations and staring spells.

Intense concentration is not always a negative phenomenon and does not always reflect difficulties with concentrations and attention. Most of us retreat into our own thoughts when anticipating or remembering an important special occasion or event.

Non-epileptic seizures

Pseudoseizures or non-epileptic seizures can be clinically difficult to differentiate from epileptic seizures. To make the diagnosis the spells should be reproducibly induced and aborted by suggestion. Methods which have been used historically to provoke and terminate non-epileptic events have included suggestion accompanied by placing a tuning fork on the forehead and even infusing intravenous saline. One must be aware of ethical issues in inducing these events. Many of these children will have underlying psychopathology, such as depression and affective or personality disorders. In some, however, the events are a response to stress in an otherwise healthy child. These spells do not tend to have an associated aura but they may have accompanying automatisms. Carmant et al. found that they tend to happen less frequently than absence seizures and that they tend to last longer than seizures.

Obsessive Thoughts

Some children will appear to have staring spells as a result of obsessions. Between 13% and 66% of children with Tourette syndrome (TS) have obsessive thoughts. Patients with TS are particularly prone to staring spells as up to 50% also have comorbid ADHD. Children seldom spontaneously report obsessions but usually readily discuss them if given the opportunity.

Staring with Developmental Delay and Autism Spectrum Disorders

Children with developmental delay or other neurodevelopmental difficulties may have staring spells which are often accompanied by stereotypes, such as hand-flapping, rocking or other self-stimulatory behavior. It may prove more difficult to interrupt these children, but with effort their attention can usually be regained.

Gratification Behavior

A particularly challenging group of patients are female toddlers, between the age of 6 months and 3 years, whose parents report staring spells associated with rhythmic pelvic and trunk movements. These spells invariably occur while the child is sitting or lying and represent self-stimulation (masturbation). The diagnosis is easier to establish if the spells are videotaped and if the parents demonstrate that the spells can be interrupted. The term gratification behavior is preferable to masturbation, as many parents are distressed by this diagnosis.

Other nonepileptic events

Another group of children who are occasionally referred because of unusual staring spells are children with the Alice-in-Wonderland phenomenon. During these migraine-related events, children experience distortions of size or space. They may perceive that some items in their surroundings are either increased or decreased in size or distorted in shape. The children are aware that the event is a misperception but may appear to stare, as they are either scared or perplexed by the experience. The events occur in children who have a family history of migraine or who will subsequently develop more typical migraine headaches. The Alice-in-Wonderland events do not coincide with headache. It is important to make a

correct diagnosis, as these children require reassurance and do not need further evaluation.

A similar phenomenon that represents misperceptions of time and speed, rather than size and shape, has been called the rushes. Its characteristics and associations are similar to the Alice in Wonderland syndrome.

The hallmark of all these non-epileptic spells is that they can be interrupted by touch or tickle and that they do not interrupt otherwise interesting activities.

Epileptic Staring Spells

Seizures are discussed in Chapters 17–34. For children referred for staring spells, only complex partial and absence seizures need to be considered. Helpful clinical features that distinguish between complex partial and absence seizures are presented in Table 20-1.

Partial seizures are divided into simple partial seizures, where there is no alteration of alertness, and complex partial seizures, where consciousness is altered but not necessarily lost. Among the generalized seizures, only absence seizures present as staring spells. Absence is further subdivided into typical and atypical absence seizures. For those with typical absence, a further subdivision into a number of epilepsy syndromes, based on seizure and electroencephalogram (EEG) characteristics, allows more accurate prediction of the response to therapy and prognosis.

Typical Absence Seizures

Childhood Absence Epilepsy

Childhood absence epilepsy (CAE) seizure (or petit mal seizures) must be differentiated from other absence syndromes to develop appropriate management strategies (Table 20-2). The clinical features of childhood absence seizures are:

- Onset between ages 4 and 10 years
- Normal neurologic and developmental status
- Frequent brief absence seizures with abrupt and significantimpairment of consciousness
- EEG discharges of generalized spike-and-wave complexes at 3 Hz lasting 4 to 20 seconds.

  Question the diagnosis of CAE if there are any of the following factors:
- Other seizures, such as generalized tonic-clonic seizures (GTCS) or myoclonic seizures before or during the active stage of absences
- Eyelid or perioral myoclonia
- Mild or no impairment of consciousness during the 3 Hz discharges
- Brief EEG 3 Hz to 4 Hz spike-wave discharges of less than 4 seconds or multiple spikes (> 3)
- Visual (photic) or other sensory precipitation of clinical seizures

TABLE 20-1. Differentiation between Absence and Complex Partial Seizures

	Absence Seizures	Complex Partial Seizures
Duration	< 20 sec	> 1 min
Aura	Absent	Present
Postictal drowsiness	Absent	Present

Seizures in CAE are characterized by brief episodes of altered consciousness, with an abrupt onset and termination. Each attack usually lasts approximately 10 seconds, and patients may have up to 100 seizures per day. During the seizure, the child suddenly stops activity and stares ahead. When the seizure ends, previous activities are resumed as if nothing occurred and the child may even complete an interrupted word. Patients are usually unaware of the seizure.

CAE occurs more frequently in girls (60 to 70%) and apositive family history exists in 15 to 44%. In pediatric studies of twins with CAE, 84% of their monozygotic twins had 3 Hz spike-wave discharges on EEG, and typical absence seizures were found in 75%.

The incidence rate for CAE in children younger than15 years of age is 6/100,000 to 8/100,000. Community based studies have determined the prevalence of CAE in children with epilepsy who were younger than 16 years of age to be 10 to 12%.

CAE is primary or idiopathic and therefore children donot require neuroimaging studies. The most prominent precipitant is hyperventilation, and the diagnosis should be questioned if a seizure cannot be provoked by 3 minutes of hyperventilation. Therefore, when absence seizures are suspected, the child should undertake 3 minutes of hyperventilation.

This is most easily accomplished by asking the child to blow a tissue or blow and count each breath. The alteration in consciousness may be subtle and the procedure should be videotaped for documentation of clinical features. If a seizure is suspected during this procedure, the physician should say a word, such as a color, which the child is then asked to repeat upon termination of the spell. Those who have had a seizure will not recount the word. The most common error made in reaching a diagnosis is failing to conduct a sufficiently long trial of hyperventilation. Children (and physicians to some degree) require constant encouragement to complete the full 3 minutes, which should be timed classified as CAE. Similarly, children whose epilepsy begins with GTCS do not have CAE, although infrequent GTCS may occur in adolescence or later.

CAE, as defined above, usually has an excellent prognosis, with seizures eventually disappearing in more than 90% of patients. If all absences, which begin in childhood, are grouped, the prognosis is less predictable. In our population, we found some children subsequently

TABLE 20-2. Major Absence Seizure Types

	Childhood Absence Epilepsy	Juvenile Absence Epilepsy	Myoclonic Absence Epilepsy
Onset age	4–10 yr	10–17 yr	1–12 yr
Seizure frequency	100/d	Morning	Several/d
Sex	Girls > Boys	Girls = Boys	Boys > Girls
Prognosis	Excellent	Need ongoing treatment	Persist in > 50%

developed juvenile myoclonic epilepsy. When strict criteria are used for CAE, it was found that GTCS developed in 16% of those with onset of typical absence before 9 years of age compared with 44% for those with onset between 9 and 10 years. In addition, when GTCS did occur they tended to be infrequent and easily treated. Absence seizures in CAE respond to ethosuximide, valproate, or lamotrigine.

Myoclonic Absences

Myoclonic absences are rare. They occur in boys twice as often as in girls and have a mean age of onset of 7 years (range 9 months to 12 years). The seizures have a sudden onset and ending and usually occur soon after awakening. As with the seizures associated with CAE, they can be precipitated by hyperventilation. Seizure duration ranges from less than 10 seconds to more than 2 minutes, and the seizure frequency is usually high. Alteration of consciousness may be mild (allowing the child to continue normal activities) or severe. The myoclonus is rhythmic and usually involves the shoulders, arms, and head. The arms may be tonically elevated, and they may have perioral myoclonus, although eyelid myoclonus is rare. The EEG shows typical bilateral 3 Hz spike-wave or polyspike activity.

Associated GTCS and atonic seizures are frequent, and the seizures respond poorly to medications, with approximately 50% of children still having seizures at 10-year follow-up. The medications of choice for this group are valproate and lamotrigine.

Juvenile Absence Epilepsy

Juvenile absence epilepsy usually begins at 12 to 13 years of age. The absences are less frequent than in CAE, but patients are more likely to have GTCS, and approximately one-third also have mild myoclonic jerks. EEG findings are similar to those observed in CAE, but polyspikes are more common.

Juvenile Myoclonic Epilepsy of Janz

Juvenile myoclonic epilepsy of Janz occurs in neurologically normal adolescents who present with early morning GTCS and myoclonic jerks, usually involving the shoulders and upper arms. About one-third of patients with juvenile myoclonic epilepsy have absence seizures, which may be associated with milder impairment of consciousness. The EEG usually shows frequent polyspike discharges.

Atypical Absence Seizures

Atypical absences have a less abrupt onset and ending and are often associated with changes in tone. The seizures usually occur in children with neurologic and developmental deficits and are frequently seen as part of the spectrum of the Lennox-Gastaut syndrome. Seizure frequency often increases with drowsiness and varies from a few a day to almost continuous. The EEG shows generalized spike and- wave discharge at less than 3 Hz.

Atonic atypical absences may also be seen with GTCS and myoclonic seizures in myoclonic astatic epilepsy, and atypical absences may occur as the only type of seizure in patients with continuous spike-waves in slow sleep. For these patients, valproate and lamotrigine are usually the antiepileptic drugs (AEDs) of choice.

Complex Partial Seizures

Complex partial seizures (CPS) may be preceded by an aura (ie, a simple partial seizure) or may manifest as an alteration of consciousness from the onset. Staring spells associated with CPS usually have a less abrupt onset than those associated with absence. CPS almost always last longer than absence seizures, typically 1 to 2 minutes, although longer seizures can occur. The automatisms that occur in CPS are often more complex than the eyelid fluttering or lip smacking seen in absences. Typical automatisms in CPS include fumbling with clothes, repetitive swallowing or chewing, and purposeless hand or body movements, although lip smacking can occur. As the seizure ends, the child is confused or irritated and may need to sleep. When violence occurs in the context of CPS, it is random and is not meaningfully directed at individuals or objects. CPS may begin at any age and are more likely to reflect underlying structural brain pathology. The distinctions between absence seizures and CPS are outlined in Table 20-1.

Frontal Lobe Absence Seizures

Partial seizures originating in the front polar or medial surface of the frontal lobe may produce frontal lobe absence-type seizures, which appear similar to absence seizures with altered consciousness but involve minimal motor activity. Frontal lobe seizures may be associated with automatisms, such as pelvic thrusting. Patients may

have a complete loss of consciousness or their responses may be slowed and inappropriate. These seizures can be brief or can last hours to days. Postictally, patients may not remember the event, although they may have appeared alert during the seizure. During a seizure, the EEG shows disorganized generalized spikewave activity.

Evaluation

Rosenow et al. studied a group of children and found that 3 questions were particularly helpful in distinguishing nonepileptic events from seizures (Figure 20-1). Nonepileptic spells do not occur during play, the children respond to touch during an episode and the initial report of the events is by a teacher or health professional rather than a parent. Combining an affirmative response to 2 of these questions was associated with a specificity of 0.94–1.0 with a sensitivity of 0.22 to 0.31. When the tickle test was the sole question the specificity was 0.87 with a sensitivity of 0.56.

In contrast seizures were much more likely if the child had twitching of the arms or legs, was incontinent of urine or had upward deviation of the eyes. The sensitivity of the questions is presented in Figure 20-2.

When a clinical diagnosis is not clear video-EEG monitoring can be very helpful. Approximately 10% of admissions to epilepsy monitoring units are for children with staring spells, who are shown not to have seizures. Interictal EEG discharges are not helpful and may be misleading. Carmant found that only 3 of 8 children with psychogenic seizures had normal interictal EEGs. The remaining 5 children had epileptic discharges with or without slowing of the background activity. Importantly none had epileptic discharges on video-EEG during the staring spells. Prior to monitoring, almost half of these children were thought to have seizures.

For children whose spells are non-epileptic, attention should be paid to possible comorbid conditions, such as ADHD, LD, psychiatric illness, sleep disorder or medication induced drowsiness.

All children with suspected seizures should have an EEG. For those with suspected absence seizures, hyperventilation should be part of the protocol. When CPS are suspected, the child should be sleep deprived on the evening before the EEG. Sleep deprivation may help provoke a seizure and obtaining an EEG in awake, drowsy, and stage II sleep states increases the chance of recording a focal epileptic discharge. The yield from EEG may also be enhanced when the test is performed in the early morning.

Routine EEG may fail to record an epileptic discharge, although this is less likely with CAE because of the high frequency of the seizures. When routine EEG is uninformative, as noted above, prolonged video EEG monitoring may be helpful.

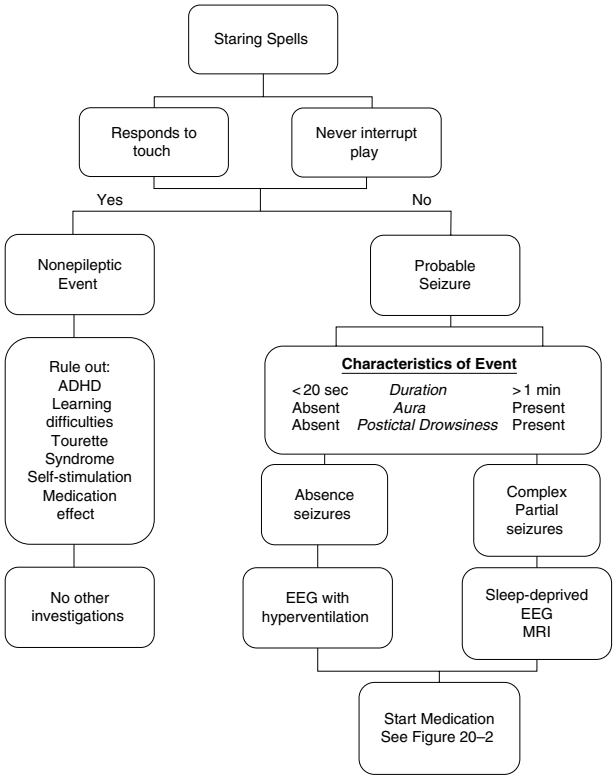


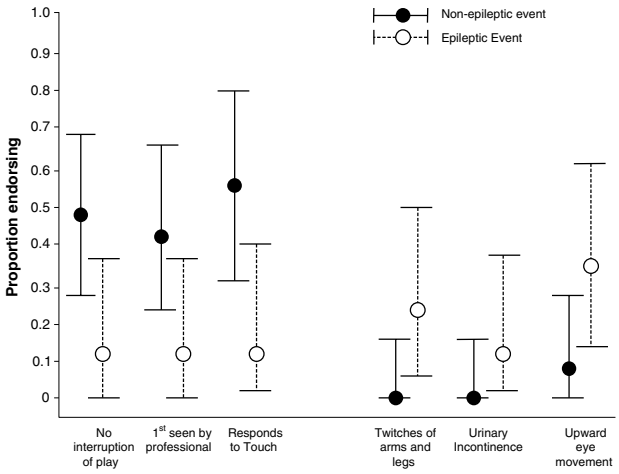
FIGURE 20-1. Approach to staring spells. ADHD = attention-deficit hyperactivity disorder; EEG = electroencephalogram; MRI = magnetic resonance imaging.

Because CAE is idiopathic, children do not require neuroimaging studies. Atypical absences are secondary or symptomatic and require further investigation. For those with CPS, magnetic resonance imaging should be performed, as underlying pathology may be detected, especially if there are abnormalities on the neurological examination or if the seizures all appear to originate from the same focus.

Management

Children with daydreaming spells almost never require intervention. Those with ADHD or LD may require treatment with medication or classroom modifications. For those who have comorbid disorders, such as Tourette's syndrome, additional interventions may be required. For example, if obsessive thoughts are problematic, therapy with a selective serotonin reuptake inhibitor may be beneficial.

When the staring is thought to reflect either psychiatric illness or distressing life events, referral to the appropriate mental health services may be warranted. When the spells are thought to be secondary to medication related adverse



Modified from: Rosenow F, Wylie E, Kotagal P, Mascha E, Wolgamuth BR, Hamer H. Staring Spells in children: descriptive features distinguishing epileptic and nonepileptic events. Jpediatr 1998;133:660–663.

FIGURE 20-2. Sensitivity of questions in differentiating non-epileptic and epileptic events.

effects, monitoring the serum drug level can be very helpful.

When epilepsy is confirmed, the child should be treated with an antiepileptic drug (AED). Figure 20-2 outlines the spectrum of activity of most of the commonly used AEDs. The most effective medications for absence seizures are ethosuximide, sodium valproate, and lamotrigine. Benzodiazepines, such as clobazam, may also be helpful. Differentiating absence seizures from CPS is essential, as some AEDs, such as carbamazepine, vigabatrin, and tiagabine, may be used for treating CPS but may aggravate absence seizures.

Absence Seizures

In our population of children with absence seizures, initial drug treatment was successful in 52 (60%) of 86 patients, with control less likely if a patient also had GTCS or myoclonic seizures. Terminal remission was more likely if the initial drug was successful than if it had failed (69% vs. 41%; $p < .02$), and children whose initial drug treatment had failed were more likely to have JME and to develop intractable epilepsy. Although sodium valproate was more likely to be effective than other AEDs, many physicians prefer to start with ethosuximide when treating CAE, as it is often better tolerated. Valproate is, however, a better choice for treating other absence syndromes and atypical absence seizures. When ethosuximide is prescribed, the usual starting dose is 10 to 15 mg/kg/d. The dose can be given once daily but is usually better tolerated when given twice daily. The dose is increased up to about 40 mg/kg/d depending on seizure control and side effects.

Ethosuximide is available as large 250 mg capsules or as a suspension of 250 mg/5 mL. Commonly encountered adverse effects include gastrointestinal upset, drowsiness, hiccups, nightmares, and behavior changes. Side effects are seldom severe. Ethosuximide is not effective against GTCS and, therefore, should not be prescribed for children who have additional seizure types.

Valproate is an excellent AED, with effectiveness against a broad spectrum of seizures (see Figure 20-2). An effective starting dose is 20 mg/kg/d divided twice daily. In general, compliance is better with twice than three times daily dosing. The dose can be increased according to seizure response but can often be maintained at this starting dose. As the dose of valproate is increased, the incidence of tremor increases. Other side effects that are less related to dose (or blood levels) are nausea, weight gain, alopecia, thrombocytopenia, hepatotoxicity, pancreatitis, and ovarian cysts. The concern over fatal hepatotoxicity is most significant for those under 2 years of age and with metabolic disorders. Valproate is available as 250 mg tablets and as enteric-coated 125, 250, and 500 mg tablets. It is also available as 125 mg sprinkle tablets and as a suspension of 250 mg/5 mL.

Lamotrigine is also effective for the treatment of absence seizures. The major adverse effect associated with lamotrigine is skin hypersensitivity, which can occur in up to 4% of children. This risk is significantly lowered if the initial dose is low and the rate of titration over the first 8 weeks is slow. This results in a rather complicated titration schedule. For children with absence seizures, delaying the achievement of an effective dose for up to 4 to 8 weeks is often unacceptable. For patients on no other AED, the starting dose is 0.2 mg/kg/d administered once or twice daily. If patients are also taking an enzyme-inducing AED (eg, carbamazepine), start with 0.3 mg/kg/d for the first 2 weeks. The dose can then be doubled for weeks 3 and 4. Thereafter, the dose can be increased at weekly intervals by 1 mg/kg/d up to as much as 15 mg/kg/d. For patients on valproate, the dose should be approximately halved. Lamotrigine is available as chewable or dispersible 2 and 5 mg tablets and as 25, 100, and 150 mg regular tablets. Other formulations are available in some countries. Patients who do not respond to their first AED may do well on a combination of valproate and either ethosuximide or lamotrigine. The role of newer AEDs, such as levetiracetam, in treating absence seizures has not yet been established.

Children who remain seizure-free for 1 year and who do not have a seizure induced by 3 minutes of hyperventilation might be weaned off their AED over approximately a 1-month period.

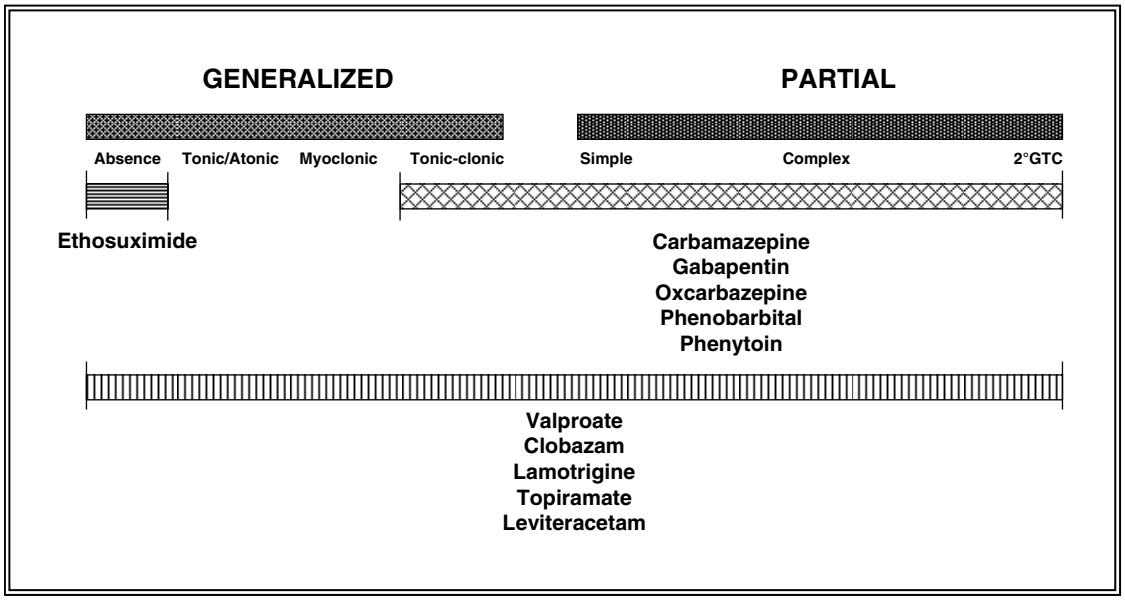


FIGURE 20-3. Activity spectrum of antiepileptic drugs.

Complex Partial Seizures

There is a wider choice of AEDs available for children with CPS (see Figure 20-3). Most pediatric neurologists choose carbamazepine as their drug of first choice, although oxcarbazepine may have similar effectiveness without the potential for hepatotoxicity and hematotoxicity. In addition, the risk of hypersensitivity skin reaction is lower with oxcarbazepine. Carbamazepine induces the hepatic enzymes responsible for its metabolism. The starting dose is usually 5 mg/kg/d divided twice daily. The dose should be increased at 5-day intervals to achieve a dose of around 15 to 20 mg/kg/d over 10 to 14 days. Further increases should be clinically determined by seizure control and adverse effects. Common side effects include drowsiness, dizziness, diplopia, and lethargy. It is available as 100 and 200 mg "chewtabs," a suspension of 100 mg/5 mL, 200 mg regular tablets, and 200 and 400 mg controlled-release tablets. Carbamazepine does not appear to be more effective than other AEDs in controlling CPS. The choice of medication is, therefore, primarily based on the potential for adverse effects.

Summary

The management of children with staring spells seldom proves difficult when approached in an organized fashion. Spells that can be interrupted by touch or tickling ("touch test") or that only occur in relatively "boring," less-stimulating circumstances are almost always due to daydreaming or inattention.

Children whose staring spells interrupt activities and are not easily terminated are more likely to have seizures. Childhood absence seizures can be precipitated by 3 minutes of hyperventilation, last less than 20 seconds, and are abrupt in onset and termination. Complex partial seizures may be preceded by an aura, last at least 1 minute, and are usually followed by a postictal phase of drowsiness or irritability.

The appropriate treatment of seizures requires this differentiation to allow a rational choice of medications. Children whose seizures fail to respond to the first AED probably require referral to a pediatric epileptologist.

In general if unsure whether the child has seizures or non-epileptic events, it is better to wait and withhold medication until a definitive diagnosis is made. For these children a referral for prolonged video-EEG monitoring is appropriate.

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Practitioner and Patient Resources

Epilepsy Foundation of America
http://www.epilepsyfoundation.org
The Epilepsy Foundation is the national organization that works for people affected by seizures through research, education, advocacy, and service. This organization of volunteers is committed to the prevention and cure of epilepsy and a positive quality of life for everyone who lives with seizure disorders. Its current strategic goals include broadening and strengthening of research, providing individuals and families with easy access to reliable information, and ensuring access to appropriate medical care for those affected by seizures.

Epilepsy Action UK
http://www.epilepsy.org.uk
Epilepsy Action is the largest member-led epilepsy organization in Britain, acting as the voice for the United Kingdom's estimated 440,000 people with epilepsy, as well as their friends, families, health professionals, and the many other people on whose lives the condition has an impact. As well as campaigning to improve epilepsy services and raise awareness of the condition, the organization offers assistance to people in a number of ways, including a national network of branches, accredited volunteers, regular regional conferences, and free phone and e-mail helplines.

Epilepsy Canada
http://www.epilepsy.ca
Epilepsy Canada is the only national nonprofit organization whose mission is to enhance the quality of life for people affected by epilepsy through promotion and support of research and facilitation of education and awareness initiatives that build understanding and acceptance of epilepsy. The Web site has both English and French versions.

American Epilepsy Society

http://www.aesnet.org
The American Epilepsy Society promotes research and education for professionals dedicated to the prevention, treatment and cure of epilepsy. Membership in the Society is made up of clinicians and researchers investigating basic and clinical aspects of epilepsy, and other health-care professionals interested in seizure disorders.

CHAPTER 21

PARTIAL SEIZURES

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Partial seizures are characterized by both clinical and electroencephalographic (EEG) features suggesting a localized or focal seizure origin within one cerebral hemisphere. Because the symptoms associated with these seizures as they begin and spread through the brain can vary widely, patients may report diverse descriptions of these events. Furthermore, symptoms may change as the brain matures, as children move through the neonatal period to infancy and then childhood.

In 1981, the revised International Classification of Epileptic Seizures (ICES) categorized partial seizures according to whether consciousness was preserved and according to associated motor symptoms. Simple partial seizures represent those with preservation of awareness, whereas complex partial seizures are characterized by altered awareness. Secondary generalization occurs when either partial seizure type progresses to generalized convulsions and loss of consciousness.

Correctly diagnosing alteration of awareness has been shown to be very challenging, especially in infants and young children. Furthermore, during relatively rapid secondary generalization, premonitory symptoms may be completely overlooked. This classification system is further challenged by mixed manifestations of focal EEG abnormalities associated with what seems to be generalized seizure symptomatology; infants may also show generalized EEG abnormalities such as hypsarrhythmia, while partial clinical symptoms clearly prevail. Thus, the classification system is somewhat imperfect.

In the 1989 classification of epilepsies and epileptic seizures, epilepsy syndromes were separated into localization related and generalized disorders. However, a variety of conditions, variably described as focal or generalized epilepsies, have shown diffuse hemispheric abnormalities, multifocal abnormalities, or bilaterally symmetrical localized abnormalities. For this reason, the International League Against Epilepsy Commission Task Force on Classification and Terminology is currently proposing a new diagnostic scheme for people with epileptic seizures and with epilepsy.

It will take time for this proposal to be accepted by all who work in the field, but an understanding of the classification is necessary. The diagnostic scheme is divided into five parts or axes. It is organized to help facilitate a logical clinical approach to the development of hypotheses necessary to determine the diagnostic studies and possible therapeutic strategies for the individual patient.

Table 21-1 shows the proposed five axes. Descriptive terms will be used to describe the seizures as ictal events believed to represent a unique pathophysiologic mechanism and anatomic substrate. It may or may not be possible to classify the epilepsy syndrome initially or during the course of the patient's epileptic disorder, as it represents a complex of signs and symptoms that define a unique epilepsy condition and must involve more than just the seizure type. This new proposal will certainly undergo some revisions. Seizure types have been divided into self-limited seizures and continuous seizures and then further divided into generalized seizures and focal seizures. Just as with all new proposals, the system seems complicated for now, but a more simplified

TABLE 21-1. ILAE Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy

Axis 1	Ictal phenomena
Axis 2	Seizure type
Axis 3	Syndrome (may not always apply)
Axis 4	Etiology (idiopathic, symptomatic, probably symptomatic [previously cryptogenic])
Axis 5	Impairment

ILAE = International League Against Epilepsy.

version will likely be constructed for teaching purposes and to provide primary-care physicians with more detailed information for those with a special interest in epilepsy, including epidemiologic studies, clinical drug trials, presurgical evaluation, basic research, and genetic characterizations.

The title of this chapter, then, could well be "Focal Seizures and Related Epilepsies" as the new classification evolves. Using the existing classification, partial seizures account for a substantial proportion of childhood epilepsies, estimated to be approximately 20 to 40% of all seizure types. As neonatal seizures and those in young infants are better classified, these numbers may rise. Partial seizures usually present as a single seizure type, but they may also occur in patients with mixed seizures, so generalized and partial seizures may coexist in certain epilepsy syndromes. As noted above, the clinical manifestations of partial seizures in childhood change with maturation of the brain. However, most older children have one or a few well-defined seizure types, and changing behavior during various seizures is highly unlikely.

Simple Partial Seizures

Simple partial seizures account for approximately 10% of childhood epilepsy. The preservation of awareness and intact recall are required to diagnose this type of seizure. Obviously, young children cannot do this reporting, and those whose seizure patterns evolve from simple to more complex may be amnestic for the initial events. Preservation of consciousness suggests that the seizures are relatively localized in a specific region of the cerebral cortex without spreading to those parts of the brain associated with awareness or organization of consciousness. The localized discharge may, however, spread to the adjacent cortical regions, with clinical symptoms as described for the jacksonian march along the primary motor cortex, directly accessing the motor pathways (secondary generalization) or propagating to the limbic circuits.

Parietal and Occipital Lobe Seizures

Children aged 5 to 10 years occasionally report alterations of somatosensory and visual sensations. Paresthesias may precede motor seizures, whereas ictal pain and temperature disturbances are less common. Visual symptoms are caused by disturbances of the occipital and temporooccipital cortex and may present as positive (eg, light flashes, colors) or negative (eg, scotomas, field defects) phenomena. Complex visual phenomenology, such as hallucinations, is relatively uncommon. Epileptic aphasia implies involvement of the language cortex in the dominant cerebral hemisphere; epileptic aphemia (pure speech arrest) has also been described.

Electroencephalogram

Routine EEG abnormalities are identified in approximately one-half of simple partial seizure disorders but are detected in 80 to 90% of patients through multiple recordings. The spectrum of interictal abnormality is variable, ranging from occasional sharp transients in drowsiness or sleep to frequent, repetitive discharges. Recordings made during periods of sleep deprivation and long-term video-EEG monitoring increase the incidence of EEG abnormality.

Clear ictal seizure patterns are observed in most partial epileptic events, but precise anatomic localization may be difficult. EEG correlates of simple partial seizures are less commonly observed because of the smaller amount of involved cortex. Seizure discharges may regionalize to the affected hemisphere or appear at homologous contralateral sites. Localized postictal slowing is a useful marker of seizure origin.

Partial Seizures

Two idiopathic partial epilepsy syndromes, benign childhood epilepsy with centrotemporal spikes (BECTS) and benign childhood epilepsy with occipital paroxysms, are recognized clinical entities and display diagnostic EEG patterns. Both syndromes present in the first decade of life in neurologically normal children.

BECTS

BECTS is the single most common partial epilepsy syndrome in childhood. It typically occurs within hours of falling asleep and is characterized by sensorimotor symptoms involving the face and oropharynx and, occasionally, the limbs. BECTS is a syndrome of brief, simple, partial hemifacial motor seizures, frequently associated with somatosensory symptoms with a tendency to evolve into generalized tonic-clonic seizures. Up to 25% of patients exhibit secondary generalized seizures. The EEG hallmark of the syndrome is the centrotemporal spike focus with a horizontal dipole overlying perirolandic cortex. Application of closely spaced electrodes reveals suprasylvian seizure origin within the facial and pharyngeal cortical homunculus. The onset of seizures in children with rolandic seizures (BECTS) peaks between 5 and 9 years of age and the age of last seizures between 8 and 12 years. Nearly all patients enter remission by 16 years of age. A number of atypical epilepsy forms may be related to BECTS, and a diagnosis must be questioned when children are not neurologically normal, have multiple recurrent seizures despite treatment, or demonstrate neurologic deterioration. Atypical features require reevaluation of the patient.

Focal spikes and sharp waves with predominantly centrotemporal localization are the EEG hallmark of BECTS. This EEG trait, but not BECTS itself, has been reported to follow an autosomal-dominant mode of inheritance with incomplete penetrance and age dependency. Thus, the EEG may serve as a neurobiologic marker. Although linkage studies in several families have been negative, one report links centrotemporal spikes to chromosome 15q14 and a possible involvement of an acetylcholine receptor subunit gene. Most likely, pedigrees with BECTS are genetically heterogeneous.

Benign Childhood Epilepsy with Occipital Paroxysms

Benign childhood epilepsy with occipital paroxysms accounts for 4.3% of epilepsy before age 12 years. It typically presents in the latter part of the first decade with simple or complex visual hallucinations or visual distortions, such as micropsia, metamorphopsia, palinopsia, amaurosis, or hemianopsia (Gastaut type). The EEG characteristically reveals occipital discharges on eyelid closure and disappearance of these discharges upon eye opening. The long-term prognosis is favorable, with remission in most patients by the end of the second decade. An association with migraine is well recognized in the juvenile-onset variety.

An early onset variant (Panayiotopoulos syndrome) is characterized by severe, protracted symptoms, including vomiting, head and eye version, and generalized convulsions or hemiconvulsions. Rare cases of spread of the occipital discharge to the ipsilateral temporal lobe leading to nonconvulsive status epilepticus have been reported. A few patients experience partial seizures as adults.

Idiopathic occipital seizures induced by photic stimulation and other forms of reflex occipital epilepsy are exceedingly rare in childhood. An unusual form of occipital epilepsy has also been described in patients with celiac disease and occipital calcifications.

Complex Partial Seizures

Complex partial seizures producing affective, cognitive, and automatic disturbances have long attracted the attention of neurologists. The association of complex partial seizures with temporolimbic activation has popularized such terms as "temporal lobe epilepsy" and "psychomotor attacks"; however, seizures may arise in other lobes as well. The ICES has, however, discarded these terms in favor of a localization-based, etiologic system of classification.

Clinical and EEG Features

The clinical manifestations of complex partial seizures are diverse. Auras similar to those adults describe are rarely reported by children, who are less able to understand the significance of internal psychic phenomena. Children who pause or stare at seizure onset may be experiencing auras that are ignored. Ictal impairment of consciousness is particularly difficult to assess in children and but must be surmised in infants without conclusive proof.

Automatisms are a more reliable manifestation of complex partial seizures in childhood, but their expression is maturationally determined. Oroalimentary movements, such as sucking and simple repetitive gestures, are seen in infants. Increasingly complex automatisms, including stereotypic motor behaviors and psychosensory phenomena ("déja vu" or complex hallucinations) are rarely described before the latter part of the first decade.

Secondary motor generalization is particularly common in young patients with complex partial seizures, especially in infants, in whom motor spread may be so rapid that seizure onset cannot be detected or localized. Spread of seizure activity to the motor cortex is less consistent in older children and adolescents, but brain-damaged patients may experience secondary generalization well into adulthood.

Interictal spiking is noted in approximately one-half the patients. Sleep is an important activator, and a few patients activate with hyperventilation. Ictal patterns may demonstrate complex evolution into generalized features. The EEG in children with complex partial seizures may contain localized spikes, rhythmic sharp waves, or electrodecremental flattening. Observable changes may also be absent on scalp recording in patients with deep foci. Video EEG capture of seizures is especially useful and occasionally is the only way to document clinical and EEG correlates.

Neuroimaging

Magnetic resonance imaging (MRI) is essential for evaluating patients with partial seizures. By virtue of its high specificity and sensitivity, the MRI evaluation can correctly identify the pathologic substrate of many developmental disorders, including dysplastic lesions. It can detect pathologic abnormalities in approximately 80% of children with intractable partial seizures. One-third of children and adolescents with partial epilepsy and negative computed tomographic (CT) findings will have lesions detected by MRI.

MRI reveals a higher incidence of hippocampal sclerosis (HS) in young patients with partial seizures of temporal lobe origin than formerly believed. In one study of 53 children with temporolimbic epilepsy undergoing detailed MRI investigations, 30 had either HS or regions of abnormal signal in the absence of a mass lesion. Hippocampal volume loss can also be identified. A developmentally delayed infant with a normal MRI reportedly developed unilateral signal increase in the hippocampus within 24 hours of status epilepticus; cortical dysgenesis was ultimately documented

after temporal lobectomy. Repeat imaging is recommended to detect new lesions or better characterize them in the more mature brain. Progression of neurologic symptomatology or medical intractability mandates repeat MRI. HS is linked to the appearance of seizures and is almost never an incidental finding.

Medical Therapy and Prognosis

Antiepileptic drugs commonly used for treating epilepsy are shown in Figure 21-1. Carbamazepine, phenytoin, primidone, phenobarbital, and, more recently, sodium valproate are first-line therapies in the treatment of partial seizures. All display a similar efficacy; major differences have to do with their adverse-effect profiles. Carbamazepine is widely used as the first agent in untreated patients. Phenobarbital and primidone are more poorly tolerated, because of excess sedation, mental slowing, and behavioral disturbances that frequently include hyperactivity and irritability, especially in young children. Several new antiepileptic drugs (AEDs) are now approved for the treatment of partial seizures in adults. These include felbamate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine, and zonisamide. Although all are available in the United States, only some have a pharmaceutic preparation acceptable for use in young children. Vigabatrin, a drug approved in many other countries, including Canada, has not been approved for use in the United States because of adverse effects, including retinal toxicity. These drugs are reviewed in detail in Chapter 34, "Current Pharmacotherapy for Pediatric Seizures and Epilepsy."

The seizures of a substantial proportion of adult patients with partial epilepsy can be adequately controlled by a single first-line AED. In the U.S. Veterans Administration (VA) Cooperative study, 44% of patients treated with carbamazepine became seizure-free for at least 12 months, compared with 32%, 22%, and 18% for phenytoin, phenobarbital, and primidone, respectively. Other studies from the United Kingdom show similar efficacy results for these drugs and valproate in the treatment of partial and generalized convulsive seizures in children. Patients who do not respond to first-line therapy are successively less likely to achieve control of their seizures through drugs administered singly or in combination. Thus, the addition or substitution of a second drug benefits only a small proportion of patients, and very few drug-resistant patients ever become completely seizure-free. The unsatisfactory nature of the multidrug regimens suggests that reduction to monotherapy is desirable in most cases and reduces exposure to adverse effects and drug interactions. The total drug burden is dependent on the adverse effects from each drug, especially as they are pushed to higher dosages, and additional concomitant neurotoxicity resulting from pharmacodynamic interactions.

Patients who have simple and complex partial seizures have a mixed prognosis. Approximately one-half enter into early sustained remission, whereas one-half remain medically refractory and often experience psychosocial and neurobehavioral deterioration. Seizure persistence is particularly vexing during adolescence, when it is associated with long-term disability and diminished quality of life. Noncompliance is a problem for adolescents who are striving for independence. This noncompliance is associated with failure not only to take the prescribed medication but also to achieve control of sleep and lifestyle.

Biologic predictors of partial seizure persistence can be established early through careful history and the physical, EEG, and neuroimaging examinations. The probability of having persistent seizures is increased by several factors. High seizure frequency in the form of daily or weekly episodes is a major predictor of long-term intractability, and clustering of seizures further increases the risk. Early seizure onset, particularly in infancy, is associated with high rates of seizure persistence. Infantile hemiconvulsive status epilepticus is specifically linked to later temporal lobe epilepsy. Generalized motor convulsions in patients with partial nonmotor seizures are an additional risk, regardless of whether the convulsions are frequent or infrequent events.

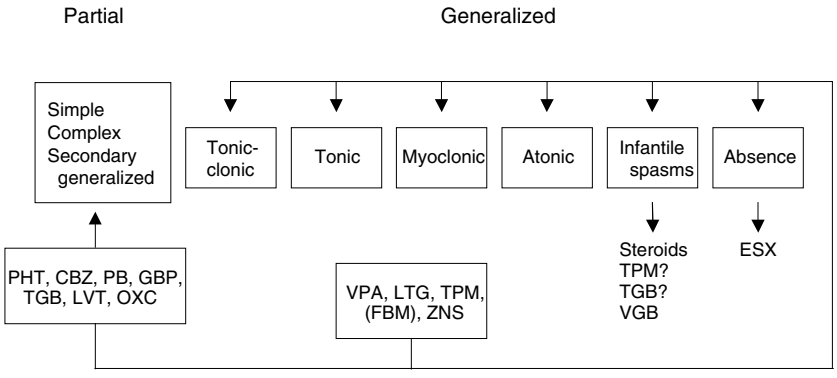

FIGURE 21-1. Antiepileptic drugs used for partial and generalized epilepsies. CBZ = carbamazepine; ESX = ethosuxamide; (FBM) = felbamate–with reservation; GBP = gabapentin; LTG = lamotrigine; LVT = levetiracetam; OXC = oxcarbamazepine; PB = phenobarbital; PHT = phenytoin; TGB = tiagabine; TPM = topiramate; VPA = valproate; ZNS = zonisamide.

Patients with organic brain damage are less likely to outgrow the seizure disorders in later life. Thus, an abnormal neurologic examination or a cognitive deficit carries a greater risk of developing epilepsy and a reduced chance of ultimate remission. As a rule, the more severe the damage, the greater the likelihood the seizures will be intractable. Nevertheless, several small studies have demonstrated that up to 50% of multihandicapped patients successfully reduce or discontinue medication when seizures are controlled for many years.

The exact choice of an agent to treat a child with partial epilepsy with or without secondary generalization remains unclear, as no medication is 100% efficacious for all children. Similarly, all have adverse effects. The first question is whether the child requires chronic AED treatment. Most clinicians do not initiate treatment after the first seizure, especially if it is part of a benign epilepsy syndrome, such as BECTS. If the patient has multiple seizures or multiple risk factors for seizure recurrence, AED treatment is usually started. The balance between seizure control and lack of adverse effects will determine the drug of choice for each child.

Several errors can be avoided by carefully establishing the diagnosis of the epilepsy syndrome before treating what seem to be partial seizures. For those with generalized epilepsy, such as Lennox-Gastaut syndrome, wherein partial seizures may coexist, AEDs such as phenytoin, carbamazepine, gabapentin, and oxcarbazepine may actually increase certain types of seizures, such as absence or myoclonic events. Phenobarbital and other sedative medications may exacerbate epilepsy in general because of chronic drowsiness. Carbamazepine has long been one of the preferred AEDs for treating children with partial seizures because of its relative safety and experience. Whether one of the new AEDs will reveal a better profile is unknown. However, studies of resistant partial epilepsy in both children and adults have shown that a substantial proportion of patients benefit from newer AEDs if they do not respond to such agents as carbamazepine, phenytoin, and primidone. Comorbid conditions, including behavioral disturbances or fear of producing them, will frequently determine the drug of choice for the individual child. Children with coexisting encephalopathy and multiple handicaps frequently show a higher incidence of adverse effects to AEDs. Sequential monotherapy, with each drug titrated to maximum benefit, may best establish the drug of choice for each child with partial seizures.

Surgical Therapy

Resecting the epileptogenic cerebral cortex remains the primary strategy for surgical management of intractable partial seizures. The subject is reviewed in Chapter 30, "Epilepsy Surgery and Cortical Stimulation." Seizure origin can be determined from scalp EEG and imaging data in conjunction with ictal seizure seminology. Electrocorticography is used to further define the epileptogenic region intraoperatively, whereas invasive recording with subdural electrodes is indicated in patients whose seizures cannot be localized by surface recording.

Children with chronic temporal lobe seizures were first shown to benefit from anterior temporal lobectomy more than 20 years ago. Patients in the initial cohort had longstanding medically resistant seizures and, often, substantial psychosocial impairment. The most prevalent histologic finding was HS, the same abnormality observed in adult patients. This experience has been repeatedly confirmed and demonstrates that temporal lobe surgery in children shares many similarities with surgery in adults, except for younger age and shorter preoperative seizure duration. A major difference is that children are more likely to harbor developmentally abnormal temporal lobe tissue.

The rate of success for temporal lobectomy is relatively uniform from center to center, with approximately 60 to 80% of children becoming seizure-free. Extratemporal cases achieve a 40 to 60% success rate. Complications occur in approximately 5 to 10% and are comparable with the adult experience. Earlier surgery leads to superior psychosocial outcome and enhanced quality of life.

Whereas the temporal lobe is the most common target of seizure surgery in adults, intractable partial seizures in children are more often extratemporal in origin. The pediatric preoperative evaluation requires extensive neocortical sampling and documentation of propagation patterns. Children are, therefore, more likely to require invasive techniques to localize the seizure origin and define eloquent cortex. Functional imaging with single-photon emission CT (SPECT), nuclear magnetic resonance spectroscopy, and functional MRI are important tools to localize the epileptogenic region and map the language and motor cortex. In contrast, depth electrodes have a more limited role.

Suggested Readings

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Ulrich S, editor. Spectrum of rolandic epilepsy: agreements, disagreements and open questions. Epileptic Disord 2000;2 Suppl 1:S1–72.

Practitioner and Patient Resources

Epilepsy Foundation
4351 Garden City Drive, Suite 406
Landover, MD 20785-4951
Phone: 1-800-EFA-1000
http://www.epilepsyfoundation.org
The Epilepsy Foundation is a national, charitable organization and the only such organization wholly dedicated to the welfare of people with epilepsy. Its mission is simple: to work for children and adults affected by seizures through research, education, advocacy, and service.

H.O.P.E. Mentoring Program
(Subset of Epilepsy Foundation)
Phone: (877) HOPE 4 YOU (877-467-3496)
http://www.efa.org/services/hope.html
H.O.P.E. was created to allow people who live with epilepsy to educate others and to share their experiences. H.O.P.E. trains people with epilepsy to be "patient educators" throughout the epilepsy and neurologic communities.

Epilepsy Information Service
Department of Neurology
Wake Forest University School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157
Phone: (800) 642-0500
http://www.bgsm.edu/neuro/disease/epilinfo.shtml
The Epilepsy Information Service is a nonprofit resource center that offers a nationwide toll-free information line for people with epilepsy and their families, professionals, and the public. Free educational packets are available to all callers.

CHAPTER 22

GENERALIZED SEIZURES

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This chapter reviews different types of generalized seizures and generalized epileptic syndromes as well as their clinical features and management.

Generalized seizures can be shown electrographically to involve, from the onset, both cerebral hemispheres simultaneously or almost simultaneously. These seizures are also called *primarily generalized seizures* and can be quite heterogeneous in their clinical manifestations, ranging from brief episodes of staring (nonconvulsive) to prolonged violent shaking involving the whole body (convulsive). Table 22-1 lists different types of generalized seizures that are included in the most recent proposal for an updated classification of epileptic seizures by the International League Against Epilepsy (ILAE). Any seizure with a focal unilateral onset can evolve into a secondarily generalized seizure. Partial seizures are reviewed in Chapter 21, "Partial Seizures."

The term *primarily generalized seizures* must be distinguished from *primary generalized epilepsies*. The latter implies a syndromic diagnosis, "a complex of signs and symptoms that define a unique epilepsy condition," and takes into consideration the type of seizures, the presence or absence of neurologic or developmental abnormalities, and the electroencephalogram (EEG) findings. For example, the syndrome of juvenile myoclonic epilepsy (JME) is characterized by the occurrence of myoclonic seizures, generalized tonic-clonic seizures, and, less frequently, absence seizures in adolescents who have normal intellectual function, with characteristic EEG findings of rapid, generalized spike-wave and polyspike-wave discharges. Generalized epilepsies are further divided into *idiopathic or primary*, *symptomatic*, and *probably symptomatic* (Table 22-2). Idiopathic (primary) generalized epilepsies are syndromes with no underlying structural brain lesion or other neurologic signs or symptoms. These are presumed to be genetic in origin and are usually age dependent, such as childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), and JME. In contrast, symptomatic generalized epilepsies are syndromes in which the epileptic seizures are the result of one or more identifiable structural or functional lesion of the brain, such as hypoxic-ischemic insult or neuronal ceroidlipofuscinosis. *Probably symptomatic* is the preferred terminology to define syndromes that are assumed to be symptomatic but without identified etiology, although it is synonymous with, *cryptogenic*.

Unfortunately, not all epileptic syndromes can fit perfectly into this categorization. An example is *severe myoclonic epilepsy of infancy* (SMEI, or Dravet syndrome), which includes features of both idiopathic (absence of etiology, high familial incidence of epilepsy and febrile seizures, massive myoclonias, generalized spike-waves, photosensitivity) as well as symptomatic epilepsy (positive neurologic signs, cognitive impairment, drug resistance). SMEI also involves both generalized and focal seizures. For this reason, in the last international classification of the ILAE, SMEI was placed separately as "underdetermined whether generalized or focal." For the purposes of this

TABLE 22-1. Types of Generalized Seizures Included in the Proposed Updated ILAE Classification of Epileptic Seizures

1. Absence seizures (typical and atypical)
2. Myoclonic seizures
3. Clonic seizures
4. Tonic seizures
5. Tonic-clonic seizures
6. Spasms
7. Atonic seizures

ILAE = International League Against Epilepsy.

TABLE 22-2. Generalized Epilepsy Syndromes

Idiopathic (with age-related onset)
Benign Familial Infantile Seizures (BFIS)
Benign Nonfamilial (Idiopathic) Infantile Seizures (BNFIS)
Benign Myoclonic Epilepsy of Infancy (BMEI)
Childhood Absence Epilepsy (CAE or pyknolepsy)
Juvenile Absence Epilepsy (JAE)
Juvenile Myoclonic Epilepsy (JME)
Epilepsy with generalized tonic-clonic seizures on awakening
Epilepsy with Myoclonic-Astatic Seizures (EMAS or Doose Syndrome)
Generalized Epilepsies with Febrile Seizures plus (GEFS+)
Symptomatic
Early myoclonic encephalopathy
Early infantile epileptic encephalopathy with suppression burst
Other symptomatic generalized epilepsies
Specific syndromes
Probably Symptomatic
West Syndrome (WS)
Lennox-Gastaut Syndrome (LGS)
Severe Myoclonic Epilepsy in Infancy (SMEI or Dravet Syndrome)

chapter and because SMEI can create an encephalopathic clinical picture that may be similar to the one that symptomatic or probably symptomatic epilepsies can create, it is listed under the *probably symptomatic* group.

Generalized Seizures

Absence Seizures

Absence seizures are subdivided into *typical* and *atypical*. They account for less than 10% of all seizure types and are more common in girls than in boys. The main characteristic feature of an absence seizure is a brief discontinuation of activity with unresponsiveness, unawareness, and subsequent lack of recollection. Onset and recovery are abrupt; there is never an associated aura or postictal impairment. Their frequency varies considerably from day to day, but they may occur hundreds of times per day. The average duration of a typical absence seizure is < 10 seconds. The vast majority of typical absence seizures have associated features (complex absences), such as clonic movements (eye blinking, nystagmus, mild jerking of extremities), change in tone (increased or decreased), subtle automatisms (oral, vocal, gestural) and autonomic signs or symptoms (change in skin color, urinary incontinence, pupillary dilatation, etc). Most children with typical absences have a normal neurologic examination.

Atypical absence seizures are longer, with a more progressive onset, a less abrupt recovery, and more change in tone. Automatisms are less likely than in typical absences. Atypical absence seizures are usually associated with diffuse or multifocal structural abnormalities of the brain and, therefore, may accompany other signs of neurologic dysfunction, such as mental retardation. Furthermore, compared with typical absence seizures, these seizures are less responsive to antiepileptic drugs.

A common problem is differentiating between absence seizures and complex partial seizures, as both may be characterized by loss of consciousness, with or without automatic behavior. The two most helpful distinguishing features are longer duration (usually > 30 seconds) and the common postictal confusion associated with complex partial seizures. An aura may also suggest a complex partial seizure. Absence seizures may be triggered by forced hyperventilation. Exercise-induced hyperventilation does not provoke absence seizures. If it is unclear whether a child stares off or has absence seizures, the parent should be instructed to say a word to the child during the questionable episodes and to ask the child to recall that word afterward.

The EEG pattern typically associated with absence seizures consists of generalized, rhythmic, frontally dominant spike and-wave discharges (Figure 22-1). One hemisphere can lead the other by a fraction of a second. Although the frequency of the spike-wave complex is said to be 3 Hz, it is usually faster at the onset of a discharge than at the end, when it slows to 2 Hz. It is also generally faster in patients with JAE than in those with CAE. In general, atypical absence seizures are accompanied electrographically by slower (2.5 Hz or less) and more irregular spike-wave discharges.

Although the term *petit mal* seizure is still occasionally used for absence seizures, the term is not included in the ILAE's classification, and it should be avoided. The term "petit mal" is not defined, it is nonspecific, and it is often used indiscriminately to refer to any type of seizure that is not generalized convulsive. Absence seizures can occur in various epileptic syndromes. These include the primary generalized epilepsies, such as CAE, JAE, JME, and myoclonic astatic epilepsy (Doose syndrome), as well as the cryptogenic or symptomatic generalized epilepsies, such as Lennox-Gastaut syndrome (LGS), epilepsy with myoclonic absences, and severe myoclonic epilepsy of infancy. Atypical absences are more commonly seen in patients with cryptogenic or symptomatic epilepsy.

Myoclonic Seizures

Myoclonic seizures are brief, shock-like muscle contractions. They are so brief (< 0.5 seconds) that, even when generalized, they are not accompanied by an identifiable impairment of consciousness. Myoclonic seizures occur either as isolated events or in clusters, in which case they are usually not rhythmic. Myoclonic seizures involve predominantly the shoulders, upper extremities, and face. The ictal EEG pattern associated with myoclonic seizures consists mainly of a polyspike and slow-wave discharge. Myoclonic seizures are not pathognomonic of any particular epileptic syndrome and

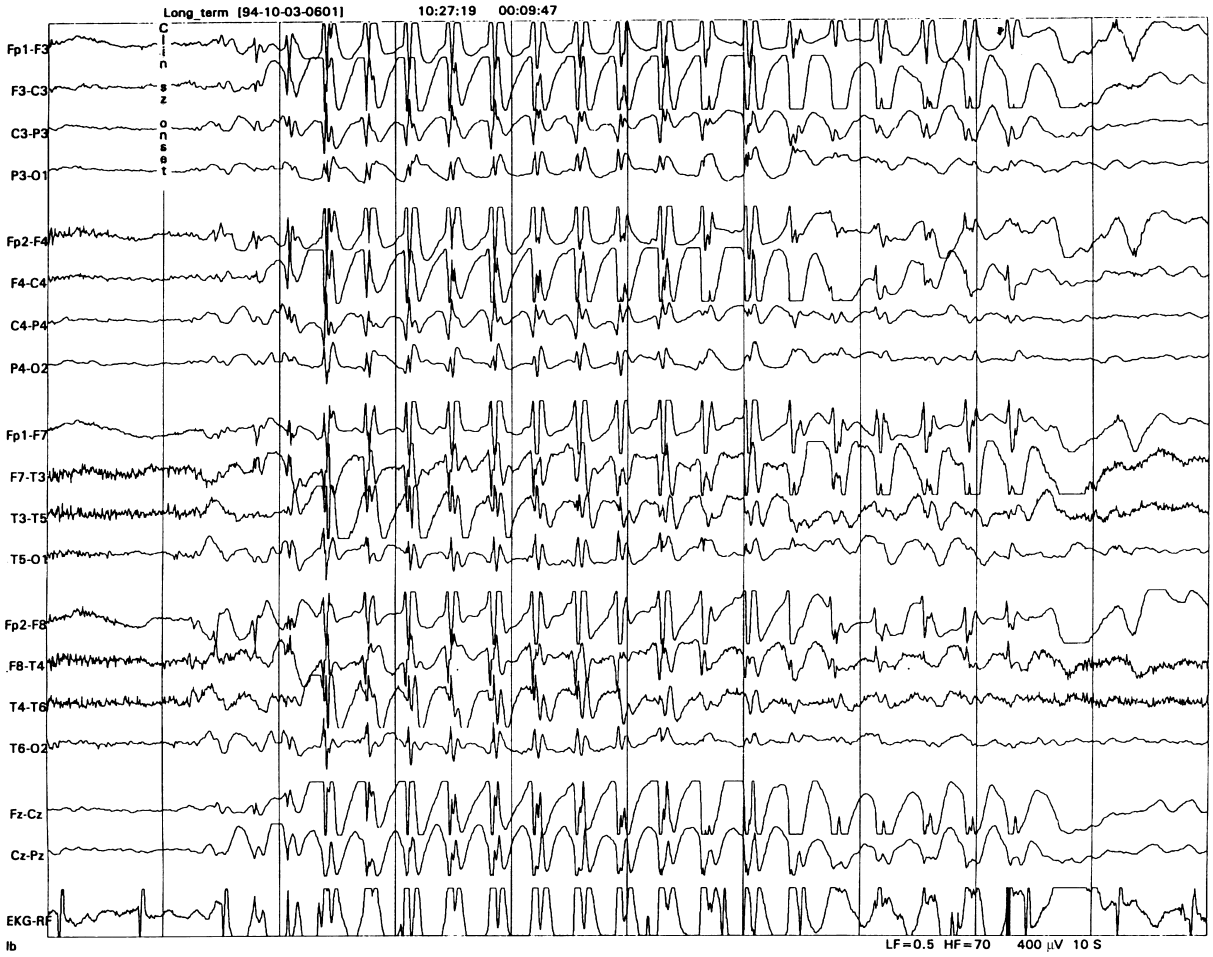


FIGURE 22-1. Generalized 3-Hz spike-wave discharge during a typical absence seizure. Note initial faster frequency, with slowing during the course of the discharge.

can be associated with a multitude of epilepsies, such as benign myoclonic epilepsy of infancy, severe myoclonic epilepsy of infancy, LGS, myoclonic astatic epilepsy (Doose syndrome), myoclonic absence epilepsy, JAE, JME, the progressive myoclonic epilepsies, and postanoxic epilepsy. It is useful to remember that not every myoclonic movement represents a seizure. A normal, common physiologic form of myoclonus is the sudden jerking movement observed while falling asleep. Pathologic but nonepileptic myoclonus is most commonly seen in association with metabolic disorders, degenerative central nervous system diseases, or anoxic brain injury. Although the distinction from other forms of myoclonus is imprecise, myoclonic seizures are considered to be true epileptic events because they are caused by cortical, as opposed to subcortical or spinal, dysfunction.

Clonic Seizures

Clonic seizures are rhythmic, repetitive muscle contractions seen more commonly in children than in adults. They may involve any group of muscles, although most frequently the arms, neck, and face. When generalized, they are accompanied by impairment of consciousness. The duration is quite variable, and they can even be a manifestation of status epilepticus. Significant autonomic changes and postictal confusion do not occur. They are also characteristic of the second phase of generalized tonic clonic seizures.

Generalized clonic seizures are not characteristic of any particular epileptic syndrome, but an underlying etiology is more likely with clonic seizures than with generalized tonic seizures. As in generalized tonic-clonic seizures, neocortical structures are implicated in the generation of clonic seizures. Nonepileptic clonic jerks may be seen in syncope and breath-holding spells and during the recovery phase of cataplexy. The interictal EEG in patients with clonic seizures reveals generalized spike- or polyspike-wave discharges. Seizures are accompanied by a fast generalized 10 Hz rhythm intermixed with slow waves of variable frequency.

Tonic Seizures

Tonic seizures consist of a sudden and sustained muscle contraction, lasting at least 1 second and usually several seconds. Impairment of consciousness and autonomic alterations may occur. Tonic seizures primarily involve extensor muscles and typically have an abrupt onset and a rapid return to baseline. They commonly occur in clusters during drowsiness and non–rapid eye movement sleep, and may happen multiple times throughout the night. During wakefulness, they may cause injuries due to sudden, unexpected falls. Tonic seizures often occur in patients with diffuse encephalopathy and are one of the characteristic features of LGS, especially with nocturnal occurrence. Tonic seizures can also be seen in patients with myoclonic astatic epilepsy. Generalized tonic-clonic seizures may at times be predominantly tonic, with only a brief and subtle clonic phase. The EEG pattern associated with tonic seizures usually consists of an initial generalized sharp and slow-wave complex, followed by a period of generalized voltage suppression (electrodecremental pattern) with low-amplitude fast activity.

Spasms

There is a continuum of seizures including myoclonic seizures (usually < 0.5 seconds), spasms (duration, approximately 0.5 to 1 second), and tonic seizures. Spasms and tonic seizures often are associated with an abrupt fall, with potential for injury. Most drop attacks in patients with LGS were shown to be spasms or brief tonic seizures and involve predominantly axial and proximal limb muscles.

Generalized Tonic-Clonic Seizures

Generalized tonic-clonic seizures usually begin abruptly without warning, although some patients describe vague premonitory symptoms (ie, headache, insomnia, irritability) in the hours or days before the seizure. This prodrome stage should be distinguished from the auras associated with focal seizures that secondarily generalize. Tonic-clonic seizures consist of an initial sudden and generalized muscle contraction that invariably leads to a fall if the patient is standing or sitting. Loss of consciousness is the rule. The purely tonic phase lasts several (10 to 30) seconds; it is often accompanied by apnea, cyanosis, hypersalivation, urinary or fecal incontinence, mydriasis, and upward deviation of the eyes. A single vocalization is common at the onset and is produced by a tonic contraction of the muscles of expiration and the larynx. The tonic phase evolves into a clonic phase, which initially has a higher frequency and lower amplitude (rapid tremor-like). The clonic activity becomes progressively slower and higher in amplitude, until the patient becomes completely limp following the last clonic jerk. This tonic phase is longer and typically lasts 30 to 60 seconds. Postictally the patient remains flaccid and unarousable for at least several minutes; confusion or agitation may follow. Potential complications of generalized tonic-clonic seizures include oral and head trauma, vertebral body stress fractures, aspiration pneumonia, pulmonary edema, and sudden death.

The ictal EEG pattern of generalized tonic-clonic seizures is initially the same as for generalized tonic seizures. During the clonic phase, sudden generalized background attenuation is followed by a low-amplitude 20 to 40 Hz fast activity and then a bilaterally synchronous and symmetric 10 Hz rhythm. During the clonic phase, generalized bursts of polyspikes interrupted by slow waves are noted, which may be synchronous with clinical clonic activity. Often, however, the ictal EEG is obscured by movement artifact. Postictally, there is generalized voltage suppression until the appearance of slow activity in the delta frequency range.

Generalized tonic-clonic seizures are not characteristic of any epileptic syndrome and can occur in many types of epilepsies. They can occur, in particular, with all primary generalized epilepsies (CAE, JAE, JME, and myoclonic astatic epilepsy) but also in patients with LGS and severe myoclonic epilepsy of infancy. Secondary generalized tonic-clonic seizures may be erroneously labeled as generalized tonic-clonic in case of rapid evolution from an initial partial seizure. Hints to suggest a secondary generalized seizure may include preceding (pre-ictal) or post-ictal state (Todd's paralysis), as well as focal or lateralized clinical behaviors. The EEG may also show lateralized slowing or epileptiform activity. Like the term *petit mal*, the term *grand mal* is not included in the ILAE's classification and should be avoided. The term grand mal often is used to refer to any type of convulsive seizure, whether primary generalized, secondary generalized, or unilateral.

Atonic Seizures

Pure atonic seizures are quite uncommon. They are characterized by abrupt loss of postural tone lasting 1 to 2 seconds. Consciousness is usually impaired, although recovery is rapid. The loss of tone may be limited to a group of muscles (for instance head drop) or can be more diffuse, leading to sudden, unexpected fall and injury. The term *atonic seizure* is often used erroneously as a synonym for drop attacks. This is incorrect, because it has been demonstrated by polygraphic recordings that the majority of drop attacks, in particular in patients with LGS, are brief tonic seizures (axial spasms). Also, the terms atonic and astatic are not synonymous. The latter refers to loss of erect posture resulting in a fall, which may occur with atonic, tonic, and myoclonic seizures. The epileptic syndrome that is most characteristically associated with atonic or myoclonic–atonic drop attacks is myoclonic astatic epilepsy (Doose syndrome). Like tonic seizures,

atonic seizures are observed mostly in neurologically abnormal children with generalized epilepsy syndromes. Atonic seizures may be mistaken for breath-holding spells, syncope, and cataplexy. The ictal EEG demonstrates polyspike-wave or spike-wave discharges. More prolonged seizures may be accompanied by generalized spike-wave discharges followed by diffuse generalized slowing that is maximal at the vertex and central regions. This slow-wave activity can be accompanied by severe, generalized hypotonia.

Generalized Epilepsy Syndromes

Idiopathic Generalized Epilepsies

Childhood Absence Epilepsy

As the name suggests, CAE has its onset between the ages of 5 and 10 years. The incidence is higher in girls than in boys. Like all idiopathic generalized epilepsies, CAE is characterized by a genetic predisposition. The relatives may have a different idiopathic generalized epilepsy syndrome. Within a short time after their appearance, absence seizures become very frequent, occurring many times daily. The EEG contains the typical 3 Hz spike-wave discharges. Clinical absence seizures as well as epileptiform EEG discharges are exacerbated by hyperventilation in nearly 80% of cases. The EEG background activity is normal, as is the case with most patients with idiopathic generalized epilepsies. Patients with CAE also experience generalized tonic-clonic seizures (about 30%), most commonly during adolescence. The tonic-clonic seizures may appear several years after the absence seizures. The absence seizures remit spontaneously in most patients (about 80%), usually after the age of 10 years. Remission rates are somewhat lower among children who experience generalized tonic-clonic seizures in addition to the absence seizures. Patients with typical CAE may later develop JME. Absence status, consisting of prolonged periods of mental clouding associated with repetitive spike-wave complexes, occurs in 10 to 20% of patients with CAE.

The neurologic examination is normal and most patients are of normal intelligence. The treatment of CAE will be discussed with the treatment of JAE.

Juvenile Absence Epilepsy

JAE begins during the early part of the second decade of life. Genders are affected equally. Characteristically, absence seizures occur less frequently, but they tend to be longer than in childhood epilepsy. Absences do not occur daily and are often initially not recognized as such. The occurrence of generalized tonic-clonic seizures is the rule (up to 80% of patients) rather than the exception, and these seizures may occur, or may be recognized, before the absences. They often occur in the morning. Occasionally, myoclonic seizures occur, in which case the distinction between JAE and JME becomes difficult or impossible. The frequency of the generalized spike-wave discharges in patients with JAE is often faster than 3 Hz, mostly 4 to 5 Hz. Polyspikes also can be present. JAE may persist into adulthood, and the rate of complete remission is not quite as high as for CAE.

Regarding treatment decisions in patients with absence epilepsies, it may be helpful to separate children into those under the age of 10 years and those above the age of 10 years. There are at least three reasons for this: (1) concomitant generalized tonic-clonic seizures are more likely after the age of 10 years in CAE and they are common in JAE, (2) the incidence of valproate-induced fatal hepatoxicity is inversely age related, especially in combination therapy, and (3) the incidence of severe rash associated with lamotrigine also appears to be inversely age related. Consequently, ethosuximide may still represent the drug of first choice in patients < 10 years old who have only absence seizures, as is usually the case in CAE (Table 22-3). When an antiepileptic drug needs to be introduced or changed in any child > 10 years with absence seizures, the choice would be valproate. It is quite safe in monotherapy at this age and

TABLE 22-3. Antiepileptic Drugs in the Treatment Sequence of Generalized Seizures and Epileptic Syndromes in Children

Generalized Tonic-Clonic Seizures	
First choice	Valproate, topiramate, lamotrigine
Second choice	Carbamazepine, phenytoin, levetiracetam
Consider	Zonisamide, phenobarbital, primidone
Absence Seizures	
Before age 10 years	
First choice	Ethosuximide (if no convulsive seizures), valproate
Second choice	Lamotrigine
Consider	Levetiracetam, topiramate, zonisamide, methsuximide, acetazolamide, benzodiazepine
After 10 years	
First choice	Valproate, Lamotrigine
Second choice	Levetiracetam, topiramate
Consider	Zonisamide, ethosuximide, methsuximide, acetazolamide, benzodiazepines
Juvenile Myoclonic Epilepsy	
First choice	Valproate, lamotrigine
Second choice	Levetiracetam, clonazepam
Consider	Topiramate, zonisamide, phenobarbital, primidone
Lennox-Gastaut and Related Syndromes	
First choice	Topiramate, lamotrigine
Second choice	Valproate
Third choice	Ketogenic diet, zonisamide, felbamate, VNS, benzodiazepine, phenobarbital
Consider	Ethosuximide, methsuximide, levetiracetam, ACTH or steroids, pyridoxine

VNS = vagus nerve stimulator; ACTH = adrenocorticotropic hormone.

highly effective against generalized tonic-clonic seizures, whereas ethosuximide offers no protection. Lamotrigine, which is also effective against absence seizures and generalized tonic-clonic seizures, is quite safe in this age group and is a valuable alternative to valproate. As experience with lamotrigine grows, and in view of the undesirable side effect of valproate in young women, lamotrigine may become a drug of first choice in adolescents with idiopathic generalized epilepsies. Recent studies have been conducted in patients with absence seizures, focusing on AED monotherapy and showed that lamotrigine is effective against this type of seizures. One open-label randomized trial revealed that lamotrigine was equivalent to valproate for the initial treatment of CAE, although equivalent seizure control was not seen for a year after beginning treatment, which was attributed to the very slow does titration of lamotrigine. It is not uncommon that the slow titration may be a limiting factor for lamotrigine's use, particularly when fast seizure control is required; this may necessitate the use of a "bridge" medication such as clonazepam until a therapeutic does is achieved. There is growing evidence that levetiracetam is effective in all seizure types of IGE, including suppression of spike-wave complexes and it is now becoming a second line treatment for this group of epilepsies. Methsuximide and acetazolamide also may be effective against absence seizures, and topiramate has been found to have some efficacy. Although efficacy of felbamate against absence seizures was suggested by uncontrolled observations, its side effect profile does not justify its use for this indication. Gabapentin, carbamazepine, phenytoin, and tiagabine appear to have no role in the treatment of absence seizures, and the efficacy of levetiracetam and zonisamide has yet to be assessed. Importantly, certain AEDs have been shown to aggravate either clinical seizures, epileptiform EEG abnormalities or both, in patients with IGEs and hence these particular drugs should be considered inappropriate choices (Table 22-4).

Juvenile Myoclonic Epilepsy

JME is one of the most common forms of idiopathic generalized epilepsies, accounting for 5 to 10% of all epilepsies. Strongly age related, the onset of JME is during adolescence (Janz: 80% occur between 12 and 18 years of age), usually slightly later than the onset of JAE. Initial seizures are usually myoclonic jerks that involve mostly the shoulders and arms and occur predominantly in the morning upon awakening. Usually the face is spared and there is no detectable loss of consciousness. The myoclonic jerks occur in brief clusters and may cause a patient to drop a comb or spill a beverage. Generalized tonic-clonic seizures will occur later in the great majority of untreated patients and are usually the motivation for the first medical consultation. These tonic-clonic seizures also tend to occur in the morning and often are preceded by clusters of intensifying myoclonic jerks. Myoclonic and generalized tonic-clonic seizures are classically precipitated by sleep deprivation, previous alcohol consumption, and stress. Approximately one-fifth to one third of patients with JME also may experience absence seizures. In these patients, the distinction between JME and JAE may become impossible, because myoclonic and generalized tonic-clonic seizures are included in the spectrum JAE. There is an additional form of idiopathic generalized epilepsy of adolescence characterized by the exclusive occurrence of generalized tonic-clonic seizures upon awakening.

It is best to consider the idiopathic generalized epilepsies as a continuum of syndromes that can include generalized tonic-clonic, myoclonic, and absence seizures in various proportions and with different ages of onset and resolution. Identifying patients with JME is of practical relevance because it is the only form of idiopathic epilepsy that is a lifelong condition in the great majority of patients. In patients who are seizure-free on medication and weaned off their medication, seizure relapse is the rule. Strong genetic predisposition is suggested, as one-third of the patients have positive family history of epilepsy. Although the short arm of chromosome 6 has been implicated in the inheritance of JME, this may not be the case for all families. An association with HLA-DR6 and its split HLA-DR13 was also found. JME does not follow an autosomal dominant or recessive inheritance pattern.

The characteristic feature in the EEG of patients with JME is the occurrence of generalized polyspike- and slow-wave discharges, which also accompany the myoclonic seizures. Brief irregular generalized spike-wave discharges also can be seen with a frequency of more than 3 Hz, as in JAE. The EEG background activity is normal. Epileptiform abnormalities can be activated by intermittent photic stimulation and by sleep deprivation.

For the treatment of JME, valproate remains the drug of choice (see Table 22-3). It has not yet been demonstrated that any of the established or newer antiepileptic drugs match or exceed the efficacy of valproate in controlling the myoclonic, tonic-clonic, and absence seizures. However, the side effect profile of valproate is a concern, especially in women of childbearing age. These side effects include weight gain,

TABLE 22-4. Antiepileptic Drugs that may Aggravate Seizures in Generalized Epilepsies

Carbamazepine	(absences, myoclonic, JME, LGS, EMAS, SMEI)
Oxcarbazepine	(absences, myoclonic, JME, LGS, EMAS, SMEI)
Phenytoin	(absences, myoclonic, JME, LGS, EMAS, SMEI)
Gabapentin	(absences, myoclonic, LGS, EMAS)
Lamotrigine	(myoclonic, JME, LGS, SMEI)
Vigabatrin	(SMEI)
Tiagabine	(absences)

teratogenicity, and the possibility of polycystic ovary syndrome. For a potentially lifelong condition such as JME, an alternative drug would be desirable. There is accumulating evidence that lamotrigine, including in monotherapy, is an effective option in patients with JME and may be considered as a first line treatment along with valproate for this population. Lamotrigine has a much lower incidence of severe idiosyncratic reactions in adults and has few other side effects; however, its slow titration may be a limiting factor. Although lamotrigine is quite effective against generalized tonic-clonic seizures, it appears to be somewhat less effective than valproate against the myoclonic seizures seen in JME and may occasionally exacerbate them. Lamotrigine may be an excellent drug, especially in patients who have rare myoclonic seizures or are not bothered by them. Inversely, clonazepam is very effective against myoclonic seizures, but less effective against generalized tonicclonic seizures. Topiramate has been shown to be effective against the generalized tonic-clonic seizures of JME, but its role against myoclonic seizures remains to be established. Felbamate also appears to be effective, but it should be considered only in unusually refractory cases because of its side effect profile. The role of zonisamide and levetiracetam in this syndrome is unknown at this point in time.

Epilepsy with Myoclonic Astatic Seizures

Epilepsy with myoclonic astatic seizures (Doose syndrome) is generally under recognized and probably, at times, mistaken for LGS. It is associated with multiple seizure types and may cause cognitive regression. As opposed to LGS, however, it occurs in a previously healthy child usually between 1.5 and 5 years of age, and genetic factors play a predominant etiologic role. More boys are affected than girls. Onset includes febrile or afebrile generalized tonicclonic seizures. Later, the typical myoclonic, astatic, or myoclonic astatic seizures develop. Falls can be triggered by a myoclonus, by sudden loss of tone, or both. Ongoing tonic-clonic seizures occur in the vast majority of patients. Absence seizures, most often atypical, are present in more than 50% of the patients, and tonic seizures may also occur frequently. The EEG can be normal initially. Later, irregular generalized spike-wave activity and polyspikes are present (Figure 22-2), as well as rhythmic posterior 4 to 7 Hz activity. Treatment of Doose syndrome is similar to the treatment of LGS, but the overall prognosis is better, both in terms of seizure control and mental development.

Benign Familial and Nonfamilial Infantile Seizures

Benign nonfamilial (idiopathic) infantile seizures (BNFIS) and *benign familial infantile seizures* (BFIS) are rare neonatal syndromes, characterized by seizures beginning in the first week of life. Most infants are neurologically normal; outcome is favorable and remission is usually spontaneous. The diagnosis of both syndromes is usually made retrospectively and after other etiologies for neonatal seizures (eg, infectious, metabolic, ischemic) are excluded.

BFIS occur, in up to 80% of the cases, on the second or third day of life. They may occur for a week and then scattered seizures may recur for several weeks or months. They usually start with a diffuse tonic phase, followed by various autonomic and motor changes. The ictal EEG shows initially generalized flattening followed by focal or generalized spikes or slow waves. Most neonates may receive phenobarbital for a few months. BFIS are inherited by autosomal dominant transmission with a genetic defect located on chromosome 20q and a positive family history supports their diagnosis.

BNFIS have been also referred to as "fifth-day fits," as 90% of the seizures happen between the fourth and sixth day of life. They usually present as clonic, mostly partial, seizures and/or apneic spells. They may be recurrent and prolonged, leading to status epilepticus, although they will finally resolve fully. The interictal EEG commonly shows "theta pointu alternant," which is a discontinuous, nonreactive theta rhythm associated with neonatal seizures of various etiologies. The ictal EEG findings may vary remarkably. Different antiepileptic drugs have been used, although the seizures stop mostly without treatment. The etiology and pathophysiology of BNFIS are unknown.

Benign Myoclonic Epilepsy of Infancy

Benign myoclonic epilepsy of infancy (BMEI) is characterized by brief myoclonic seizures starting between 4 months and 3 years of age in neurologically normal children. Boys are more frequently affected than girls. A history of febrile seizures is not uncommon, and a family history of seizures is reported in 30% of cases. Generalized tonic-clonic seizures may develop rarely during adolescence. The interictal EEG is usually normal; ictally, the EEG shows generalized fast (poly) spike-waves. Valproic acid is the drug of choice. With early diagnosis and treatment, the outcome is favorable for both seizures and cognition. This syndrome is considered by some investigators to be the infantile equivalent of JME, although the two conditions have never been reported with confidence in the same patient. BMEI should be differentiated from SMEI (Dravet syndrome), which appears in the first year of life, often as prolonged, recurrent febrile seizures. In SMEI, affected children are initially normal, but psychomotor retardation is developed by the second year of life. Medical treatment is generally ineffective, and prognosis is poor.

Generalized Epilepsies with Febrile Seizures Plus

Generalized epilepsies with febrile seizures plus (GEFS+) is a recently described benign, childhood-onset, genetic

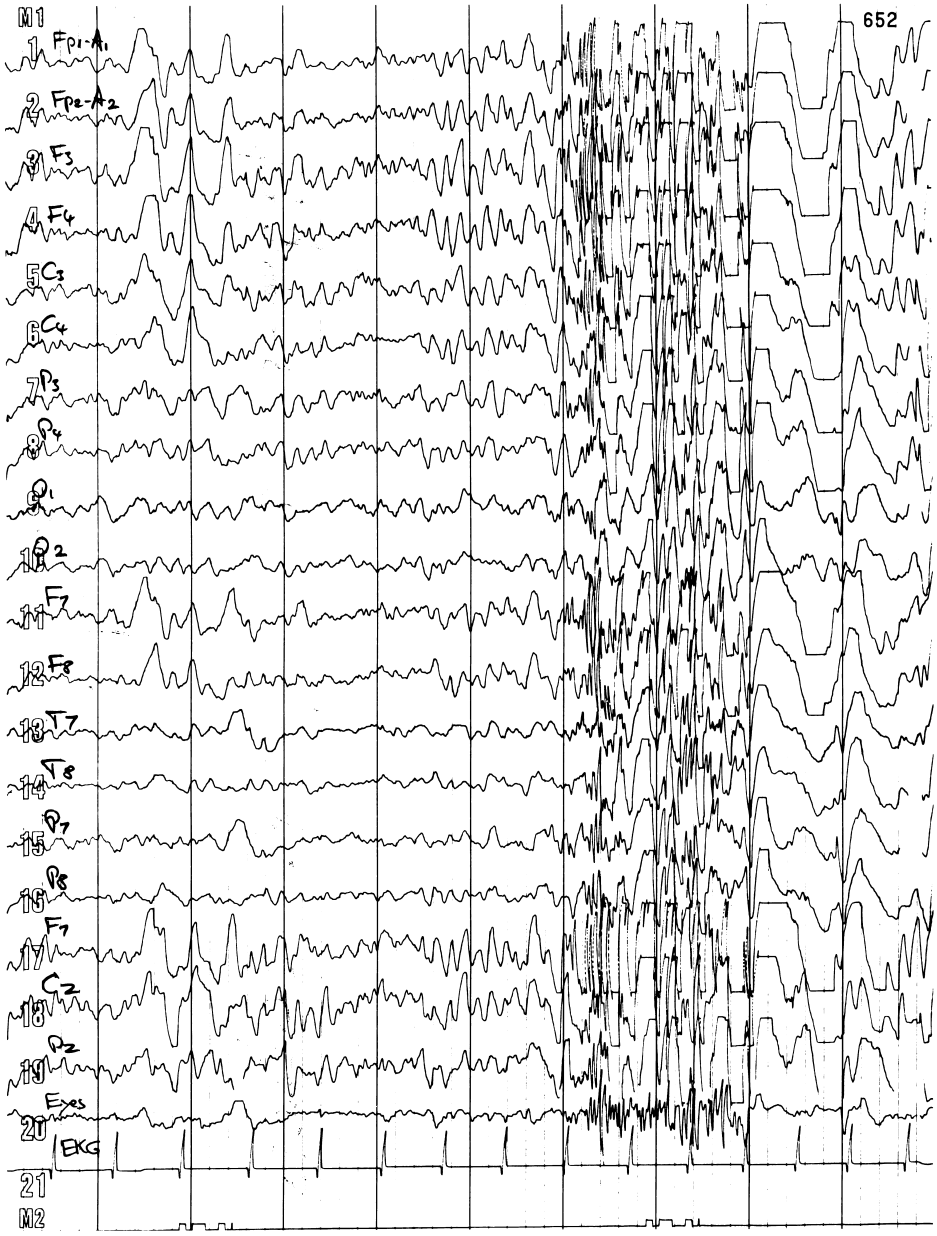


FIGURE 22-2. Generalized polyspike-wave discharge during a myoclonic seizure in a patient with myoclonic-astatic epilepsy (Doose syndrome).

epileptic syndrome with autosomal dominant inheritance. This disorder is associated with mutations in a gene encoding a voltage-gated subunit of a neuronal sodium channel. Although there are heterogeneous phenotypes, the most common one includes febrile seizures (which may persist beyond the age of 6 years) and generalized tonic-clonic seizures that are not associated with fever. In approximately one-third of patients, additional seizure types occur, including absence, myoclonic, or atonic seizures. The outcome is favorable.

Other Generalized Epilepsies

West's Syndrome

West's syndrome (WS), or infantile spasms, is a malignant epileptic encephalopathy initially described by W.J. West in 1841. It is characterized by the triad of clusters of spasms, chaotic EEG abnormalities called hypsarrhythmia (interictally), and profound regression of psychomotor development. The peak age of onset is between 4 and 6 months, with the great majority of

affected children starting before 1 year of age. WS has many different etiologies and may respond well to hormonal treatment such as adrenocorticotropic hormone (ACTH) and steroids. WS is discussed extensively in Chapter 25, "Management of Infantile Spasms."

Lennox-Gastaut Syndrome

LGS is the best-known example of a cryptogenic or symptomatic generalized epilepsy. It is characterized by multiple seizure types (tonic axial seizures are almost always present) and a slow spike-and-wave pattern, and often by mental retardation. Its onset is usually after infancy, in preschool-aged children and usually before 8 years of age. Boys are affected more often than girls. Almost one-fifth of the patients were previously normal neurologically. In symptomatic cases, multiple etiologies have been identified, usually involving diffuse or multifocal CNS pathology, such as tuberous sclerosis, perinatal hypoxia, cerebral dysgenesis, and neuronal ceroid lipofuscinosis. At least one-fourth of patients diagnosed with LGS previously presented as having WS. The seizure types typically associated with LGS include daytime and nocturnal generalized tonic seizures, astatic seizures (drop attacks), mostly in the form of axial spasms, and atypical absence seizures. Generalized tonic-clonic, myoclonic, and partial seizures also may occur. Nonconvulsive status with intermittent myoclonic and tonic seizures, as well as pseudoataxia, are characteristic feature. Patients invariably exhibit developmental or cognitive dysfunction, although development may be normal until the seizures declare themselves. The characteristic EEG pattern consists of generalized, irregular 1.5- to 2.5-Hz sharp and slow-wave activity, invariably with an abnormally slow background rhythm (Figure 22-3). During sleep, bursts of sharp rhythmic discharges (around 10 Hz) can be seen (Figure 22-4). The long-term prognosis of patients who have LGS is almost invariably poor. Overall, it can be assumed that 90% or more of the patients will have persistent seizures and/or mental retardation.

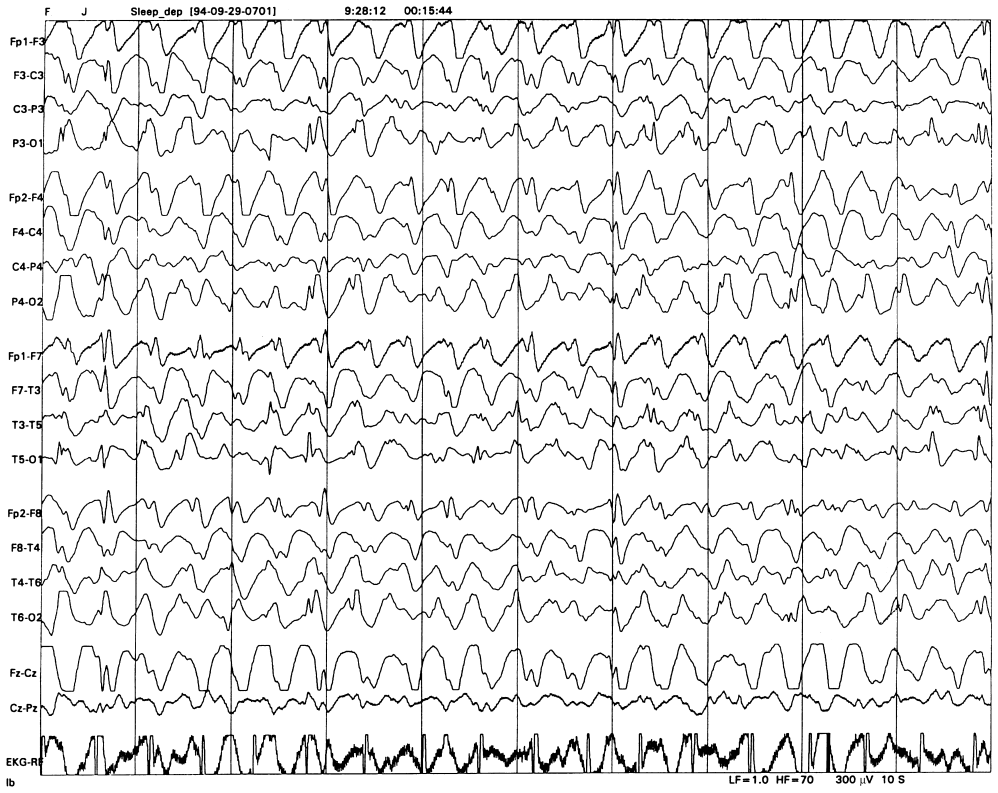
In general, the seizures associated with LGS, particularly the tonic and astatic seizures, do not respond well to treatment. Valproate can still be considered to be the drug of first choice in these patients. Because the age of onset is after 2 to 3 years, in these patients the risk of hepatic failure from valproate is relatively low, especially in monotherapy. Among the newer antiepileptic drugs, three have been shown in double-blind, controlled trials to be superior to placebo in the treatment of LGS, specifically against astatic seizures, which are the most debilitating. Among these three, topiramate and lamotrigine are now commonly used as the drugs of second choice. Felbamate may be the most effective drug in patients with LGS, on the basis of clinical experience. This is currently the main indication for felbamate, but its side effect profile, including a high risk of aplastic anemia, makes it a drug of third choice. In a recently reported double-blind add-on trial rufinamide, a newly developed AED, has been shown to have good responder rates for astatic seizures in patients with LGS. Anectodal reports suggest that seizures in LGS may also improve with levetiracetam or nitrazepam, although their role as well as that of zonisamide, thalamic electrical stimulation or transcranial magnetic stimulation (TMS) remains to be established. In patients with recurrent seizures on two or three initial drugs, it is now common to try the ketogenic diet. Preliminary experience with the vagal nerve stimulator is very encouraging in the treatment of astatic seizures associated with LGS. Finally, carbamazepine, phenytoin, gabapentin, and tiagabine have little or no role in the treatment of LGS.

Severe Myoclonic Epilepsy of Infancy

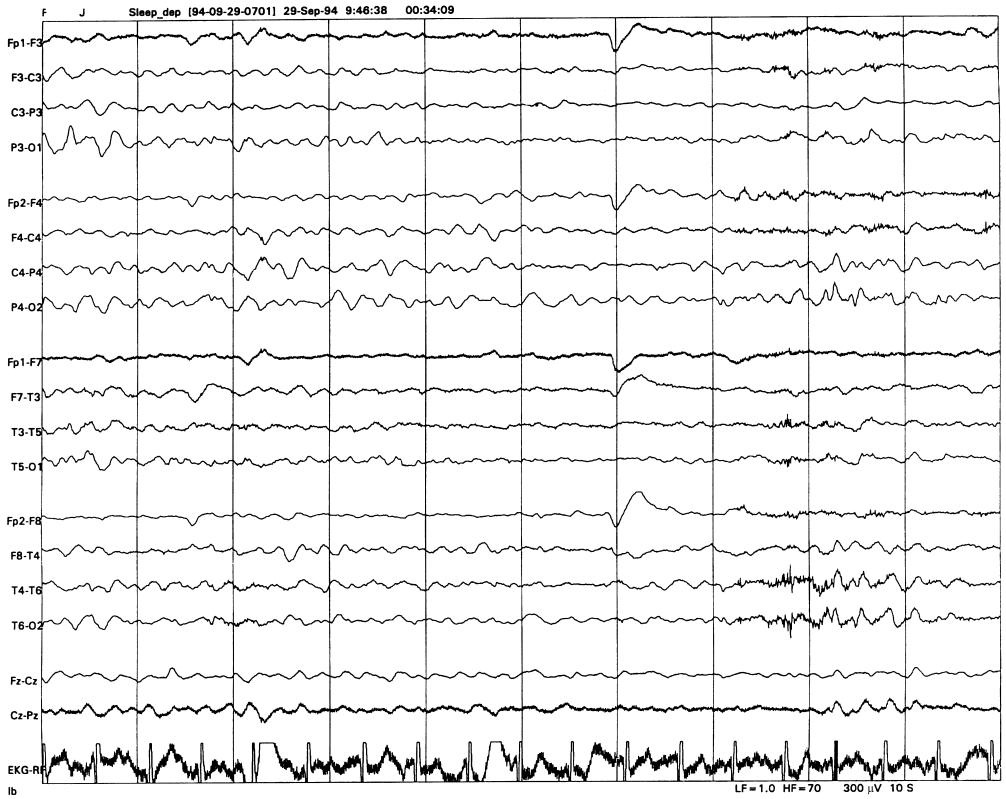
Severe myoclonic epilepsy in infancy (SMEI or Dravet syndrome) is a malignant epilepsy syndrome of unknown etiology, although complex inheritance is presumed. It may be the result of a channelopathy, as a mutation of the sodium channel (*SCN1A*) gene was found at least on some occasions. Genetic testing for the SCN1A gene is currently available. SMEI is characterized by generalized convulsions or hemiconvulsions typically induced by fever, in an otherwise normal child during the first year of life. Various seizure types will subsequently develop, including myoclonic seizures, which may be generalized or partial, atypical absences, and focal seizures. Developmental delay becomes obvious during the second year of life and is followed by definite cognitive impairment. Because both generalized and focal seizures occur in this syndrome, a broad-spectrum AED is recommended, although usually all seizure types are resistant to treatment. Anecdotal evidence exists for treatment with valproate, benzodiazepines, ethosuximide, topiramate, and intravenous immunoglobulins. The prognosis is grave for both seizure resolution and developmental outcome. On a more optimistic note, a double-blind placebo-controlled add-on trial of stiripentol found it to be dramatically effective for clonic/tonic-clonic seizures with 43% of children with SMEI remaining seizure-free during the second month of treatment compared to 0% with placebo.

Progressive Myoclonic Epilepsies

The progressive myoclonic epilepsies are a group of familial disorders characterized by myoclonic and GTC seizures and progressive neurologic deterioration. The two main forms are Unverricht-Lundborg disease and Lafora disease. Other diseases, such as myoclonic epilepsy with ragged red fibers, neuronal ceroid lipofuscinosis, and



A.



B.

FIGURE 22-3. *A*, Ongoing generalized irregular 2.0- to 2.5-Hz sharp- and slow-wave activity. *B*, Slow occipital background activity in a patient with Lennox-Gastaut syndrome.

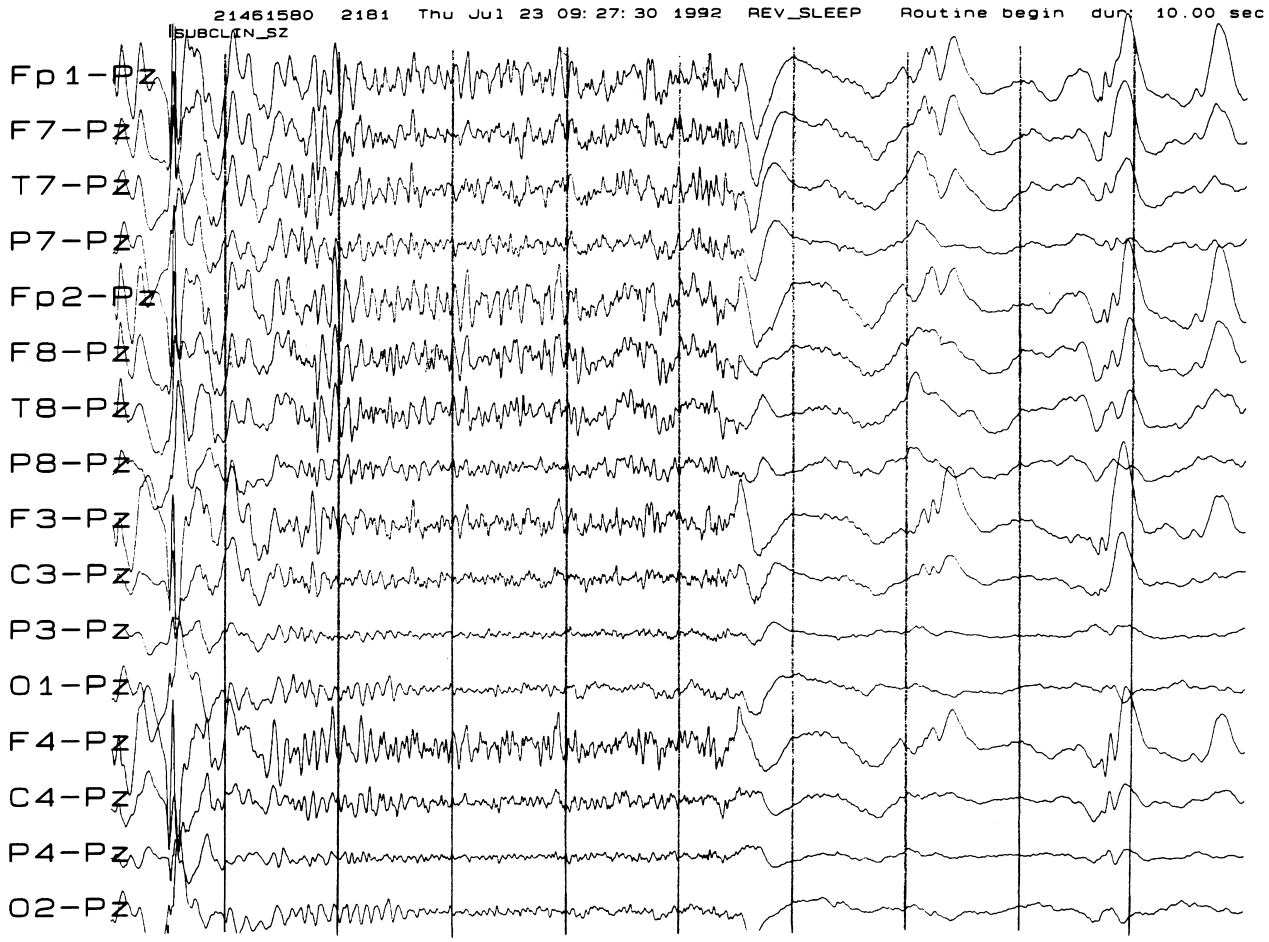


FIGURE 22-4. Fast sharp rhythmic discharge during sleep in a patient with Lennox-Gastaut syndrome.

sialidosis also can present as myoclonic epilepsy. Unverricht-Lundborg disease does not differ from "Baltic myoclonus" and "Mediterranean myoclonus." It is an autosomal recessive disease linked to the long arm of chromosome 21. The mean age of onset is about 10 years, with myoclonic seizures that are often stimulus-induced, and GTC seizures. The clinical course is variable, although the myoclonus and the ataxia, which is generally also present, slowly but steadily worsen. A few patients die within a few years, and some may reach old age. Treatment is mostly with valproate and clonazepam. Recently, zonisamide has been identified as being particularly and selectively effective in this disorder. Phenytoin must be avoided, as it can have a deleterious effect.

Lafora disease has a slightly later age of onset (mean, 14 years). The first symptoms are GTC seizures, often associated with partial visual seizures (hallucinations or scotomas). The course is invariably more rapid than in Unverricht-Lundborg, with steadily increasing intellectual deficits, and with fatal outcome within 2 to 10 years. So-called Lafora bodies can be found in various tissues and are most practically identified in sweat glands by skin biopsy. Lafora disease is also autosomal recessive, and the locus was identified on chromosome 6. AEDs most commonly used are valproate and clonazepam. Epileptiform activity in the EEG is highly sensitive to intermittent photic stimulation in both Unverricht-Lundborg and Lafora disease.

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Practitioner and Patient Resources

Epilepsy Foundation of America
4351 Garden City Dr., Suite 406
Landover, MD 20785-2267
Phone: (301) 459-370 or (800) EFA-1000
E-mail: postmaster@efa.org
http://www.epilepsyfoundation.org
The Epilepsy Foundation is a national, charitable organization and the only such organization wholly dedicated to the welfare of people with epilepsy. Its mission is simple: to work for children and adults affected by seizures through research, education, advocacy, and service.

The Epilepsy Research Foundation
Registered Charity # 326836
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Phone: 020 8995 4781
E-mail: info@erf.org.uk
http://www.erf.org.uk
"Devoted solely to sponsoring effective research for all who now suffer from epilepsy."

H.O.P.E. Mentoring Program
(part of the Epilepsy Foundation)
http://www.epilepsyfoundation.org/services/hope.html
H.O.P.E. was created to allow people who live with epilepsy to educate others and to share their experiences. H.O.P.E. trains people with epilepsy to be "patient educators" throughout the epilepsy and neurologic communities.

Epilepsy Information Service
Department of Neurology
Wake Forest University School of Medicine
Medical Center Blvd.
Winston-Salem, NC 27157
Phone: (800) 642-0500
http://www.bgsm.edu/neurology/department/diagneuro/neuro1.html
The EIS is a nonprofit resource center that offers a nationwide toll-free information line on epilepsy for people with seizures and their families, professionals, and the public. Free educational packets are available to all callers.

CHAPTER 23

FIRST-CHOICE ANTIEPILEPTIC DRUGS

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Childhood epilepsy differs from epilepsy in adulthood because of age-related seizure types, etiologies of seizures, the presence of both benign and malignant epilepsy syndromes, and the frequent presence of concomitant neurologic abnormalities, mental retardation, or behavioral difficulties in those with refractory seizures. Children may also respond differently to antiepileptic drugs (AEDs) during treatment; what seems to be a natural first-choice drug for an adult with a particular seizure type may be more or less preferred at different stages of childhood. Defining the presumptive syndrome of epilepsy for each patient, even upon presentation with a possible first seizure, allows one to tailor initial treatment and choose the most appropriate drug.

One must carefully differentiate between seizures seen in the neonate, child, or adolescent, as the same seizure type may represent completely different epilepsy syndromes and may require different types of therapy depending on the patient's age. In addition, for those with lesional epilepsy who are possible candidates for surgery, brain plasticity offers a special opportunity for early surgical intervention. These children may need only brief drug treatment after more definitive therapy.

Perhaps most importantly, a single seizure may not need therapy at all, especially if it was unprovoked. A decision to treat usually depends on whether seizure activity recurs or whether multiple risk factors for recurrence are present. Efficacy is the first consideration, but AED selection may be equally dependent upon concomitant diagnoses, expected length of therapy, and perception of side effects.

Diagnostic Considerations

Most seizures should be treated acutely if the child is actively seizing when presenting to the physician. Most acute treatment centers offer the use of benzodiazepines, phenobarbital, phenytoin (PHT) (fosphenytoin), and, most recently, intravenous valproate. Treating with loading doses of medication after the event has ceased only clouds the examination and one's initial diagnostic evaluation. The finding of hypoglycemia or electrolyte imbalance removes the need for drug treatment. If seizures recur after the first event, they should be carefully investigated before chronic therapy is initiated.

A description of the event is crucial, especially in young children. In neonates and infants, contradictory information may arise from the electroencephalogram (EEG) and clinical description. Seizures, furthermore, may change their clinical appearance (semiology) as they recur in the same child or as the child matures. So determining the exact seizure type in some children may actually be difficult. Furthermore, in some children with generalized encephalopathic processes, partial seizures may be the first presentation, only to be complicated later by generalized seizures such as infantile spasms, atypical absences, and atonic or myoclonic events.

Electroclinical correlation is extremely important before embarking on a choice of the initial AED. Diagnostic studies may also distinguish seizures resulting from benign syndromes from those that are symptomatic and typically more difficult to control.

Choice of Drug

The AED of choice should completely control seizures without producing adverse effects. The optimal drug for all children with all seizure types is still not known. The physician, then, must make a decision to treat with a given drug

that is likely to control symptoms in the individual child while producing the least amount of toxicity. In children with concomitant diseases, behavioral disorders, or other symptoms, one must select drugs that would be least likely to exacerbate side effects.

Children who are hyperactive should not initially be given agents that will make them more irritable, less attentive, and more of a behavioral problem. Those with motor disturbances should not be given medications likely to aggravate incoordination. Those already exhibiting tremor will probably worsen on medications that produce or intensify tremor. Children who have eating disorders must not receive medications that would exacerbate obesity or anorexia. Because generalized seizures are more common in children, clinicians treating pediatric epilepsy are more likely to use medications such as ethosuximide (ESX), valproic acid (VPA), lamotrigine (LTG), topiramate (TPM), and zonisamide (ZNS) that are broadly effective in partial and generalized seizures. Carbamazepine (CBZ), PHT, gabapentin (GBP), tiagabine (TGB), and oxcarbazepine (OXC), along with the broader-spectrum AEDs listed above and vigabatrin, should be given appropriately for partial seizures and convulsions. The exact role of levetiracetam (LVT) and ZNS is being further explored but may well extend beyond partial seizures. Phenobarbital (PB) was, for many years, the mainstay of therapy for many types of epilepsy. The practice of prescribing phenobarbital should be reconsidered because of its considerable toxicity and the availability of equally effective AEDs with fewer adverse events, especially neurotoxicity. Similarly, the use of benzodiazepines for chronic therapy may produce more behavioral and neurotoxic adverse effects.

In general, monotherapy is desirable. Unfortunately, physicians treating children who have seizures do not always possess up-to-date, comparative data concerning childhood epilepsy and treatment with antiepileptic drugs, especially the new drugs. Clinical studies designed for the licensing of new compounds rarely give sufficient information to determine the ultimate dosing and use characteristics that will be determined after long-term use in much larger populations of patients. In addition, pediatric studies are typically performed well after the initial studies are done in adults with refractory partial seizures.

Almost all drugs shown to be efficacious in adult partial seizures have been of similar utility in children, and none has been shown to be useful as adjunctive therapy and not useful as monotherapy. The most challenging question is when to use the new agents as monotherapy and in children, as the initial data will first favor use as adjunctive therapy in adults. Several drugs, however, have been studied in children with encephalopathic epilepsy, such as Lennox-Gastaut syndrome. Although similarities exist, differences allow some distinction of these agents.

AED Characteristics

This section briefly reviews the properties associated with both classic and newer AEDs. Table 23-1 lists drugs introduced since 1993 for the treatment of epilepsy. Not all have undergone trials in children and therefore, in a strict sense, they are not "indicated for use in childhood epilepsy." Nevertheless, approval of these agents has demanded that further studies be done to establish their efficacy, safety, and pharmacokinetics when used in children of different ages. Figure 23-1 demonstrates the seizure types for which drugs are useful.

Classic AEDs

CBZ, clonazepam, ESX, PB, PHT, primidone, and VPA have been reviewed extensively for their use in both children and adults.

Carbamazepine

CBZ is the drug of choice for many physicians in treating partial seizures and generalized tonic-clonic seizures. Its mechanism is similar to that of PHT and is through the modulation of neuronal sodium channels. It remains one of the classic drugs in the treatment of both benign and refractory partial seizures with or without secondary generalization. The most common adverse effects involve neurotoxicity. This is frequently dose-related or dependent on too-rapid titration initially. Although doses of 15 to 20 mg/kg/d may be needed in children on monotherapy, usual starting doses are one-third to one-half of this total dose, with increments performed every 1 to 2 weeks. With a relatively short half-life in children (especially when using combination therapy or switching from another enzyme-inducing compound), CBZ should be taken at least three times daily, which usually can be accomplished in school-aged children before and after school and in the evening. With the availability of extended- or continuous-release formulations, twice daily dosing is acceptable.

In the past, the rare complications of aplastic anemia and organ toxicity were feared, and frequent complete blood counts and liver function tests were recommended.

TABLE 23-1. New Antiepileptic Drugs Approved for Use in the United States

1993	Felbamate (Felbatol®)
1993	Gabapentin (Neurontin®)
1994	Lamotrigine (Lamictal®)
1996	Topiramate (Topamax®)
1997	Tiagabine (Gabitril®)
1999	Levetiracetam (Keppra®)
2000	Oxcarbazepine (Trileptal®)
2000	Zonisamide (Zonegran®)
Pending	Vigabatrin (Sabril®)

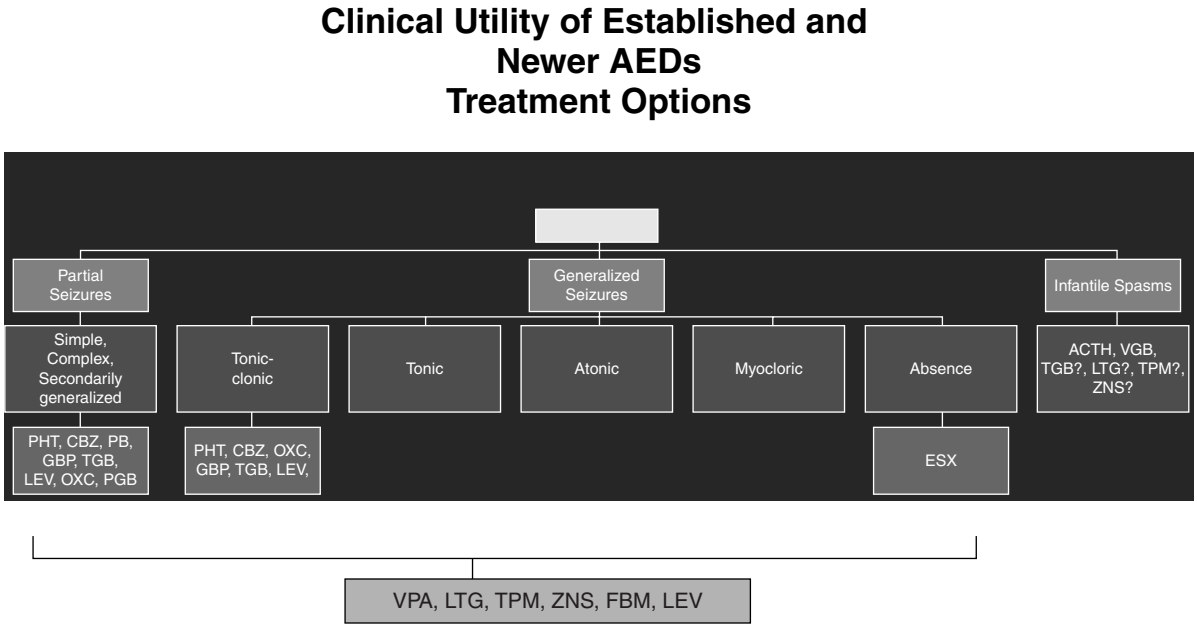

FIGURE 23-1.

Pellock JM. Epilepsy in patients with Multiple Handicaps. In: Wyllie E (ed). The Treatment of Epilepsy: Principles and Practice, 4th Edition. Baltimore: Lippincott Williams and Wilkins, 2006.

Clinical monitoring seems the most appropriate, with blood testing only at initiation of therapy as one is evaluating the patient for causes of epilepsy and when clinical symptoms suggest the need for further studies. Neurotoxic effects typically include diplopia, ataxia, nausea, vomiting, incoordination, and somnolence. The use of extended release CBZ may help decrease these symptoms when they are transient and dose related. An idiosyncratic rash may develop, and hyponatremia seems to be a rare complication. Overall, the rash rate is approximately 10%, and idiosyncratic serious rash seems to be much less common.

Ethosuximide

ESX is indicated for use in children with absence seizures. Its mechanism of action involves reduction of low-threshold T-type calcium currents, with disruption of slow rhythmic firing of thalamic neurons. The efficacy of this agent is against absence seizures, with little effect on other types of epilepsy. For some, this agent remains the first-line antiabsence AED because of its long-established safety and efficacy. It should be titrated gradually to reduce dose related side effects, which include neurotoxicity and very significant gastric distress. Ultimate doses of 14 to 40 mg/kg/d are usually divided and given with meals to decrease gastric discomfort. Besides abdominal pain, nausea, vomiting, weight loss, and psychological or behavioral disturbance, drowsiness, rash (rare), and lupus-type syndrome have been noted.

Phenobarbital

Some clinicians view PB as the primary AED for nearly all seizure types in children. It has no efficacy against absence seizures, and its effects against myoclonic or atonic seizures are questionable. This drug has a long half-life and has been proved to have similar efficacy to CBZ or PHT, but its behavioral side effect profile has made it less preferred worldwide. However, it remains a treatment of choice in neonates because of its availability in a parenteral formulation. Its mechanism of action involves γ-aminobutyric acid (GABA)-mediated chloride channel opening and decreased central nervous system (CNS) excitability. It can be given once daily because of its long half-life but is frequently given in divided doses. It is a CNS depressant and may cause somnolence, irritability, and even depression but will frequently produce a hyperactive irritable state in many children. Other adverse effects include incoordination, nausea, and, rarely, rash. Because of its hepatic metabolism with induction of cytochrome P-450, it is not a preferred agent when children need to be maintained on other medication and for those whose metabolism may be induced through this pathway.

Phenytoin

PHT is indicated for use against partial seizures with or without secondary generalization. Its mechanism of action is through the sodium channel to stop repetitive neuronal firing and spread of abnormal discharges. Available as a parenteral formulation for years, the PHT

prodrug fosphenytoin should replace most parenteral PHT use because of decreased peripheral vascular complications and cardiovascular toxicity resulting from the absence of the diluent used in parenteral PHT. Additionally, fosphenytoin can be loaded, 20 mg/kg, three times faster than PHT when needed acutely. Maintenance doses usually are between 4 and 12 mg/kg/d. Because of its nonlinear kinetics, this drug is more difficult to dose precisely while keeping in the therapeutic range without increased toxicity or subtherapeutic serum levels. In neonates, it has a more prolonged half-life, but shortens by the time a child reaches 3 months of age. The half-life may be as short as 8 to 12 hours in younger children, whereas it nears 24 hours in adolescents and adults. It is an enzyme-inducing AED and will complicate therapy with other agents. Its metabolism may be induced. In addition, it is highly protein-bound. When other drugs with significant protein binding are administered, interactions are likely. Its nonlinear pharmacokinetics and cosmetic side effects have made it a less preferred drug for chronic therapy.

Nevertheless, PHT remains a favorite of general practitioners for the treatment of new-onset epilepsy in adults. Besides neurotoxic dose-dependent CNS effects (including nystagmus, ataxia, dysarthria, and somnolence), gingival hypertrophy (seemingly patient specific) and idiosyncratic effects (including rash, rare hepatic dysfunction, and lymphadenopathy) have been noted. Coarsening of features seems to be more common when PHT is used in combination with barbiturates.

Primidone

Primidone is less frequently used as first-line therapy in children with partial and secondary generalized seizures. In the adult Veterans Administration Cooperative Study, its efficacy was similar to that of PB, PHT, and CBZ, but it was poorly tolerated during initial phases of dosing. It is, therefore, not considered a primary first-line drug for the treatment of childhood epilepsy.

Valproic Acid

Valproic acid was the first of the AEDs with broad-spectrum efficacy introduced to treat not only partial but also generalized seizures of various types, including absence (both typical and atypical), atonic, and myoclonic seizures. It is reported to be effective against infantile spasms as well. Its primary drawback is the potential for producing hepatotoxicity, especially in young children. VPA-associated hepatotoxicity of this type occurs most frequently in the first 90 days of therapy and rarely after the first year of chronic therapy. A potentially idiosyncratic type of liver failure is associated with microvesicular steatosis and may be associated with specific underlying inborn metabolic defects or acquired mitochondrial dysfunction. It is most commonly noted when used in polytherapy with enzyme-inducing AEDs in children under the age of 2 years who have preexisting encephalopathy or metabolic disease. During polytherapy, omega oxidation through cytochrome P-450 is enhanced with the production of a toxic (4-ENE) metabolite. This compound, along with other possible toxic metabolites, may be responsible for mitochondrial failure. When used as monotherapy, even in very young children, the risk of potentially fatal hepatotoxicity is markedly decreased.

More common side effects include neurotoxicity, including somnolence, tremor, and behavior change. Tremor is certainly dose-related. Thrombocytopenia may be seen when doses are significantly elevated. Rarely, pancreatitis has been reported as a probable idiosyncratic effect, most commonly associated with hepatotoxicity.

VPA should be initiated at or below approximately 15 mg/kg/d and increased to 60 mg/kg/d if symptoms havenot yet been controlled and depending on tolerability. Higher doses frequently are given to children, especially to those on enzyme-inducing AEDs. The VPA preparation has a relatively short half-life, and gastrointestinal side effects are more common. Administration with food and in divided doses, three or four times daily, allows better tolerability. Enteric-coated preparations are preferred, with a marked reduction of digestive tract symptoms. Sprinkle and extended-release preparations require less-frequent dosing and offer smoother pharmacokinetics.

The association of VPA therapy with weight gain has been long established. Also, an increased incidence of polycystic ovary syndrome is noted in some women, especially those who experience weight gain. Increased incidence of neural tube defects also has been documented in offspring of mothers receiving VPA during the first trimester; folate administration and specific fetal monitoring should be instituted.

Nevertheless, with appropriate clinical monitoring, this drug is the best-accepted long-term therapy for patients with primary generalized and symptomatic generalized epilepsy because of its proven efficacy. The efficacy of VPA and its side effect profile are being compared with those of newer drugs as they are introduced. More data are required before concluding that newer agents are preferable to VPA for first-line therapy.

Newer AEDs

The anticonvulsants listed in Table 23-1 have been approved for use in the United States since 1993. With few exceptions, initial approval was for use as adjunctive therapy in adults with partial seizures. Felbamate (FBM) and OXC were evaluated in monotherapy trials as part of their early testing, which allowed labeling, including their use

as monotherapy. Monotherapy trials in children followed the initial treatment protocols in adults. In some cases, withdrawal of adjunctive treatment provided data on monotherapy. This experience, of course, is of extreme importance in establishing the possible utility of these new agents as first-line treatment. Other needed information balances advantages over existing therapy by examining reported adverse effects, ease of use, and, perhaps most importantly, overall efficacy against partial seizures and other seizure types that may not have been included during initial studies.

A brief review of each new AED is presented below. Special considerations in children, such as possible effects on behavior, cognition, sleep, and growth, and positive or negative effects on comorbid disease states and their treatment ultimately decide the first-choice AED.

Felbamate

FBM was the first of the new AEDs approved for use in partial and generalized seizures in adults and in children for the treatment of seizure types associated with Lennox-Gastaut syndrome. FBM is a lipophilic, watersoluble dicarbamate thought to act as a blocker of glycine at the *N*-methyl-D-aspartate (NMDA) receptor, decreasing neuronal permeability to calcium. There is also evidence that FBM acts, in part, by blocking voltage dependent sodium channels, as seen for CBZ and PHT. In a cryosurgical trial, 64 adults were randomly assigned to receive either FBM rapidly titrated to 3,600 mg/d for 3 days or placebo added to any remaining AEDs after withdrawal. Only 46% of the patients who received FBM had a fourth seizure within 28 days as opposed to 88% of patients taking placebo. In monotherapy studies, lowdose VPA (15 mg/kg/d) was used as a control in adult patients with uncontrolled partial seizures. A seizure frequency reduction of 50% or more was achieved in 29% of patients on FBM and in 11% receiving low-dose VPA. In the Lennox-Gastaut syndrome trials, patients treated with FBM versus placebo had significantly fewer generalized tonic-clonic and atonic seizures, making this drug one of the most efficacious in the treatment of this encephalopathic epilepsy of childhood.

Drug interactions and adverse events are increased with FBM rapid-dose titration. In adults, a dose of 1,200 mg/d is recommended during the first week, with a reduction of concomitant antiepileptic dose by approximately one-third. It is recommended that the FBM dose be increased to 2,400 mg during the second week of treatment and that the concomitant AED dose be further decreased over the second and subsequent weeks. In the third week, the FBM dose should be increased to 3,600 mg. In children, doses of 15, 30, and 45 mg/kg/d were recommended in a titration schedule similar to that of adults. Slower titration schedules and removing one concomitant medication at a time after the initial one-third reduction allows better success for titration. Some children with refractory epilepsy require daily doses of 75 to 90 mg/kg/d, while adults may require doses of 5,000 to 6,000 mg/d.

For most patients, FBM is not a first-choice therapy because of the associated risk of aplastic anemia. The incidence of aplastic anemia linked to FBM administration is estimated to be approximately 1 in 5,000 to 1 in 4,000 treated patients. At highest risk are female patients with prior blood dyscrasia, immune disorders (especially lupus), and prior hypersensitivity to other medications. No child younger than 13 years of age has been reported to have developed FBM-related aplastic anemia, and most cases occurred during the first 6 months of therapy. A toxic metabolite of FBM has been identified, and its concentration or host susceptibility through inadequate glutathione reductase or other scavenger system deficiencies may lead to idiosyncratic reactions. A urine test to assess this metabolic pathway is available. Severe hepatotoxicity also has been associated with FBM administration without a clear predominance in young children, as seen with VPA. The most common adverse reactions associated with FBM administration include anorexia, vomiting, insomnia, headache, and somnolence. As noted above, slow initial titration and monotherapy administration reduce the frequency of side effects.

Thus, FBM should be reserved for treatment of those adults and children with severe epilepsy refractory to other therapies. Those with resistant partial epilepsy that does not respond to other agents or those with resistant broader syndromes, such as Lennox-Gastaut syndrome or myoclonic epilepsy, may benefit from FBM when other agents fail.

Gabapentin

GBP is approved in the United States and throughout the world as adjunctive therapy in the treatment of partial and secondarily generalized seizures in adults. Its use has been extended to increased dosage and monotherapy, and it is now generally used in children, as are all other AEDs shown to be effective for the treatment of partial seizures in adults. GBP was the first of the new AEDs to be extensively tested in children of all ages older than 1 month to demonstrate efficacy and safety in children with refractory and benign syndromes of partial epilepsy. Although synthesized as an analogue of GABA, it may produce its anticonvulsant action through various other mechanisms. Initial clinical trials demonstrated a $\geq$ 50% reduction in seizures in about 25% of adult patients who received dosages between 1,200 and 1,800 mg/d as adjunctive therapy. Subsequent clinical experience and investigations have shown increased efficacy with increasing doses of GBP as adjunctive or monotherapy, extending the dosage to 6,000 mg/d or

above. The initial recommendation for daily dosages in adults of 1,200 to 1,800 mg now seems too low for many patients, and a range of 2,400 to 4,800 mg/d seems more appropriate for those with refractory partial seizures. In children, initial studies were performed using 20 to 30 mg/kg/d, but as has been seen in adults, increased dosing to at least 60 to 100 mg/kg/d should be considered in those who continue to have refractory partial seizures.

GBP does not bind to plasma proteins and crosses the blood-brain barrier in concentrations similar to those in plasma. It has no metabolism, does not induce hepatic microsomal enzymes, and does not interact with other drugs. This lack of interaction makes GBP an AED of choice in the treatment of patients on multiple other medications, whether for the treatment of epilepsy or for other medical conditions. Renal clearance is linearly related to creatinine clearance, and the elimination half-life is estimated to be between 5 and 9 hours. Initial GBP dosing recommendations for adults are to begin with 300 mg/d, 1,600 mg taken in two divided doses on day 2, and 900 mg in three divided does on day 3. Titration is then continued rapidly to reach approximately 1,200 to 1,800 mg. Many tolerate 900 mg GBP on day 1, but in some patients, transient neurotoxicity occurs with more rapid dose escalation. The side effects of GBP are generally mild and transient, including drowsiness, fatigue, somnolence, and occasional weight gain. A relatively rarely noted adverse effect is the exacerbation of myoclonic seizures in those who most likely have primary generalized epilepsy. Neurotoxic adverse effects tend to increase with dosage escalation. Positive effects on mood and adjustment are seen to the greatest degree with lowdose GBP. Irritability, temper outbursts, aggressive behavior, and dysphoria have been reported and may be more frequent in mentally retarded children and adults. Although hyperactivity and aggression have been noted in some children, few have required discontinuation of drug because of these side effects.

GBP is the easiest new AED to use because of its lack of pharmacokinetic interactions and the ability to perform dosage titrations relatively rapidly. Because of its properties, GBP may have substantial advantages for treatment of the elderly, women, children, those with multiple handicaps, and those receiving concomitant therapy for other disease states. It has been shown to be very effective in the treatment of neuropathic pain. No life-threatening adverse reactions have been reported. Multiple daily doses are required, but it is available in larger capsules and a liquid preparation. There is no parenteral formulation.

Lamotrigine

LTG is a chemically unique compound with anticonvulsant potential against numerous seizure types. It appears to block the release of glutamate through stabilization of the presynaptic membrane by blocking voltage-dependent sodium channels, but additional mechanisms of action may well be responsible for its broad range of clinical efficacy. Placebo-controlled studies have demonstrated LTG's efficacy as add-on medication in partial seizures and in the treatment of Lennox-Gastaut syndrome. In addition, LTG is commonly used for the treatment of other primary generalized epilepsy in both adults and children.

The pharmacokinetic profile of LTG indicates that it has a peak plasma concentration achieved in 1 to 3 hours and a volume of distribution in adults of 1.0 to 1.3 L/kg. Plasma protein binding is approximately 55%, thus having no clinical significance. The drug is eliminated through urinary excretion in the form of two glucuronide compounds, with an additional portion of the drug eliminated as the unchanged parent drug. Although LTG has few interactions on other agents, its clearance is influenced by concomitant AEDs. The half-life of LTG is 25.4 hours in adults, when administered alone, but is shortened to 14 hours if the patient receives other AEDs that induce hepatic enzymes. VPA inhibits glucuronidation and prolongs the half-life to a mean of 59 hours. A half-life of $\leq$ 10 hours is seen in children younger than 12 years who are taking enzyme-inducing drugs, 15 to 26 hours in children taking combined VPA and enzyme-inducing drugs, and 44 to 94 hours in children taking only VPA with LTG. These pharmacokinetic properties must be remembered as cotherapy is added or removed throughout the course of epilepsy treatment. Also, pregnancy and hormonal therapy, including birth control preparations, may significantly lower LTG levels.

The efficacy of LTG against refractory partial epilepsy was demonstrated in multiple double-blind, add-on, placebo-controlled studies, with an overall 50% reduction in approximately 25% of patients. Monotherapy studies comparing LTG to PHT and CBZ revealed the similar or slightly superior efficacy of LTG. Studies in children with Lennox-Gastaut syndrome and refractory partial seizures show similar efficacy. An exacerbation of myoclonic seizures has been noted in some children and adults treated with LTG, whereas it has been helpful in other patients. It has not consistently demonstrated efficacy in the treatment of infantile spasms.

The monotherapy studies, when combined, demonstrate that the tolerability of LTG was approximately twice that of PHT and CBZ when assessed by comparing withdrawal rates for adverse effects. The most frequently cited adverse events are dizziness, diplopia, ataxia, nausea, amblyopia, and somnolence. Overall rash occurred in 10% of patients taking LTG during trials. This overall rash rate is similar to that associated with CBZ. Numerous reports have cited the observation that patients seem more alert when treated with LTG. In

some children, mild appetite suppression and insomnia have been reported. Some encephalopathic children become hyperactive as they brighten.

The significance of potentially serious rash associated with the use of LTG has resulted in special labeling because of this potentially fatal complication. Stevens-Johnson syndrome and toxic epidermal necrolysis are two related serious cutaneous disorders that may be part of a single spectrum Less than 5% of cases of Stevens-Johnson syndrome are fatal, but the estimated mortality of toxic epidermal necrolysis is 30%. These cutaneous reactions may also be accompanied by symptoms suggestive of hypersensitivity, with multiorgan involvement. Initially, rash appeared during the first few weeks of treatment, and, in most cases, it was self-limited, whether or not treatment continued. Subsequently, potentially fatal rashes of the type described above led to an estimate that hospitalization for rash had occurred in approximately 1 per 1,000 adult patients. Patients who had a history of allergy to any drug before LTG treatment had a 2.8-fold increased risk of discontinuation due to rash or fever, whereas patients with a history of allergy to AEDs had a 3.9-fold increased risk. In children the rash rate is higher, approximately 1 in 200 to 1 in 100. Most rashes, however, are benign and promptly resolve on discontinuation of treatment. Mortality from rash is extremely rare and, on the basis of worldwide estimated exposures and spontaneously reported deaths recently attributed to rash, is approximately 1 in 100,000. LTG associated rash almost entirely occurs within the first 8 weeks of exposure. Unfortunately, mild rash may progress to severe rash. Three factors may increase the risk of rash: (1) the patient's age, (2) cotherapy with VPA, and (3) the rate of dose escalation. It is, therefore, suggested that physicians do not exceed the manufacturer's dosing guidelines and that they follow particular attention to whether the patient is receiving VPA.

Patients and their families must be educated about rash as they will be the first to determine this symptom. It is highly recommended that a patient be seen urgently and that LTG be stopped if there is not an alternative explanation for the patient's rash. Slow titration of dosing and removal of VPA from the patient's AED regimen may well decrease the overall rash rate and, most importantly, the potentially serious rash. Rapid titration is not recommended. Recent data confirm the success of this strategy.

LTG is a very useful addition to the armamentarium of AEDs used in the treatment of partial and other generalized seizure types. It is frequently used as initial monotherapy. Favorable pharmacokinetics and efficacy and its nonsedating properties should be balanced by its rash risk and titration schedule.

Levetiracetam

LVT is a pyrrolidine derivative with antiepileptic properties. Its antiepileptic effect does not derive from any known mechanism involved in inhibitory and excitatory neurotransmissions. However, a brain-specific binding site has been demonstrated in synaptic plasma membranes, and the drug shows efficacy in a kindling model of epilepsy. LVT is rapidly and almost completely absorbed after oral administration and is not affected by food. LVT is not protein-bound and its metabolism is not cytochrome P-450 dependent, with 66% of the dose renally excreted unchanged. The pharmacokinetics are linear, with peak plasma levels at 1 hour after administration and a plasma half-life of 6 to 8 hours, yet dosing can be successful twice daily.

There have been three multicenter, double-blind, multinational studies in adult patients with partial-onset seizures. In the first, LVT was compared as an add-on therapy at 3,000 mg/d and 1,000 mg/d with placebo in 293 patients. A responder was defined as having a > 50% decrease in seizures. Response rates of 39.8%, 33%, and 10.8% were seen in the 3,000 mg and 1,000 mg groups of levetiracetam and placebo, respectively. The second trial was a multinational European trial that enrolled 322 patients who were assigned either to treatment groups of 2,000 mg/d or 1,000 mg/d of LVT or to a placebo arm. Following a 4-week titration and a 12-week treatment phase, good efficacy also was demonstrated with the higher-dosing group, with a responder rate (> 50% seizure reduction) of 30.9% and a responder rate of 22.8% in the lower-dosing group. A response rate of 11.2% was seen in the placebo group. In the third study, LVT was started as add-on followed by a monotherapy treatment period. The study involved 261 patients, with 171 randomly assigned to 3,000 mg/d and 90 randomly assigned to a placebo control group. In the treatment group, responder rates as defined above were 42.1% during the add-on phase and 59.2% in the monotherapy phase. Combined (for all three trials in 904 patients), efficacy rates were 12.6%, 27.7%, 31.6%, and 41.3% for placebo, 1,000 mg, 2,000 mg, and 3,000 mg LVT, respectively.

Although formal trials continue, LVT use in children has increased. In one open-label trial in 24 patients aged 6 to 12 years, LVT was started at 10 mg/kg/d divided into two doses and titrated to 40 mg/kg/d. Twelve of 24 achieved a > 50% response rate. Applicability to other seizure types is currently being investigated. Dosing in children is approximately one-third higher on a mg-per-kg basis than in adults.

LVT is well tolerated and has a good safety profile. The most common adverse events were asthenia (32.4%),

somnolence (19.2%), and dizziness (18.7%). These were considered minor, and 79.6% improved. No potentially life threatening complications were seen. In children, similar adverse effects were reported, along with nervousness. This post-marketing experience with LVT has identified behavioral reactions characterized by hyperactivity and aggression, with rare reports of psychosis. All were reversible with discontinuation and in many instances pretreatment reactions or diagnoses placed these individuals at higher risk for these behavioral manifestations. The role of LVT in pediatric and adult epilepsy is still evolving, with reports of success against a broader spectrum of seizure types, including generalized epilepsy, such as juvenile myoclonic epilepsy (JME). Its potential effect on altering epileptogenesis because of its effect in the kindling model makes it an attractive AED to use early in childhood. Controlled studies are under way in both partial seizures and other types of epilepsy.

Oxcarbazepine

OXC is a homologue of CBZ. It was developed as an alternative to CBZ for patients who had adverse reactions to CBZ or PHT. OXC is the 10-keto derivative of CBZ. It is not metabolized into a 10,11 epoxide, leading to improved tolerability. OXC is similar to CBZ in its mechanisms of action and has its antiepilepsy effect through its active metabolite 10,11-dihydro-10-hydroxy-5H-dibenzo (b,f) azepine-5-carboxamide (monohydroxy derivative). Most of the clinical development took place during the early 1990s, though use in several countries dates back more than 15 years.

Typical dosing is recommended to start at 300 mg/d in adults, increasing to 900 to 1,200 mg/d, though it has been effectively increased to 3,000 mg/d. Typical dosing in children is 10 mg/kg/d, advanced to a mean dosage of 60 mg/kg/d. Early experience with OXC suggests that starting at half the initial recommended dose (ie, 150 mg/d in adults or 5 mg/kg/d in children) may lead to better tolerability. Absorption is about 95% following oral intake, and peak concentrations are reached within 4 to 6 hours. OXC is 38% protein bound. The plasma half-life is 8 to 13 hours and linear.

Numerous studies have been carried out using OXC both as adjunctive and monotherapy in adults and children. In one early trial, OXC was compared with CBZ in an add-on, randomized, crossover trial in 40 adult patients. Mean dosages for CBZ were 500 to 2,000 mg/d and 900 to 3,600 mg/d with OXC. No difference in efficacy was seen.

In the Scandinavian multicenter trial, 235 drug-naive patients with newly diagnosed epilepsy were randomized to treatment with either OXC or CBZ. The study comprised patients with partial seizures with or without secondary generalization. In both groups, more than 80% of the patients experienced at least 50% seizure reduction with no significant difference in the two treatment arms. However, with regard to toxicity, a significant difference in favor of OXC was demonstrated, with a higher number of patients stopping CBZ.

A recent study looked at OXC in children younger than 7 years of age, including a 7-month-old infant. A mean maximum dose of 50 mg/kg/d (range, 21 to 86 mg/kg/d) was reported. Thirty-three of 53 patients had a > 50% seizure reduction, and 12 of 44 with a focal-onset seizure became seizure free.

The most commonly reported side effects are tiredness, headache, dizziness, and ataxia. The side-effect profile is very similar for OXC and CBZ, but the number of side effects seems to be higher with CBZ than with OXC. Skin rash has been seen but is rare, and some patients demonstrating sensitivity to CBZ have not developed a reaction with OXC. OXC treatment is sometimes associated with the occurrence of hyponatremia, probably through regulatory changes in antidiuretic hormone. This effect is mild and reversible, but it increases at doses higher than 25 to 30 mg/kg/d. In those with multiple handicaps with altered fluid intake patterns, hyponatremia may be more frequent. No significant systemic toxicity, such as bone marrow suppression or hepatic failure, has been seen.

This drug possesses an advantage in producing less in toxicity and rashes, making it a welcome addition to the AED armamentarium. CBZ is available in numerous dosing formulations, allowing it to be easily given to children. With the development of these formulations for OXC, this AED will certainly become one of the drugs of choice for the treatment of partial and secondarily generalized seizures.

Pregabalin

Pregabalin (PGB) is a new anti-epileptic drug related to gabapentin and approved for the treatment of partial seizures with or without secondary generalization. It has a linear pharmacokinetic profile and is readily bioavailable. Maximum serum levels are achieved in less than 1.5 hours. Its plasma half life is 6.3 hours in adults but it is dosed on a twice daily schedule there is no protein binding, and no active metabolism, and it is 90% renally excreted as an unchanged compound. This AED, like gabapentin (GBT) and levetiracetam (LEV), has no demonstrated pharmacokinetic interactions but pharmacodynamic interactions are to be expected, as with other medications.

Efficacy was noted in a number of studies demonstrating a significant reduction in seizure frequency when PGB was added to existing treatment in those with refractory epilepsy at a dose of 200–300 mg taken two or three times daily. Pregabalin binds to the alpha 2 delta subunit of

voltage gated calcium channels in the central nervous system, which are felt to modulate calcium influx in hyperexcited neurons and to reduce neurotransmitter release, but the exact mechanism of action is yet to be determined. Adverse effects are typically symptoms of neurotoxicity such as dizziness and somnolence. Weight gain and peripheral edema have also been reported. PGB is a scheduled V controlled substance with very little likelihood of drug abuse and dependence.

Adult dosing with PGB is recommended to start at 150 mg daily in divided doses with an increase to 300 mg per day as tolerated. Pediatric trials are underway with PGB dosing beginning at 2–4 mg/kg/day in divided dosing with suggested increases to 5–7 mg/kg/day.

Tiagabine

TGB is one of two new drugs whose action directly affects the GABA system. By increasing GABA, the primary inhibitory neurotransmitter, seizures are decreased. Barbiturates and benzodiazepines act on the GABA receptor, and VPA is a GABA analogue. Whereas VGB (see below) is an irreversible inhibitor of GABA transaminase, which blocks degradation and therefore increases levels of GABA, TGB consists of nipecotic acid joined to a lipophilic anchor that was designed to block GABA uptake by presynaptic neurons and glial cells. TGB actually binds to a GABA transport protein, thus competing for GABA binding sites in the transporter. Thus, there is an increase in GABA concentrations and duration of action in the synaptic cleft without substantially altering total brain GABA levels. TGB has undergone extensive clinical trials in adults with intractable partial epilepsy and pediatric trials show similar results.

TGB is rapidly absorbed, with peak blood levels achieved within 2 hours. The mean half-life is 4 to 9 hours, but no significant change in efficacy has been demonstrated in clinical trials that evaluated dosing twice or more frequently daily. TGB is metabolized by the hepatic cytochrome P-450 system and is, thus, induced by barbiturates, CBZ, and PHT, but it does not appear to induce or inhibit hepatic microsomal enzyme systems. Although highly protein-bound (over 95%), it does not appear to interact with most commonly used drugs.

Clinical trials in adults suggest that TGB is an effective AED against partial seizures, with a favorable adverse event profile. When dosages of 16, 32, and 56 mg/d were compared, there was a higher proportion of patients receiving TGB in either 32 or 56 mg/d doses showing a > 50% reduction in the frequency of complex partial seizures. In children, initial doses of 0.1 mg/kg/d are given, with weekly increases to 0.5 mg/kg/d, depending on cotherapy, tolerability, and efficacy. Monotherapy trials clearly show the effect of enzyme-inducing AEDs on the metabolism of TGB. These studies suggest that a response rate of 20 to 25% is common. It has demonstrated some efficacy against infantile spasms but is not used as a first line agent.

Adverse events reported with TGB are frequently dose related and indicate that side effects are better tolerated when the drug is started slowly and titrated upward. The most common adverse events are dizziness, asthenia, and nervousness. Tremor, diarrhea, depression, and emotional lability also were noted. Similar findings have been seen in children. The side effects of weakness and hypotonia have actually been used to advantage to treat spasticity. Nonconvulsive status epilepticus has been noted in patients treated with TGB, but its incidence seems no greater than that seen in the general epilepsy population. No visual disturbance secondary to retinal toxicity, as seen in VGB, has been noted with TGB. Conversion to TGB monotherapy was associated with positive changes of varying degrees on psychological tests, whereas continued adjunctive therapy produced neither positive nor negative changes.

This drug, which is the first available GABA-ergic compound in the United States, offers a significant difference in mechanism of action in the treatment of partial seizures, and controlled studies as well as clinical use show it to be a relatively well-tolerated agent. TGB's efficacy as first-line treatment for patients with partial epilepsy is really untested. Whether it can be an option for treating infantile spasms in children unable to receive alternative medications, such as steroids or VGB, is a real consideration. Also, it may be considered as first-line monotherapy for patients with partial seizures and spasticity.

Topiramate

TPM, a fructopyranose compound, is a structurally novel AED. It has multiple mechanisms of action. It blocks seizure spread and elevates seizure susceptibility by acting on kainate (glutamate) and GABA receptors, sodium channels, and calcium channels; it appears to have a carbonic anhydrase inhibitory effect. It is a drug with a broad spectrum of activity. The pharmacokinetic properties of TPM include high bioavailability, a half-life of approximately 24 hours in adults, linear elimination kinetics, low binding to serum proteins, and few pharmacokinetic interactions with other drugs. Its clearance, however, is increased by enzyme-inducing AEDs, such as PB, CBZ, and PHT. Patients receiving PHT, especially those with higher therapeutic levels, may experience an increase in PHT levels from an inhibition of metabolism.

TPM clearance in children is approximately 50% greater than in adults, so the plasma concentrations of TPM in children will be approximately 33% lower than that seen in adults when both are given an identical dose. TPM is indicated as adjunctive therapy in patients aged

2 to 16 years with partial onset seizures or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with Lennox-Gastaut syndrome. The safety and efficacy of TPM were demonstrated in six double-blind, placebo-controlled clinical trials in adults with partial onset seizures. Adjunctive TPM in dosages ranging from 200 to 1,000 mg/d significantly improved seizure control, and neurotoxicity was found to be related to the speed of dosage titration and increased with higher doses. Taking all studies together, approximately 44% of TPM-treated versus 12% of placebo patients had a 50% reduction in seizures. TPM is not indicated as monotherapy in patients with seizures. A monotherapy trial compared patients receiving 1,000 mg/d with those receiving 100 mg/d of TPM. Among patients completing 16 weeks of double-blind treatment, including 11 weeks of TPM monotherapy, 23% of the high-dose TPM group became seizure free, but none in the low-dose group achieved this outcome. In an extension of the above trial, 66% of patients remained seizure free for > 3 months. Pediatric trials in children with partial seizures and one combining children and adults with Lennox-Gastaut syndrome have shown a broader spectrum of seizure activity beyond partial seizures and have further demonstrated the safety of this agent. Its efficacy against absence seizures seems only moderate, but it has demonstrated efficacy in JME.

The most common side effects in adults and children receiving TPM during controlled trials were dizziness, mental slowing, somnolence, ataxia, fatigue, and fusion impaired concentration and paresthesia. Side effects tend to be mild to moderate in severity, prompting discontinuation in 14% of adult patients receiving TPM versus 3% receiving placebo. The incidence and severity of side effects is directly dependent upon scheduled titration, starting dose, and ultimate dosage of TPM. TPM has also been associated with weight loss, nephrolithiasis, and paresthesias. Open label studies allowing slower titration starting at 25 mg/d and reducing adjunctive AEDs resulted in a much lower adverse-effect rate and fewer TPM discontinuations.

At present, the recommended eventual total daily dose of TPM in adults as adjunctive therapy is 200 to 400 mg/d in two divided doses. Some patients respond equally well to doses as low as 100 mg/d; others require higher doses above 400 mg/d. To control the appearance of adverse effects, it is recommended that the dose be initiated at 25 to 50 mg/d with weekly titrations of an additional 25 to 50 mg. In most children, initial dosing of 0.5 to 1 mg/kg/d should be followed by titration of approximately equal amounts every 1 to 2 weeks to doses of 4 to 10 mg/kg/d.

In summary, TPM appears to be an extremely potent new AED with a broad spectrum of antiseizure activity. Its side effects may be substantially reduced by proper dosing and careful dose titration at the onset of therapy. Although its interactions are few, patients on high-dose PHT should be clinically monitored because of an interaction that may inhibit the metabolism of PHT, with resultant toxicity as PHT levels rise. The full impact of this agent is still being realized, but it appears to be a major AED with broad-spectrum potential that some are now considering a firstline therapy. No hypersensitivity or idiosyncratic reactions have been associated with TPM.

Vigabatrin

VGB is an amino acid that is highly water soluble and acts intracellularly as an irreversible inhibitor of GABA transaminase, thus allowing increased GABA levels to be present at GABA-binding sites and allowing increased inhibitory neurotransmission. Although its serum half-life is only 5 to 7 hours, it effective half-life is much longer, as it irreversibly binds to the enzymatic site. VGB does not appear to interact significantly with most other AEDs because it is not metabolized and is excreted unchanged in the urine. At a dose of 50 mg/kg, VGB causes a 200 to 300% increase in GABA in the cerebrospinal fluid (CSF) and brain tissue. A reduction of VGB dose in adults from 3 g/d to 1.5 g/d results in a proportional reduction of GABA concentrations in the CSF. However, there does not seem to be a direct relationship between efficacy and percentage increase in GABA in the CSF. Development of VGB in the United States was delayed because of the presence of intramyelinic vacuolization and edema in specific areas of rodent and canine brains. These effects were reversible when VGB was stopped. More recently, visual field changes secondary to retinal toxicity have been reported in more than 30% of those treated.

The efficacy of VGB against partial seizures has been assessed in multiple studies in adults and children. Remarkable response rates (50% reduction) in adults receiving 2 to 3 g/d of vigabatrin as add-on therapy in double-blind, placebo-controlled studies revealed response rates ranging from 33 to 64%. VGB is most effective against partial seizures but may exacerbate myoclonic seizures.

Numerous studies have demonstrated similar data for pediatric partial seizures, but perhaps the most exciting reports have come from trials on the treatment of infantile spasms, where VGB has shown superior results, especially in children with tuberous sclerosis. Results of trials with children and adults with Lennox-Gastaut syndrome are less encouraging.

Sedation and fatigue are the adverse effects most commonly reported in clinical trials, followed by dizziness, weight increase, agitation, abnormal vision, amnesia, and nystagmus. Depression, confusion, and other behavioral abnormalities have also been reported. A small number of

patients have developed psychoses. In children, hyperactivity and agitation are reported in up to 50% of patients, especially when high doses of VGB are administered.

VGB is commonly administered once or twice daily, beginning with 500 to 1,000 mg daily and increasing by approximately 500 mg weekly, up to 3 g or 50 mg/kg/d for the treatment of partial seizures. Very young children with infantile spasms frequently receive doses in excess of 100 mg/kg/d.

The further development of VGB in the United States has been delayed because of its toxicity profile, but its effect in infantile spasm remains superior.

Zonisamide

ZNS is chemically similar to indole. ZNS has been demonstrated to affect voltage-dependent sodium channels as well as block T-type calcium channels. ZNS is rapidly and almost completely absorbed. Peak levels are achieved in about 3 hours. Protein binding is 50 to 60% in humans. ZNS has a half-life of 50 to 68 hours and is extensively metabolized. The drug undergoes reductive biotransformation to the open ring metabolite 2-sulfamoylacetylphenol. Typical starting dose in adults is 100 mg/d and in children 1 to 2 mg/kg/d twice or three times daily. Maintenance is typically 200 to 600 mg/d in adults and 4 to 10 mg/kg/d in children.

The drug's efficacy was evaluated initially in adults with partial complex seizures. These studies yielded very similar results, with 29 to 30% achieving > 50% seizure reduction. Studies comparing the efficacy of CBZ for partial seizures and of VPA for generalized seizures showed similar efficacy. Early reports of ZNS efficacy in myoclonus are of particular interest to practitioners treating children with epilepsy. Though numbers are small, responses have been seen in patients with Baltic myoclonus and other patients with progressive myoclonic epilepsy, myoclonic epilepsy with ragged-red fibers, and severe myoclonic epilepsy of infancy.

ZNS is a preferred AED for the treatment of JME in Japan, but not for childhood absence epilepsy. Growing evidence demonstrates ZNS efficacy in infantile spasms. Open studies in both Japan and the United States have demonstrated approximately two-thirds of children for whom other therapies have failed have become spasm free. Initial elevated dosing of 5 to 10 mg/kg/day is recommended. Lethargy and irritability are the most common adverse effects in these infants.

Overall, adverse events reported were somnolence, ataxia, anorexia, confusion, and abnormal thinking, with the incidence rate significantly higher in the ZNS group than in placebo group (92 versus 58% and 59 versus 28%, respectively). Discontinuation rates because of adverse events in the U.S. studies were 14% in the ZNS group and 1% in the placebo group. In the European studies, the discontinuation rate because of adverse events was 3% in the ZNS group; there were no discontinued cases in the placebo group.

In further studies, 13 of 505 patients developed nephrolithiasis. Ten of the 13 patients had positive histories of renal calculi or urinary tract abnormalities. The following adverse events were reported: Stevens-Johnson syndrome, Lyell's syndrome, agranulocytosis, and acute renal failure. A small number of patients with hyperthermia associated with decreased sweating (oligohydrosis) has been reported. These individuals are almost all children or mentally retarded adults. Adequate hydration leads to recovery without drug discontinuation.

The role of ZNS in the treatment of pediatric epilepsy is still evolving. Certainly, if results in myoclonic seizures and infantile spasms hold true, this drug will receive much wider use in the pediatric population than its current adjunctive indication for partial seizures in adults. Although new in the United States, ZNS is considered to be the drug of choice in Japan for the treatment of certain generalized seizure syndromes, such as JME.

A Rational Approach to Treatment

With numerous agents now available for the treatment of epilepsy, one needs to consider which is best for the individual patient. As shown in Figure 23-1, the selection of the first-choice drug should be made on the basis of a patient's seizure type or types. Unfortunately, the initial clinical studies designed for the licensing of new compounds rarely give sufficient information to establish the ultimate dosing and use characteristics that will be determined after long-term use in much larger populations of patients. Furthermore, comparative studies that have evaluated a number of the new AEDs frequently employ strategies for starting doses of medication, titration schedules, and restrictions on dosage alterations that do not reflect typical clinical practice. Thus, although these studies are valuable, they may not be absolutely clinically relevant. Metaanalysis studies also give information of comparative value by determining odds ratios for 50% responders, the likelihood of withdrawal, and the number needed to be treated to find the responder. Unfortunately, confidence intervals do not allow a true separation of agents. The pitfalls of meta-analysis studies are such that they can be used only to a certain degree.

Perhaps a starting point for the selection of initial AED therapy would be to consider which drugs may be considered first-line monotherapy for specific epilepsy types. For partial seizures, all the classic AEDs (CBZ, PHT, PB, primidone, and VPA) have been shown to be useful. The side effect profiles and experience using each agent may well determine the drug of choice for individual physicians and patients. Such issues as risk

factors for idiosyncratic effects because of a prior drug reaction, likelihood of weight gain or weight loss, and likelihood of developing behavioral side effects (eg, irritability, hyperactivity, lethargy, or potential effects on cognition) will certainly be factored into the equation. For this reason, most patients will not receive a barbiturate as a first-line drug. Of the newer AEDs, reports support the use of GBP, LTG, TPM, OXC, TGB, ZNS, or FBM as monotherapy. Nearly all would be appropriate for the treatment of partial seizures. One might ask whether most patients who were previously considered for treatment with CBZ should now be started on OXC because of its potential for decreased deleterious effects. For generalized seizures seen in children, ESX and VPA remain the two most widely used AEDs for the treatment of absence seizures; LTG has been demonstrated to have good antiabsence activity and also should be considered as first-line therapy in some individuals. The titration schedule for LTG and the relatively rare occurrence of rash when used as monotherapy at a proper titration rate will certainly influence the choice of this agent sooner or later.

Similarly, adverse effects of VPA and ESX must be balanced. In the treatment of generalized symptomatic epilepsies, such as Lennox-Gastaut syndrome, FBM demonstrated the highest degrees of adequacy against atonic seizures, but its toxicity profile, even though young children seem to be the least at risk, make it a fourth- or fifthline drug. First choices for Lennox-Gastaut syndrome include VPA and, more recently, LTG and TPM. LTG tends to be a better agent against absence seizures, whereas TPM in our clinical experience does not demonstrate the exacerbation of myoclonic type seizures seen with LTG.

A balance between potential serious adverse effects and idiosyncratic reactions and efficacy is probably the leading factor in determining the drug of choice for monotherapy. If the first drug is unsuccessful, a second monotherapy trial should be undertaken. Just as with the first-choice drug, the adverse effects associated with the second-choice drug—including cosmetic, weight gain, and women's issues, and the likelihood of behavior changes or neurotoxicity—also must be considered. Table 23-2 depicts a suggested approach to sequencing the choice of AEDs.

The ultimate question is whether a "drug of choice" is truly established for every patient with epilepsy. Certainly, individual patient characteristics will determine some choices. Data reveal slightly increased efficacy of one agent over another but do not clearly place one of the new or classic AEDs as the drug of choice for all patients. In selecting the drug of choice for the individual patient with epilepsy, seizure type, epilepsy syndrome, pharmacokinetic parameters, ease of use, and, above all, drug tolerability and lack of adverse effects should be considered. Effects on comorbid conditions, positive or negative, also must be considered. New and established AEDs must all be considered when selecting the first-choice AED.

Suggested Readings

Levy RH, Mattson RH, Meldrum BS, editors. Antiepileptic drugs. 5th ed. New York (NY): Raven Press; 2000.

Pellock JM, Bourgeois BFD Dodson WE, Nordli D, Sankar R. editors. Pediatric epilepsy, diagnosis and therapy. 3rd ed. New York: Demos; 2007, in press.

Pellock JM. Treatment of epilepsy in the new millennium. Pharmacotherapy 2000;20 (8 Pt 2):129S–38S.

Wheless JW, Clarke DF, Carpenter D. Treatment of pediatric epilepsy: expert opinion, 2005. J Child Neurol 2005 Dec;20 Suppl 1:S1–S5.

Practitioner and Patient Resources

The Epilepsy Foundation of New Jersey
2150 Highway 35 North, Suite 207-C
Sea Girt, NJ 08750
Phone: (732) 974-1144 or (800) 372-6510
E-mail: fscnj@aol.com
http://www.efnj.com
The Epilepsy Foundation of New Jersey is dedicated to the education and support of people with developmental disabilities including epilepsy, cerebral palsy, autism, mental retardation, spina bifida, and traumatic brain injury, their families, caregivers, and health care professionals.

Epilepsy Foundation
4351 Garden City Drive, Suite 406
Landover,MD 20785-2267
Phone: (301) 459-3700 or (800) EFA-1000
E-mail: postmaster@efa.org
http://www.epilepsyfoundation.org
The Epilepsy Foundation will ensure that people with seizures are able to participate in all life experiences and will prevent, control, and cure epilepsy through research, education, advocacy and services.
www.epilepsy.com
General epilepsy information

TABLE 23-2. Comparison of Recommendations for the Treatment of Pediatric Epilepsy

Seizure Type or Epilepsy Syndrome	Pediatric Expert Consensus Survey[a]	ILAE[b]	SIGN[c]	NICE[d]	French Study[e]	FDA approved[f]
Partial onset	OXC, CBZ	A: OXC; B: None	PHT, VPA, CBZ, LTG, TPM,OXC, VGB, CLB	CBZ, VPA, LTG, OXC, TPM	OXC, CBZ, LTG (adult males)	PB, PHT, CBZ, OXC, TPM
BECT	OXC, CBZ	A, B: None	Not specifically mentioned	CBZ, OXC, LTG, VPA	Not surveyed	None
Childhood absence epilepsy	ESM	A, B: None	VPA, ESM, LTG	VPA, ESM, LTG	VPA, LTG	ESM, VPA
Juvenile myoclonic epilepsy	VPA, LTG	A, B, C: None	VPA, LTG, TPM	VPA, LTG	VPA, LTG	TPM
Lennox-Gastaut syndrome	VPA, TPM, LTG	Not reviewed	Not specifically mentioned	LTG, VPA, TPM	Not surveyed	FLB, TPM, LTG
Infantile spasms	VGB, ACTH	Not reviewed	Not specifically mentioned	VGB, corticosteroids	Not surveyed	None

ACTH: adrenocorticotropic hormone; BECT: benign childhood epilepsy with centro-temporal spikes; CBZ: carbamazepine; CLB: clobazepam; ESM, ethosuximide; FLB: felbamate; LTG: lamotrigine; OXC: oxcarbazepine; PB: phenobarbital; PHT: phenytoin; TPM: topiramate; VPA: valproate; VGB: vigabatrin.

[a] Drugs rated as treatments of choice listed.

[b] International League Against Epilepsy, 2005 Recommendations listed according to levels of evidence supporting the efficacy of the options. Level A: > 1 Class I RCT or > 2 Class II RCTs; Level B: 1 Class II RCT; level C: > 2 Class III RCTs. A Class I study was defined as a randomized clinical trial (RCT) or meta-analysis of RCTs that meets all the following 6 criteria: primary outcome variable is efficacy or effectiveness; treatment duration: > 48 weeks; double-blind study design; superiority demonstrated or detectable non-inferiority boundary (DNIB) < 20%; study exit not forced; appropriate statistical analysis. A Class II study was defined as a RCT or meta-analysis meeting all the Class I criteria except no superiority was demonstrated and DNIB 21-30% or treatment duration > 24 weeks but < 48 weeks. A Class III study was defined as a RCT not meeting all criteria for any Class I or Class II category; open-label study or DNIB > 30% or forced exit criterion. (Note these ratings did not take safety data into consideration.)

[c] Scottish Intercollegiate Guidelines Network. Diagnosis and management of epilepsies in children and young people: A national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network; March 2005 (Copies available at: http://www.sign.ac.uk/pdf/sign81.pdf).

[d] National Institute for Clinical Excellence, Technology appraisal Guidance 79; Newer drugs for epilepsy in children (www.nice.org/uk/TA 079 guidance) and Clinical Guideline 20, The epilepsies: The diagnosis and management of the epilepsies in adults and children in primary and secondary care, October 2004 (www.nice.org/uk/CGO20NICE guideline). CBZ, VPA suggested as first choices when appropriate; if they do not benefit the child or are unsuitable, clinical can try newer antiepileptic drugs.

[e] Semah et al. 2004.

[f] FDA approval for each seizure type or epilepsy syndrome. Standard antiepileptic drugs (PB, PHT, CBZ) often have no specific seizure type listed in approval. Newer drugs are listed only if they have a monotherapy approval (except for Lennox-Gastaut syndrome and juvenile myoclonic epilepsy, where listing indicates adjunct therapy) extending into the pediatric age range (< 16 years). Topiramate is approved for the treatment of general epilepsies, including juvenile myoclonic epilepsy.

In: Wheless, JW, et al. Treatment of Pediatric Epilepsy: Expert Opinion, 2005. JCN Vol, Suppl 1, Dec. 2005.

Chapter 24

Home Management of Breakthrough Seizures

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There is a clear clinical and economic rationale for rapid termination of breakthrough prolonged or acute repetitive seizures within the home or school setting. Rectal, nasal, or buccal administration of benzodiazepine anticonvulsant medication by parents or other caregivers is a safe and effective technique for accomplishing this goal. When indicated, development of an abortive therapy plan should take place early during the assessment of a first or recurrent seizure. Such a plan should be in place for all children with convulsive epilepsy, regardless of control.

Having parents and other caregivers administer abortive medication for breakthrough seizures is usually recommended for a relatively narrow spectrum of pediatric seizure patients. This group includes children with a history of status epilepticus or recurrent complex febrile seizures or those with poorly controlled epilepsy who are prone to develop prolonged or clustered seizures. For children with first-time seizures, recurrent simple febrile seizures, or controlled epilepsy, the recommended components of home management for breakthrough seizures include reassurance, seizure education, safety instructions, and use of emergency medical services if needed. This approach appears effective in part because most children with seizures have a favorable prognosis and because previously available delivery systems had limitations, including cost and safety concerns. However, the inherent unpredictable nature of seizures and recent study findings that raised concerns about possible deleterious effects of short-duration seizures and seizure clusters point to an expanded role for in-home abortive medication. The demonstrated safety and effectiveness of rectal diazepam and nasal midazolam, along with improved delivery systems, should enhance use of this therapeutic option.

First-Time Seizures

Most first-time seizures do not recur, and if they do, they are not prolonged or clustered. Analysis of various risk factors allows some predictability regarding future episodes of febrile and unprovoked seizures. Yet, there is no way to eliminate the possibility of a second or more serious seizure event for a particular child after a first-time seizure. In general, first-time febrile seizures that are complex may also be prolonged at recurrence. These patients may be candidates for abortive therapy.

Current practice guidelines rightly recommend not prescribing daily anticonvulsant medication for recurrent febrile seizures or after a first-time unprovoked seizure. Reassurance and education for parents are important components of the initial evaluation of these children. However, in spite of this conservative approach, repeat seizures trigger anxiety and fear in most parents. This may lead to unnecessary, costly visits to the emergency room, adding to parental frustration. Additional morbidity and expense may occur when seizures are treated inappropriately in the emergency department. This is a particular problem in rural areas and in small community hospitals. Although an abortive seizure therapy plan may not always be needed after first-time seizure events, it should be discussed with parents and may be appropriate in many cases.

Established Epilepsy

Despite significant advances in medical and surgical management, 25 to 30% of children with epilepsy remain

intractable. These patients are at higher risk for prolonged seizures or seizure clusters. Even when epilepsy is apparently well controlled, breakthrough seizures may occur. Although less common, breakthrough seizures in this group may become prolonged or repetitive, or develop into status epilepticus. Breakthrough seizures may occur as the result of illness, sleep deprivation, or missed medication. Medication adjustment or planned medication withdrawal may also produce periods of vulnerability. For established epilepsy patients, an abortive home therapy plan is very important for those with intractable seizures, but it is also useful for those with established control who occasionally experience periods of vulnerability.

Morbidity from Prolonged Seizures

The potential for brain injury from convulsive status epilepticus is well known, although most pediatric patients have good outcomes. Findings from recent animal studies and magnetic resonance imaging in children have revealed acute and long-term alterations in hippocampal structure after recurrent seizure clusters or, in some cases, after seizures lasting less than 30 minutes. Effects on brain function from these changes may not be recognized early or easily in at-risk populations. At present, long-term follow-up studies of epilepsy patients and of those with febrile seizures do not indicate that preventing additional seizures or prolonged seizures prevents later development of epilepsy. Yet, the reported association of temporal lobe epilepsy in adults with a history of complex febrile seizures during childhood is of concern. Change in neuronal function and synaptogenesis in the hippocampus after recurrent or prolonged febrile seizures in certain at-risk patients is one explanation for this association that has not been ruled out.

Administering Abortive Medication

Terminating acute repetitive seizures and those extending beyond 5 minutes may prevent status epilepticus. Patients with intractable complex partial epilepsy who typically experience seizure clustering are at significantly higher risk for convulsive status than are patients with nonclustered seizures. In one population study that included both children and adults, 57% of those with afebrile seizures lasting 10 minutes failed to stop without antiepileptic drug treatment. Early intervention for acute breakthrough seizures also facilitates eventual control.

Studies of benzodiazepine use during status epilepticus in animals have revealed a relatively short time window for efficacy, owing to evolving γ-aminobutyric acid receptor insensitivity during continuous seizure activity. In some cases, this window is as short as 10 to 15 minutes. This may be one reason why benzodiazepines lack efficacy when administration is delayed or inadequate doses are used. Optimally, abortive medication should be administered approximately 5 minutes after seizure onset. In most cases, this terminates seizures within 5 to 10 minutes. Avoiding continuous seizure activity longer than 15 minutes may prevent benzodiazepine resistance, hippocampal injury, and development of status epilepticus. Optimal timing for termination of seizure clusters varies and depends on a child's seizure history. In general, we recommend administering abortive medication after the third convulsive seizure in 1 hour, regardless of length.

Training Parents and Other Caregivers: Tips and Pitfalls

The need to administer abortive medication within 5 to 10 minutes after onset of seizure activity precludes reliance upon paramedics or the hospital emergency department. Adequately training parents and other caregivers is crucial to the safe and effective use of abortive seizure medications, and there are some pitfalls to avoid.

Once the diagnosis of a seizure disorder or epilepsy is established, parents should be counseled as much as possible regarding cause, risk of recurrence, and what to do during the next episode. The need for an abortive therapy plan will depend upon several variables. These include the nature of the initial event, recurrence risk, parental anxiety, access to emergency medical care, and compliance with taking daily medication. In some areas, consultation with a child neurologist may take several weeks; thus, an abortive medication plan is particularly useful after a first or second unprovoked seizure, while the family waits for more testing and consultation. This is often a better option for primary care physicians because they can avoid prematurely placing a child on medication, which might not be needed or could potentially worsen an emerging epilepsy if the wrong drug is chosen.

In addition to discussing routine seizure safety measures, parents should be counseled to record details of future seizure events. These include date, time of onset, presence of fever, abortive medication used, medication dose, and seizure duration. Other details, such as bladder incontinence, oral trauma, and localizing features, should be included if present. If possible, home video of the seizure should be recorded. Instructions should be written in a clear, stepwise format and reviewed with parents and other caregivers, such as grandparents. Appropriate personnel at school, camp, or other venues should also be trained. Instructions should include when to use abortive medication, at what dose, and when to repeat a dose. Use of nasal midazolam for in-home abortive therapy is off label, and this should be discussed. A number of sources for preprinted instructions that include many of

these points exist. We recommend in-office teaching for nasal midazolam administration and use of the available Diastat® training video as a way to ensure successful medication administration. Parents should be counseled that calling paramedics or transporting a child to the emergency department is not necessary if seizures are controlled and the child is otherwise stable. Anyone administering rescue seizure medication should learn cardiopulmonary resuscitation (CPR) for children, although it is rarely, if ever, needed. Rescue breathing and airway maintenance are the two components of pediatric CPR most likely to be used. A follow-up phone call to parents 2 to 4 days after initiating a home management plan is another technique that can improve success. Common pitfalls to avoid include unclear instructions, administering an inadequate dose, excessive delay of administration, parents failing to fill or refill the prescription, and leaving medication at home when traveling. The plan should be reviewed at each office visit and modified as needed.

Medication Options

Benzodiazepines (namely diazepam) given rectally and midazolam administered via the nasal or buccal route are currently available options for rapid termination of breakthrough prolonged seizures or acute repetitive seizures at home or school. The demonstrated efficacy and safety of diazepam and midazolam used for the control of status epilepticus, prolonged seizures, and seizure clusters is supported by numerous studies and years of clinical experience. The relatively aqueous insolubility of parenteral diazepam makes it unsuitable for nasal or buccal administration. Use of intermittent oral diazepam tablets or solution for febrile seizures may be an option in selected cases. A dose of 0.3 to 0.5 mg/kg is used and repeated every 8 to 12 hours if a patient's temperature is 38°C or more. A maximum of four to five doses is given per illness. A potential drawback of intermittent medication is that a seizure could occur before fever is noticed.

Other orally administered benzodiazepines, clonazepam, lorazepam, and oral loading with Dilantin® may be considered for breakthrough seizure clusters in exceptional cases of intractable epilepsy if other measures are ineffective. The usual sublingual dose for lorazepam is 0.05 to 0.15 mg/kg. Lorazepam is absorbed more rapidly when given sublingually than orally or intramuscularly, and peak plasma levels are achieved no later than 60 minutes after administration. Disadvantages with oral or buccal lorazepam include irritability and occasional vomiting. This problem and the slow rectal absorption of lorazepam make it unsuitable for rapidly terminating seizures at home. In-home loading with intramuscular fosphenytoin (Cerebyx®) for intractable cases of recurrent status epilepticus is another off-label technique used occasionally. Fosphenytoin requires a large volume when used intramuscularly, which limits its use in infants and small children. Use of Cerebyx® in this manner is rarely indicated and usually reserved for families living far from emergency medical care. Such use requires close supervision and careful training.

Although rectal diazepam is effective for all ages, in general it is best suited for infants and toddlers. Rectal diazepam can be difficult to administer to patients using wheelchairs or during a tonic seizure, and constipation or bowel movements can interfere with absorption. Rectal administration becomes more socially unacceptable to preteens and older children. In addition, school officials are often uncomfortable with rectal administration. For these reasons, we believe nasal or buccal midazolam is the preferred option for school-age children, adolescents, and young adults, although its use in this way is off-label at this time. In one study, 83% of parents or caregivers preferred intranasal or buccal midazolam to rectal diazepam. In a few limited studies, midazolam had a slight edge over diazepam in overall efficacy and speed of action. Whether this observation is clinically significant is not clear.

Rectal Diazepam

Diazepam is a 1,4-benzodiazepine available in tablets, oral solution, parenteral solution, and a rectally administered gel format (Diastat®). For abortive therapy using diazepam, rectal administration is preferred. A rectal gel preparation can be compounded by many pharmacies, and the parenteral solution can be diluted and given via a small, lubricated tube inserted rectally. However, the commercial preparation Diastat® is preferred, because of reliable dosing, absorption characteristics, and a well-designed, easy-to-use administration system. At present, Diastat® is the only commercially available preparation of rectally administered diazepam available in the United States. It is also the only Food and Drug Administration–approved medication for in-home therapy to abort acute seizures. It is approved only for the management of selected refractory patients with epilepsy 2 years of age and older on stable regimens of antiepileptic drugs who require intermittent use of diazepam to control bouts of increased seizure activity. However, its off-label use for patients younger than 2 years and for other acute seizure situations as described earlier is widely accepted and appropriate.

Diastat® rectal delivery system is a nonsterile diazepam gel containing 5 mg/mL of diazepam provided in a prefilled unit dose rectal syringe. It comes packaged with two doses and has a shelf life of 3 years. It does not have to be refrigerated. Available dose sizes are 2.5 mg, 5 mg, 10 mg, 15 mg, and 20 mg. Dosing is based on body weight and age. The recommended doses for ages 2 to 5 years is 0.5 mg/kg, ages 6 to 11 years, 0.3 mg/kg, and ages 12 years and

older 0.2 mg/kg. Because Diastat® is supplied in a fixed-unit dose, the prescribed dose is obtained by rounding up to the next available size. More precise dosing may be obtained by using combinations of the various dose sizes. Plasma concentrations of diazepam, necessary for acute seizure control, are achieved in infants and children within 2 to 4 minutes after rectal administration of 0.5 to 1 mg/kg diazepam. After single-dose rectal diazepam administration, acute prolonged seizures resolved in 60 to 96% of cases, depending on the study. We instruct parents to administer a second dose if seizures continue more than 15 minutes after the first dose. Because of its long half-life, rectally administered diazepam may provide seizure control for up to 12 hours. Parents are told Diastat® may be used more than once in a 24-hour period if needed, but they should call the office if this is necessary. Serious adverse effects from the proper use of Diastat® are exceedingly rare. As of September 2003, 1.6 million rectal gel syringes have been prescribed and more than 1.2 million doses are estimated to have been administered. Thus far, only seven spontaneous reports of respiratory adverse events have been reported. In our own practice, no cases of serious respiratory depression requiring additional medical intervention have been encountered, with approximately 400 doses being administered.

Intranasal Midazolam

Midazolam, another 1,4-benzodiazepine, has an imidazole ring that is open at low pH (3.3), which allows it to dissolve in water; at physiologic pH, the ring closes, which renders it lipophilic, allowing rapid penetration of the central nervous system. Beta activity can be seen on an electroencephalogram 2 to 5 minutes after intranasal administration. The low pH causes nasal irritation and burning or a bitter taste when given buccally but is of no consequence in a seizing child. The mean lag time of midazolam after intranasal administration is 0.84 ± 0.74 minutes. A mean peak concentration is reached after 14 ± 5 minutes. Mean bioavailability is 0.87 ± 0.19 minutes after intranasal administration and 0.24 to 0.45 minutes after oral administration. Mean initial and terminal half-lives are 8.4 ± 2.4 and 79 ± 30 minutes, respectively. Intranasal or buccal administration allows rapid absorption into the systemic circulation, bypassing the portal circulation and avoiding the high first-pass metabolism of midazolam, which occurs after oral administration. Although the half-life of midazolam may be short, its longer duration of effectiveness is likely owing to early interruption of prolonged seizures, seizure clusters, or status epilepticus.

For many years, intranasal midazolam has been used by anesthesiologists as a preanesthetic for children and by dentists for sedation. Buccal midazolam appears to be as effective as rectal diazepam in reducing time to seizure cessation. In one study, intranasal midazolam was found to be more effective than rectal diazepam in terminating status epilepticus in children. In the diazepam group, the seizures of 60% of the patients stopped at 10 minutes, whereas 87% of the seizures stopped in the intranasal midazolam group at 10 minutes.

Since 1994, we have used intranasal midazolam as an alternative to rectal diazepam for the home treatment of acute seizures. Disadvantages of intranasal midazolam include small nares and nasal congestion in infants, which would require alternative buccal administration or use of rectal diazepam. The cost of midazolam is approximately 10 to 20% that of rectal diazepam. Usually 0.5 to 0.8 mg/kg is given after a certain length of seizure, usually 5 minutes. For children who always or almost always have status epilepticus or prolonged seizures, it may be given immediately. Midazolam for intravenous use is available in 5 mg/mL, 1 or 2 mL vials and is usually given in 5 mg aliquots (ie, 5, 10, 15, and 20 mg). To avoid the use of needles, parents can use a blunt plastic cannula (Becton Dickinson Inc. order No. 303345) (Figure 24-1), to withdraw the midazolam from the vial; then remove the cannula from the syringe, attach the MAD® atomizer, (Figure 24-2) (available from Wolfe Tory Medical Inc., www.wolfetory.com), and administer the midazolam intranasally. Do not allow the pharmacist to prefill the syringe because the stability of the midazolam once placed in the syringe is uncertain. If the child has severe nasal congestion, the midazolam can be applied to the buccal mucosa and gums. Specific parent directions of administration are provided in Table 24-1. We have found intranasal midazolam to be an extremely effective treatment for acute seizures. It has a rapid onset of action and we have encountered no significant respiratory suppression in thousands of treatments.

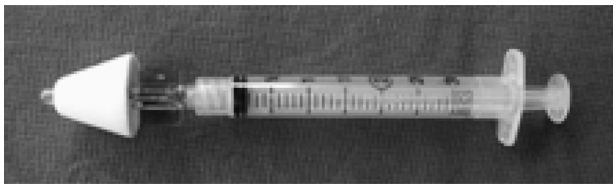

FIGURE 24-1. Blunt plastic cannula.

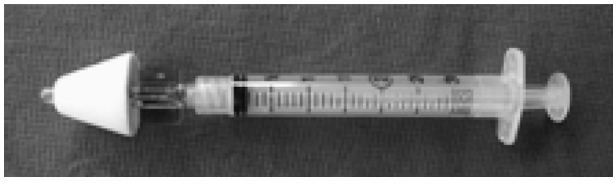

FIGURE 24-2. MAD® atomizer.

TABLE 24-1. Sample Intranasal Midazolam Instruction Sheet

Dose: _____mL (_____mg) to be given after ____ minutes of seizure or _____.

Midazolam is a very potent anticonvulsant that is rapidly absorbed into the bloodstream through the membranes in the nose and mouth. It will usually stop a seizure within 2 to 10 minutes. Midazolam is a short-acting medication. If seizures recur, follow your neurologist's instructions. Midazolam may produce a burning sensation in the nose, but most children are not aware of it during a seizure. Common side effects of midazolam are similar to those caused by a seizure and include drowsiness, dizziness, slurred speech, and loss of memory. If breathing slows or stops, stimulate by gently shaking the child until breathing resumes. It is recommended that caregivers know cardiopulmonary resuscitation (CPR). If a child's nose is very congested or if any midazolam remains in the atomizer, it can be poured between the cheek and gum.

Equipment

1. Midazolam solution for injection (5 mg/mL concentration), supplied in 1 mL or 2 mL vials.
2. 3 mL syringe with attached MAD® atomizer and a blunt plastic cannula (needle) to remove the midazolam from the vial.

Instructions for using the MAD® atomizer

1. Remove the plastic cap from the midazolam vial.
2. Unscrew the MAD atomizer device and remove it from the 3 mL syringe.
3. Remove the plastic protector from the blunt plastic cannula (needle) and screw the cannula onto the end of the MAD atomizer syringe.
4. Holding the midazolam vial upside down, push the plastic cannula (needle) tip through the rubber stopper of the vial and withdraw _____ mL of midazolam into the MAD atomizer syringe.
5. Remove the cannula from the syringe and replace it with the MAD atomizer device.
6. The child's head can be in any position for administration.
7. Place the tip of the atomizer into one nostril and press the plunger until one-half of the midazolam has been atomized, and then atomize the remainder into the other nostril.

Suggested Readings

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Practitioner and Patient Resources

Diastat.com
http://www.diastat.com
Information on Diastat® from Xcel Pharmaceuticals.

CHAPTER 25

MANAGEMENT OF INFANTILE SPASMS (WEST SYNDROME)

RAILI S. RIIKONEN, MD, PHD

Infantile spasms, also known as West syndrome, is an epileptic encephalopathy with heterogenous etiology. The only constant feature is their limitation to a certain time period of infancy. A favorable outcome is only possible when the spasms are controlled and the hypsarrhythmia resolves.

Infantile spasms or West syndrome consists of infantile spasms, hypsarrhythmia, and mental retardation. The spasms are usually resistant to conventional antiepileptic drugs. The typical syndrome has its onset between 3 and 7 months of age and seldom after one year of age.

Now, however, it is known that there is a great variability of the features. Any feature of this classical triad may be missing. According to the up-to-date classification (ILEA 2001), West syndrome is an epileptic syndrome consisting of clinical spasms usually in clusters with epileptiform EEG, and with onset usually at less than two years of age.

The incidence of West syndrome has been estimated to vary from 1.6 to 4.3% of live births. There has been no change in this incidence over the last 30 years.

Two main types of the syndrome are recognized: symptomatic and cryptogenic. In symptomatic (80%) spasms, there is a history of pre, peri, or postnatal damage or disease, and the predisposing etiology can be identified. In cryptogenic (15–20%) spasms, there is normal development prior to the onset of the spasms, and no known cause is revealed by clinical and neuroradiologic examinations. The cryptogenic group of infantile spasms probably also has a symptomatic etiology, but underlying causes remain hidden. The rare idiopathic (5%) form refers to a pure functional cerebral dysfunction. Genetic factors play an important role.

The terms idiopathic and cryptogenic have been used synonymously in some studies. Classification depends heavily on the extent of the investigations performed. Furthermore, patients who have been classified cryptogenic by conventional means have been recently shown to have focal regions of altered perfusion and metabolic function. If positron emission tomography (PET) and single photon emission tomography findings are incorporated into this classification, the number of cryptogenic cases will decrease markedly.

Spasms

The spasms may be flexor, extensor, or most commonly, mixed. One child can have various types of spasms. The presence of subtle spasms, asymmetric or asynchronous spasms, and focal signs suggests a symptomatic etiology and an unfavorable outcome in the long-term. A number of investigators have documented the coexistence of partial seizures occurring in patients with infantile spasms. Spasms occur in series. They are common in drowsiness and especially on arousal or soon thereafter. A vast number of spasms are missed by parents when compared with those seen in video monitoring. The diagnosis of infantile spasms is easy when they are typical. However, the spasms are often misinterpreted and considered to be colic, startle responses, or normal infant behavior. Repetitive, stereotyped characterization of any movements in infancy should arouse the suspicion of infantile spasms and lead to an immediate EEG examination.

EEG

Hypsarrhythmia consists of a pattern of irregular, diffuse, asymmetric, high-voltage slow waves interspersed with

sharp waves and spikes, distributed randomly throughout scalp recordings (total chaotic disorganization of cortical electrogenesis) (Figure 25-1). The term "modified hypsarrhythmia" (occurring in about 40%) is used if there is some preservation of background rhythm, synchronous bursts of generalized spike-wave activity, significant asymmetry, or burst-suppression of tracing. A constant focus of abnormal discharges may also precede, accompany, or follow hypsarrhythmia. Multifocal spikes may also evolve into hypsarrhythmia if there is a long delay before treatment of spasms. A transition from typical hypsarrhythmia to a pattern of multifocal spike activity during treatment with vigabatrin (VGB) is observed in a number of patients.

The most common ictal pattern associated with symmetric spasms is a generalized slow wave, usually followed by attenuation of background activity. A constantly normal tracing, including sleep recording, rules out the diagnosis of infantile spasms. Sometimes the infant ceases to take interest in his surroundings, and blindness is suspected. This functional amaurosis is seen in association with missing or grossly abnormal patterns of visual evoked potentials and probably corresponds to perfusion defects involving the parieto-occipital areas. In addition, behavioral regression of an infant less than one year of age should lead to an EEG examination, in which hypsarrhythmia may reveal the cause of the regression.

Differential Diagnosis

Benign myoclonus of early infancy may closely mimic infantile spasms, but the EEG is constantly normal. Benign myoclonic epilepsy may also be misdiagnosed as infantile spasms, but the EEG shows generalized spike-wave complexes during early stages of sleep. Syndromes closely related to West syndrome include early infantile epileptic encephalopathy, early myoclonic encephalopathy, and the syndrome of periodic, lateralized spasms. The two former syndromes both have a burst-suppression pattern in EEG. The three syndromes include patients with very serious brain pathology and outcome. In a quarter of patients, West syndrome evolves into Lennox-Gastaut syndrome, which is an important differential diagnosis in patients older than one year of age.

Investigations before Starting Treatment

The EEG is currently the only laboratory test that provides specific information useful for the diagnosis of

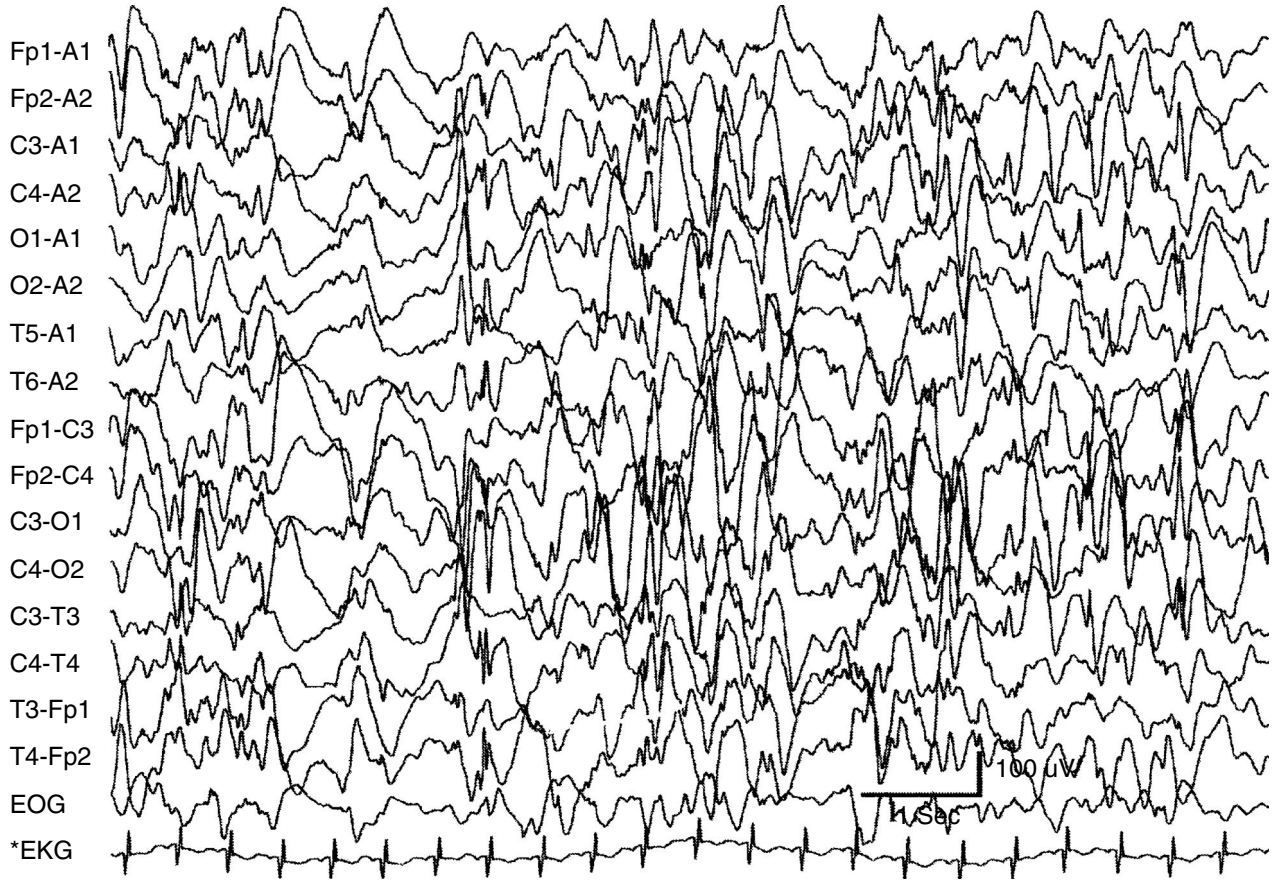

FIGURE 25-1. Classic hypsarrhythmia in a 6-month-old boy with cryptogenic infantile spasms. Irregular, diffuse asymmetric, high-voltage slow waves interspersed with sharp waves and spike arising multifocally.

infantile spasms. The interictal EEG is nearly always abnormal. The EEG should always include recordings in the awakening, awake, and sleeping states. The initial diagnosis of infantile spasms requires video-EEG studies in infants with symptomatic etiology, who may show only subtle spasms (head nodding, shoulder shrugging, grimacing, eye deviation).

Careful search for etiologic factors should be done in every case for formulation of a more accurate prognosis and establishing the need for genetic counseling (Table 25-1). More than 200 potential etiologic factors are reported. In a large population-based study, the etiologic factors were brain malformations and tuberous sclerosis (TS), 35%; undetermined pre/perinatal factors, 19%; perinatal insults, 9%; symptomatic neonatal hypoglycemia, 8%; familial or metabolic causes, 9%; early infections, 2%; and cryptogenic, 18%.

Genetics

TS is the most important genetically defined disorder. Other conditions associated with West syndrome are Aicardi syndrome, Miller-Dieker syndrome (type I lissencephaly), and PEHO syndrome (progressive encephalopathy, hypsarrhythmia, optic atrophy). Rarely, West syndrome occurs with single-gene metabolic disorders. The empirical occurrence risks are estimated at 1.5% for siblings and 0.7% for all first-degree relatives. A positive family history of epilepsy has been found in 40% of those with infantile spasms. It seems that heritable factors could play an important role in idiopathic but not symptomatic groups.

An X-linked mode of inheritance in association with this disorder (*ARX* gene mutation) has been recently reported. A mutation in the *ARX* gene has also been reported in sporadic cryptogenic infantile spasms. The children do not have characteristics of any other specific disorder.

Best Practice for Treatment?

More than 150 trials have carried out in the treatment of infantile spasms (Table 25-2). Steroids and Vigabatrin (VGB) are the first-line drugs for infantile spasms. There have been only a few prospective studies. The numbers of patients in many of these studies have been too small to reach meaningful conclusions.

TABLE 25-1. Etiologic Investigations

1. A comprehensive history with familial disorders and pre and perinatal events
2. Careful clinical examination, eg, to check for signs of tuberous sclerosis
3. Ophthalmologic study (intrauterine infections, signs of TS, anomalies)
4. Neuroradiology (preferably MRI)
5. Virologic investigation: cerebrospinal fluid (cell count, protein, glucose, IgG index, CMV DNA) if suspicious of congenital infection
6. A screen of serum and urine for inborn errors of metabolism including amino acids.
7. Chromosomal analysis when dysmorphic features or structural anomalies of the brain.

TS = tuberous sclerosis; MRI = magnetic resonance imaging; CMV = Cytomegalovirus.

Adrenocorticotrophic Hormone or Oral Steroids?

In a small prospective, randomized study, the efficacy of high-dose adrenocorticotrophic (ACTH) (150 IU/m^2 for two weeks) was better than that of prednisone (2 mg/kg for two weeks) but a small prospective double-blind study found otherwise. Furthermore, in the follow-up of 2 to 3 months, there was no difference between the two groups in either study.

In a new prospective study from the UK (Lux and colleagues, 2004), 107 patients were randomized to tetracosacide (synthetic ACTH), 0.5 mg/d (40 IU) on alternate days, and prednisolone, 40 mg/d. The response rates were 76 and 70%, respectively. The difference was not significant on day 14 of treatment. TS was excluded in this study because VGB was considered to be the drug of choice in TS.

Dose of ACTH?

The doses vary in different countries: Japan, 3 to 14 IU/d; Finland, 18 to 36 IU/d; and USA, 40–80 IU/d.

It is not clear why infants in the United States would need considerably larger doses than in Japan.

Corticotrophin, so-called "natural ACTH", acts for 12 to 18 hours. Its synthethic derivate, tetracosactide, lasts for 24 to 48 hours. The international units of ACTH and tetracosactide are believed to be equivalent: corticotrophin of 80 to 100 IU is equivalent to tetracosactide of 1 mg. Tetracosactide is used on alternate days because of its prolonged action. The relatively serious side effects of tetracosactide are probably due to its prolonged action. ACTH should be given in the morning in conjunction with the peak of normal pituitary ACTH secretion.

In a small-blind prospective study by Hrachovy and his colleagues (1994), high doses (150 IU/m^2) given for

TABLE 25-2. Alternative Therapies in the Treatment of Infantile Spasms. Pooled Data from Different Studies

Therapy	Number of Patients	Response Rate (%)
ACTH	476	59
Prednisone	26	31
High-dose prednisolone*	30	70
Vigabatrin	478	44
High-dose valproate	41	54
Nitrazepam	27	52
Pyridoxine	118	13
Zonisamide	119	27
Lamotrigine	30	17
Topiramate	35	29

ACTH = adrenocorticotrophic hormone.
*not recommended because of side effects.

3 weeks was not more effective than lower doses of ACTH (20–39 IU/d) given for 2 to 6 weeks or hydrocortisone given for shorter periods. Recently, in a large data-based critical literature review by the American Academy of Neurology and Child Neurology Society in 2004, nine prospective studies with small numbers of patients in each study were analyzed. It was concluded that there are insufficient data to recommend the optimal dosage and duration of infantile spasms.

This review does not include two Finnish studies. The first study included 162 children (Riikonen, 2001). Large doses of ACTH (120 IU/d) given for a relative short period of six weeks were not more effective than smaller doses (20–40 IU/d). The long-term outcome was better with low doses. The two groups were very homogenous with respect to the definition of response ("all or nothing"), the number of drop outs, the proportion of cryptogenic and symptomatic groups, and the treatment lag and duration of treatment.

In another prospective study, 30 children were included, and therapy was individualized according to the etiology (Table 25-3). I recommend treatment to be started with oral pyridoxine 150 mg daily for 3 to 4 days to exclude the possibility of underlying pyridoxine dependency or deficiency. If there is no response, corticotrophin, preferably natural ACTH, is commenced and used in stepwise manner based on etiology and response as suggested in Table 25-3. Subsequently, appropriate cortisol substitution is given after ACTH therapy and during periods of stress.

With this regimen, adverse effects of ACTH treatment were kept to a minimum. All the cryptogenic and 50% of the symptomatic spasms could be controlled within 2 to 3 weeks of therapy. If relapse occurs, return to the lowest preceding effective dose of ACTH. A new course of ACTH is effective in two-thirds of the cases. In refractory cases, valproate, nitrazepam, topiramate, or VGB are recommended. Surgery should also be considered.

Steroids or VGB?

VGB has gained popularity because of its ease of use and its efficacy. In Europe, opinions are divided with regard to VGB as initial treatment. The dose has ranged from 40 to 120 mg/kg/d, usually 40 to 60 mg/kg/d, given in two daily doses. In one open, randomized prospective study, ACTH and VGB were of equal efficacy with similar relapse rates.

In a Finnish prospective crossover study, VGB was given as the first-line drug to all patients. In all, 26% responded to VGB, most within one week. ACTH was then offered in combination with VGB. The total response rate was 60%. The conflicting values from another multicenter VGB study in Europe, which included 192 children, could probably be explained by the lack of EEG evaluation and the high rate of drop outs in that study.

After pooling the data of 8 separate prospective and retrospective studies, VGB was effective in 44 % of 478 patients. In the pooled data of 9 separate prospective and retrospective studies, ACTH was effective in 59% of 476 patients. In the recent UK study (which excluded TS patients), the cessation of the spasms was more likely with hormonal treatment. VGB was effective for spasms in 54% and for the hormonal treatment, 70% on day 14. Hypsarrhythmia also resolved significantly more often with hormonal treatment.

Tuberous Sclerosis

VGB is used in TS. The response rates to VGB and ACTH are similar, more than 70%. However, relapse rates are high after both drug trials. Because the use of ACTH is always given for a specified period and VGB for an indefinite period, VGB is a better choice.

Relapses

The relapse rate after ACTH treatment is estimated to be 15 to 24%. There is not enough information on relapse rates after VGB therapy. In one study, the relapse rates after hormonal or VGB treatment were similar. The numbers

TABLE 25-3. Regime for the Use of ACTH in Infantile Spasms. Zn tetracosactrin (Synthetic Analog of ACTH) 0.03 mg/kg on Alternate Days is Equivalent to Natural ACTH 3 IU/kg/d. All cases are started with intramuscular ACTH 3 IU/d and assessed at 2 weeks

Cryptogenic, responding	Symptomatic, responding	Cryptogenic or symptomatic, non-responding
Week 3: ACTH, 1.5 IU/d Week 4: ACTH, 0.75 IU/d	Weeks 3 and 4: continue ACTH of 3 IU/d Week 5 onwards: half dose of ACTH each week (1.5 IU/d, 0.75 IU/d, etc)	Weeks 3 and 4: ACTH, 6 IU/kg/d Week 5 onwards: half dose of ACTH each week
Start hydrocortisone of 1 mg/kg/d with later reduction and withdrawal once basal cortisol in ACTH test normal	Start hydrocortisone of 1 mg/kg/d with later reduction and withdrawal once basal cortisol in ACTH test normal	Start hydrocortisone of 1 mg/kg/d: 7 days before the end of the ACTH therapy with later reduction and withdrawal once basal cortisone in ACTH test is normal

ACTH = adrenocorticotrophic hormone.
Stress cortisol substitution (20–40 mg/m2/d) during fever and in other stress situations when basal serum cortisol < 110 nmol/l or ACTH-stimulated cortisol < 500 nmol/L (standard dose test).

of patients who were seizure-free at 3 to 4 months after ACTH or VGB treatment are also very similar (42–44%). In the recent UK study, the number of patients who were spasm-free at 14 months was very similar.

Cognition

In the recent prospective UK study (Lux and colleagues, 2005), the developmental outcome of children treated with hormonal (n = 55) or VGB (n = 52) therapy was compared at an age of 14 months. In infants with no identified underlying etiology (n = 46), the mean IQ was higher in those allocated to hormone treatment than those allocated to VGB treatment. This difference was even greater at the age of 4.2 years (20 scores). Hormone treatment, therefore, seems to be the better first-line treatment.

Taken together, both drugs are effective. VGB seems to be less effective than hormonal treatment of infantile spasms in the short term. The response is usually seen within a few days to weeks of initiation of treatment. Relapse rates are high with both treatments. We know the long-term outcome after ACTH therapy but less is known about the long-term consequences of VGB treatment. One recent prospective study suggests that the cognitive outcome may be better after hormonal than after VGB treatment in patients with cryptogenic spasms.

Side Effects

Both drugs have severe side effects. The side effects of ACTH are infections, arterial hypertension, and adrenal hypofunction after therapy. For infants with a history of frequent respiratory infections, I recommend prophylactic trimetoprim-sulfaxazole therapy. Hypertension should be monitored and treated (β-blocker). In hypertensive patients, the heart should be studied by ultrasound to recognize hypertrophic cardiomyopathy. Hydrocortisone substitution should be given after ACTH therapy and continued until the function of adrenal axis has normalized. Contraindications for treatment are acute infection, history of herpes simplex or congenital CMV infection, and severe heart failure. In Finland, we give the therapy at minimal effective dose and for the minimal effective time. With such treatment, no serious side effects were found. The side effects of ACTH are all treatable and reversible.

A serious concern with regard to concentric visual field defects (VFDs) has arisen in relation to the use of VGB. The VFDs it causes seem to be permanent. The risk for infants is not known. They occur in 35% of older children (6 series). Similar figures are seen in adults, 39% based on 15 series. VFDs can be seen as soon as at 6 to 8 weeks. VFD defects are sufficient to prevent a person from driving. There are also concerns with children who might have a poor underlying function as a part of their overall neurologic disabilities. The risk increases in duration and with increase of the mean dose. Age was not identified as a risk factor for VFD.

Recent reports of studies in animals have also been alarming. Drugs that increase synaptic concentrations of β-aminobutyric acid in the brain, like VGB, can also cause apoptotic degeneration in the developing brain. The problem is that as of yet, there is no method to identify the risk for VFDs in children with infantile spasms because the lack of cooperation does not allow for perimetry or measurement of the loss of the retinal nerve fiber layer by noninvasive computed tomography. It is not clear that advantages of VGB treatment outweigh the potential risks.

Pathophysiology of Infantile Spasms

It has been suggested that infantile spasms may result from a failure or delay of normal developmental processes. This is supported by the following facts; infantile spasms and hypsarrhythmia have a tendency to spontaneously disappear with age. It has been suggested that corticotrophin-releasing hormone synthesis and activity is increased secondary to early stress (injury or insult) during a critical perinatal period, which can result in long-term effects.

Other considerations in the pathogenesis are dysfunction of the brain stem and abnormal cortical-subcortical interaction. Focal or diffuse cortical abnormalities might be triggers of the neuronal population of the brain stem, and the spasms arise in subcortical structures.

Understanding of these altered maturational processes might help to understand why so many seemingly independent etiologic factors can lead to the same syndrome.

Effects of ACTH and Corticosteroids on the Brain

ACTH might accelerate physiologic events during critical stages of brain development through its action as a trophic hormone. It may improve the balance between low trophic factors and high excitatory factors. Highly damaged brain seems to be unable to synthetize growth factors and to adequately react to early stress. Furthermore, it has been suggested steroids decrease cortisol releasing factor via melanotrophic receptors.

Long-term Outcome

There were 214 Finnish patients who participated in a prospective study in the 1960s. The patients followed up for 20 to 35 years or until death. One-third of the patients died, with one-third of these dying before the age of three years. All but one of those who died was mentally retarded. Many had brain malformations. ACTH therapy accounted for 12% of the deaths.

In the survivors, intellectual outcome was normal or only slightly impaired in a quarter. They completed their education in normal schools or in schools for children with

learning differences. Nine of them attended secondary schools, seven had professional occupations, ten were married, and five had children. Another four were in training schools, and the remaining 50% were uneducated.

Psychiatric disorders, such as infantile autism and hyperkinetic behavior, occurred in a quarter of our cases. Infantile autism was associated with temporal pathology in 70%.

Do the Seizures Stop?

One-third of the patients were seizure-free. Twenty percent had daily seizures, and the rest had less frequent seizures. Twenty-six patients still presented with Lennox-Gastaut syndrome.

EEG at the Follow-up

The EEG was normal in a quarter. In the patients with a normal outcome, 60% had a normal EEG as opposed to only 13% in those with a poor outcome. Focal abnormalities on the EEG were not associated with a poor outcome.

Can the Outcome be Predicted?

Structural abnormalities strongly influence the prognosis. Magnetic resonance imaging (MRI) is crucial for clarifying patients as cryptogenic or symptomatic, which in turn is the most important prognostic indicator. Normal development is recorded in 12 to 25% of all cases. In cryptogenic cases, normal development is seen in up to 70 to 80%. However, patients with cryptogenic spasms and normal IQ have slight cognitive deficits when studied at preschool age.

Treatment Lag?

It seems highly likely that the gross EEG abnormality of hypsarrhythmia is responsible, at least in part, for the cognitive decline, irrespective of other seizure types. It is important to treat without delay!

Is the Initial Response Important?

Our large Finnish cohort showed that patients with infantile spasms who responded to ACTH had a better cognitive outcome than other treatment groups. This held true both for patients with a cryptogenic etiology (70%) and known etiology (23%). Also, in the UK study, the response rate correlated favorably with the cognitive outcome at age 14 and 4 years but only in the group with cryptogenic spasms. The outlook is much improved for children who respond to treatment.

Surgery

Surgery may be the treatment of choice in a small number of patients in which localized lesions are present. The authors recommend that surgical intervention should be considered early in the medically refractory cases prior to the onset of epileptic encephalopathy. When a single lesion is present on the MRI and there is a good correlation with EEG localization, surgical treatment is quite favorable in terms of both seizure control and cognitive development.

PET complements MRI by defining the full extent of the lesion and evaluating the integrity of the full lesion. PET abnormalities may also guide placement of intracranial electrodes. To achieve the best cognitive outcome with surgery, it is important to resect the entire "nociferous" area (zone of cortical abnormality) rather than just the seizure focus. The long-term effects of the surgery on cognitive functions should be carefully evaluated.

Development of newer, more specific PET probes for epilepsy has led to improved and more accurate localization of seizure foci, that is, the recently developed PET probe, (11C) methyl-L-tryptophan, which is capable of differentiating between epileptogenic and nonepileptogenic tubers in patients with TS. Recent advances in pediatric epilepsy surgery include the resection of multiple tubers in children with TS. Thus, this development should ultimately improve the outcome of epilepsy surgery in West syndrome.

Conclusions

1. Use ACTH as the first choice for treatment because it is a safe drug when used at the minimal effective dose and duration. It might have a favorable effect on cognitive function in patients with cryptogenic etiology. Consider VGB as the first-line drug for TS.
2. Treat without a delay.
3. Side effects of ACTH, unlike those of VGB, are well known, treatable, and reversible.
4. We know the long-term effects of ACTH.

Suggested Readings

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CHAPTER 26

RECURRENT SEIZURES

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Uncontrolled or recurrent seizures affect a large number of children in the United States. Compliance with medical therapy is a crucial component to address when seizures recur. The clinician should strive for seizure freedom or maximum reduction of recurrences balanced by the fewest adverse effects possible. If a child continues to have seizures and no other cause is identified, a rational treatment plan should be formulated. This may require further diagnostic testing.

Epilepsy and seizures affect at least 2.3 million people in the United States. The treatment of febrile seizures (Chapter 18, "Febrile Seizures"), initial treatment of first unprovoked seizures (Chapter 19, "First Unprovoked Seizure"), and acute seizure emergencies (Chapter 90, "Status Epilepticus") are discussed elsewhere. Once the seizure type or epilepsy syndrome has been classified, therapy may be initiated. Antiepileptic drugs (AEDs) are the primary form of treatment. However, 25 to 30% of children with epilepsy continue to have recurrent seizures. In addition, many patients experience significant adverse drug effects. Children with epilepsy characterized by uncontrolled seizures face a variety of risks, including higher mortality rates, higher rates of accidents and injuries, a higher incidence of cognitive and psychiatric impairments, poor self-esteem, higher levels of anxiety and depression, and social stigmatization or isolation. Thus, effective treatment to control seizures is fundamental to improving overall outcome. When the first-choice AED is prescribed, less than 50% of children are initially seizure-free. With adjustments in dose, this percentage improves. If the child has failed initial AED therapy (see Chapter 23, "First-Choice Antiepileptic Drugs"), all treatment options (Table 26-1) should be considered and a treatment plan developed. With all the treatment options currently available, the clinician should strive for freedom from seizures or maximum reduction of recurrences balanced by the fewest adverse effects possible.

TABLE 26-1. Treatment Options in Pediatric Epilepsy

Antiepileptic drug therapy (standard and new antiepileptic drugs)
Vagus nerve stimulation
Epilepsy surgery
Ketogenic diet

Causes of Recurrent Seizures

The initial step in the treatment of epilepsy involves correctly identifying the event (seizure type) and associated conditions that define the epilepsy syndrome. Etiology should be established from the history, physical examination, and selective laboratory tests. All children with recurrent afebrile seizures should have an electroencephalogram (EEG) performed while they are awake and asleep and a magnetic resonance imaging (MRI) study of the brain. Children in the first 2 years of life may require special MRI sequences and serial MRI scans to identify abnormalities during early brain development. This work-up will allow classification of the seizures and epilepsy syndrome. Some seizure types (ie, absence, benign centrotemporal epilepsy of childhood, genetic epilepsies) are well controlled with initial therapy. However, some seizure types, epilepsy syndromes, and specific etiologies are known to be treatment resistant and typically lead to recurrent or intractable seizures (Tables 26-2 and 26-3). Once a child is identified as having one of these etiologies, the physician can describe the typical natural history and prognosis of the epilepsy for

TABLE 26-2. Seizure/Types Epilepsy Syndromes Associated with Recurrent Seizures

Simple partial seizures
Complex partial seizures
Myoclonic seizures
Atonic seizures
Tonic seizures
Severe myoclonic epilepsy in infancy (Dravet Syndrome)
Ohtahara syndrome
Infantile spasms (West Syndrome)
Lennox-Gastaut syndrome

TABLE 26-3. Syndromes of Intractable Childhood Epilepsy

Neurocutaneous
Sturge-Weber syndrome
Tuberous sclerosis complex
Dysplasias
Focal pachygyria
Focal cortical dysplasia
Band heterotopia
Lissencephaly
Hemimegalencephaly
Hemispheric dysplasia
Hypothalamic hamartoma
Rasmussen syndrome
Landau-Kleffner syndrome
Polymicrogyria

TABLE 26-4. Predictors of Medically Intractable Childhood Epilepsy

Seizure onset in infancy
Symptomatic etiology (organic brain disease–cerebral palsy, mental retardation)
Seizure type (Table 26-2)
Presence of multiple seizure types
High seizure frequency
Long duration of uncontrolled seizures
Failure of previous medical treatment

the family. This prognosis includes the likelihood that the child will respond to certain treatment options, allowing a logical, sequential treatment plan to be formulated.

In addition to the epilepsy type and the etiology, other factors are important in predicting medically refractory childhood epilepsy (Table 26-4). Onset in infancy, evidence of organic brain disease, multiple seizure types (especially tonic and atonic seizures), clustering of seizures, a persistently abnormal EEG, and a long duration of epilepsy are dire prognostic indicators.

A number of factors are responsible for inadequate control of seizures. Incorrect identification of the seizure type results in faulty diagnosis (Table 26-5). The inability to distinguish between absence seizures and complex partial seizures may lead to use of inappropriate medication. This may result in a choice of medication that has the potential

TABLE 26-5. Recurrent Seizures: Faulty Diagnosis

Incorrect identification of seizure type or epilepsy syndrome
Failure to correctly identify the event
Failure to recognize underlying disease state
Failure to recognize precipitating factors

TABLE 26-6. Recurrent Seizures: Antiepileptic Drugs Associated with Seizure Exacerbation

Antiepileptic Drug	Seizure Type Exacerbated
Carbamazepine	Absence, atonic, myoclonic
Oxcarbazepine	Absence, atonic, myoclonic
Phenytoin	Absence, atonic, myoclonic
Phenobarbital	Absence, atonic
Vigabatrin	Absence, myoclonic
Tiagabine	Absence, myoclonic
Gabapentin	Myoclonic
Lamotrigine	Myoclonic

to exacerbate the underlying seizure type (Table 26-6). The clinician should be aware of this possibility, and if this appears to be occurring, therapy should be changed.

The epileptic seizure must be distinguished from other nonepileptic events, as failure to do this can often lead to incorrect treatment or overmedication. This is especially important in children with other neurologic abnormalities (ie, cerebral palsy, autism, and mental retardation) for which video-EEG monitoring may be necessary to correctly identify all the events. Failure to recognize underlying disease processes, such as porphyria, hypoglycemia, or hypocalcemia, may lead to apparent recurrent seizures. Failure to recognize precipitating factors (ie, reflex epilepsies, sleep deprivation, other medicines) that should be eliminated may lead to lack of seizure control.

Faulty treatment may cause recurrent seizures (Table 26-7). Some specific seizure etiologies are known to be medically unresponsive and may be best treated with the ketogenic diet, vagus nerve stimulation, or epilepsy surgery. Additionally, certain medications may exacerbate seizures. Drug interactions between AEDs or an AED and another drug may lower the efficacy of the AED, resulting in increased seizure activity. Overexpression of multidrug "efflux" transporters and alteration of AED targets may be important and co-existent mechanisms of pharmacoresistance: current research with selective inhibitors of efflux transporters might lead to prevention or reversal of drug resistance in epilepsy For children, especially in the first

TABLE 26-7. Recurrent Seizures: Faulty Treatment

Failure to use all available treatment options (see Table 26-1)
Inappropriate medicine or therapy
Drug interactions
Polypharmacy
Inadequate drug dosage

2 years of life, the drug dose may need to be significantly higher on a mg-per-kg basis than the dose for adolescents or adults to achieve the same serum level. Children aged 2 to 10 years typically require 50% higher doses, whereas infants (aged 2 to 24 months) may require up to 100 to 200% higher doses on a mg-per-kg basis than the dose for adults. Serum blood levels, along with clinical response, help guide dosing decisions, as a set maintenance dose may lead to an inadequate trial of the AED.

Patient factors may contribute to recurrent seizures (Table 26-8). One of the most common causes is partial compliance. This may be improved by patient education and use of an AED formulation that allows twice-daily dosing. Nonavoidance of precipitating factors, including sleep deprivation, emotional stress, and other medicines, may lead to continuation of seizures that might otherwise be controlled. Classic antihistamines may lower the seizure threshold in preschool children and promote apparent intractability. New research suggests several inherent patient factors may predispose some children to recurrent seizures. Unfortunately, there is currently no way to screen for these or to modify treatment. Perhaps in the future, magnetic resonance spectroscopy or another technology may allow insights into a given patient's brain neurochemistry and help guide treatment decisions.

Management of Recurrent Seizures

The treatment of epilepsy requires the physician to determine the drug of first choice (see Chapter 24 and Tables 26-9 and 26-13) and use it to its maximum effectiveness by increasing dosage up to the limit of tolerability. Effectiveness is defined as a measure encompassing both efficacy (ie, seizure control) and tolerability. If the first drug is unsuccessful, an alternative medication should be prescribed (Figure 26-1). This decision may be influenced by other factors (eg, dose formulation, comorbidity, other medicines, pharmacokinetics) (Table 26-10).

Use of a single drug reduces the chance for potential side effects or drug interactions and often allows the best quality of life. When changing from the first to a second drug, the medicines usually overlap to prevent a withdrawal or rebound increase in seizures. This allows time for the second drug to be increased in dosage to achieve efficacy. When seizures continue to recur, a small number (10 to 20%) of

TABLE 26-8. Recurrent Seizures: Patient Factors

Partial compliance with AED therapy
Nonavoidance of precipitating factors
Use of other drugs—lower seizure threshold or altered AED levels
Possible patient brain factors:
MDR1 overexpression
Low brain GABA levels or abnormal GABA receptor
EAAT3 dysfunction
Alteration in drug binding at the Na^+ channel

AED = antiepileptic drug; EAAT3 = excitatory amino acid transporter; GABA = γ-aminobutyric acid; MDRI = multiple drug resistance gene.

TABLE 26-9. Recurrent Seizures: AED Treatment Options for Epilepsies and Epilepsy Syndromes

Cryptogenic or symptomatic generalized epilepsies
Infantile spasms
First choice: ACTH, vigabatrin
Second choice: topiramate, zonisamide, valproate
Lennox-Gastaut syndrome
Valproate, topiramate, lamotrigine, felbamate, zonisamide, vigabatrin
Generalized idiopathic epilepsies
Benign myoclonic epilepsy in infancy
Valproate, topiramate, lamotrigine, zonisamide
Childhood absence epilepsy
Ethosuximide, valproate, lamotrigine
Juvenile absence epilepsy
Valproate, lamotrigine
Juvenile myoclonic epilepsy
Valproate, lamotrigine, topiramate, levetiracetam, zonisamide
Epilepsy with GTC seizures on awakening
Valproate, lamotrigine, topiramate, levetiracetam
Localization—related (partial) epilepsies
Benign childhood epilepsy with centrotemporal spikes
Gabapentin, oxcarbazepine, carbamazepine (extended release)
Partial seizures ± secondary GTC
Carbamazepine (extended-release), phenytoin, valproate, gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, zonisamide, pregabalin

ACTH = adrenocorticotropic hormone; AED = antiepileptic drug; GTC = generalized tonic-clonic.

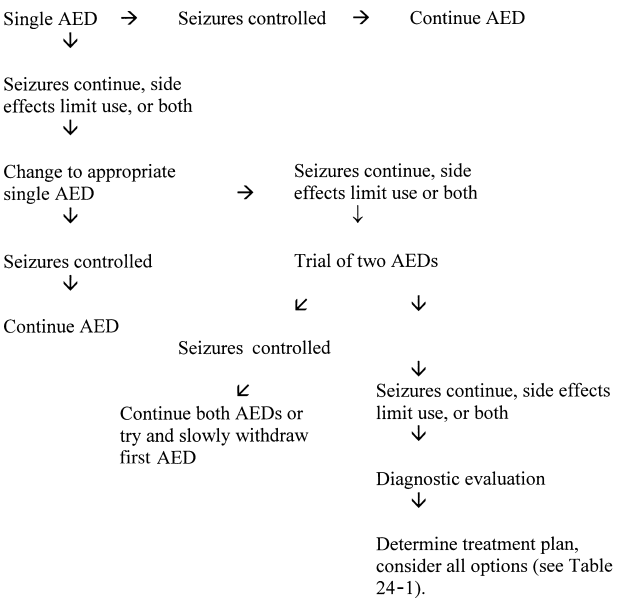

FIGURE 26-1. Treatment of recurrent seizures. AED = antiepileptic drug.

TABLE 26-10. Considerations in the Selection of Antiepileptic Drug Therapy

Efficacy for seizure type, epilepsy syndrome
Safety
Side effect profile
Mechanism of action
Drug interactions
Need for laboratory monitoring
Dosing requirements/drug formulations
Cost
Regulatory approved

patients may benefit from treatment with two AEDs. Strategies include combining drugs with different mechanisms of action (rational polypharmacy) or drug combinations felt to be synergistic (eg, valproate [VPA] and lamotrigine [LTG], VPA and ethosuximide). In the past, the teaching was to "change only one thing at a time" to learn as much as possible about which drug is most effective. For example, if seizures recurred despite maximal dosing of carbamazepine (CBZ), it was customary to add VPA without simultaneously decreasing the CBZ doses. Although it is still the case that a combination of drugs may be effective when no single agent provides satisfactory seizure control, there has been a shift in practice, whereby drugs are increasingly used sequentially as monotherapy rather than in combination. This practice has evolved because of the ready availability of new effective AEDs and recognition that polypharmacy is associated with significant toxicity. However, polypharmacy with the newer AEDs appears to be better tolerated and accompanied by fewer pharmaco kinetic interactions than was true of the AEDs available prior to 1993 (standard AEDs). Also, a new option, combining an AED with vagus nerve stimulation (see Chapter 30, "Epilepsy Surgery and Cortical Stimulation"), allows patients to have improved seizure control without the neurotoxicity of polypharmacy.

Children who have failed two to three AEDs require more intensive diagnostic effort. This typically consists of video-EEG monitoring with scalp electrodes, a high quality MRI with a specific epilepsy protocol, and possibly other laboratory studies to search for an underlying etiology. Referral to a comprehensive pediatric epilepsy program is recommended. This information is used to assess the risks, benefits, and expected outcome of all treatment options (see Table 26-1) for the child's epilepsy type or syndrome. A plan is formulated, and a sequence of treatment steps, based on response to therapy, is outlined. This is communicated to the local pediatric neurologist. If the child's seizures continue, periodic reevaluation is suggested at the comprehensive pediatric epilepsy center. This allows review of the treatment plan and the use of newer diagnostic tests or treatments.

Currently, many children continue to have recurrent seizures despite the use of all available treatment options. Following the approach outlined above allows the best seizure control and subsequent quality of life for each child with epilepsy.

Since 1993, several new AEDs have been released in the United States. As a group, these newer drugs differ from the established or first-choice drugs in terms of their pharmacokinetics (Table 26-11), interaction potential, and adverse effects. In addition, the newer drugs may achieve seizure control or improved tolerability in situations in which an established drug had not. However, the availability of new AEDs represents a therapeutic dilemma for the clinician because optimal use of these drugs has not yet been established. There is little information on the comparable benefits of new AEDs. In the next section of this chapter, the clinical pharmacology of the newer AEDs and seizure types or epilepsy syndromes for which each is useful will be discussed, with the realization that with more experience, this may change.

TABLE 26-11. Pharmacokinetics of New AEDs

	F (%)	T_{max} Hour	Vd L/kg	Protein Binding	T½ Hours	Tss Days	Therapeutic Range mg/L	Dose mg/kg/d
Felbamate	> 90	2–6	0.75	25	14–23	4	30–100	15–60
Gabapentin	35–60	2–3	0.85	0	5–9	1–2	4–20	30–90
Lamotrigine	> 90	1–3	1.0	55	15–60	3–10	3–20	1–15
Levetiracetam	100	0.6–1.3	0.5–0.7	< 10	7	2	5–50	20–60
Oxcarbazepine	> 95	1–2	—	—	2	—	—	15–45
Monohydroxy derivative	—	3–5	0.75	40	10–15	2	10–35	—
Pregabalin	> 90	1.5	0.5	0	6.3	1–2	3–10	2–10
Tiagabine	> 90	1–2	1.4	96	2–9	1–2	5–70	0.25–1.25
Topiramate	> 80	1–4	0.65	15	12–30	3–5	2–25	2–20
Vigabatrin	80	0.5–2	0.8	0	5–7	2	—	40–150
Zonisamide	82–88	2–5	1.5	40	50–70	10–15	10–30	4–10

AED = antiepileptic drug; F = bioavailability; T_{max} = time interval between ingestion and maximal serum concentration; Vd = volume of distribution; Protein Binding = fraction bound to serum proteins; T½ = elimination half-life; Tss = steady-state time.

Clinical Pharmacology and Use of New Antiepileptic Drugs

Felbamate

Felbamate (FBM) was released in the United States in 1993. FBM was tested in the first-ever double-blind, placebo controlled study in patients with Lennox-Gastaut syndrome. A decrease in total seizure number was significant for FBM, and FBM was particularly effective in reducing the frequency of drop attacks. Efficacy for monotherapy and adjunctive treatment of partial-onset seizures was established in adolescents and adults, but pediatric studies were stopped because of marked restrictions on the use and promotion of FBM due to the emergence of reports of aplastic anemia and hepatic failure. Uncontrolled reports suggest that FBM might be efficacious against absence seizures, infantile spasms, Doose syndrome, juvenile myoclonic epilepsy, and acquired epileptic aphasia. Even with its broad spectrum of activity, FBM's main indication is in children with Lennox-Gastaut syndrome who have failed to respond to other treatments (eg, VPA, topiramate [TPM], LTG, ketogenic diet, vagus nerve stimulation) or as a third-line option in children with refractory partial-onset seizures.

Nausea, vomiting, anorexia, weight loss, dizziness, insomnia, headache, and somnolence were the most commonly recognized side effects of FBM. Anorexia and weight loss were the most prominent and can be significantly worsened by cotreatment with other drugs sharing these side effects (eg, stimulant medication, TPM, zonisamide [ZNS]). One year after FBM's release, it became evident that FBM was associated with aplastic anemia, and the drug came close to being removed from the market. Additionally, cases of severe hepatotoxicity, some with fatal outcome, were reported. Although severe hypotoxicity has occurred in children, no cases of aplastic anemia have been reported in children under the age of 13 years. Known risk factors for FBM toxicity include a history of allergy or cytopenia with other AEDs and evidence of a concomitant immune disorder. These should be sought by careful history-taking before beginning therapy with FBM. Baseline hematologic and liver function tests should be performed and families informed of potential risks. Cautious introduction of FBM reduces the occurrence of early adverse events.

Therapy is typically initiated at 15 mg/kg/d (maximum of 1,200 mg) and increased weekly by 15 mg/kg/d to 45 mg/kg/d (maximum 3,600 mg). Some children tolerate much more rapid dose escalation or benefit from doses up to 60 to 90 mg/kg/d (5,000 to 6,000 mg/d). Serum levels and clinical response guide dosing decisions. It is our policy to continue FBM only when seizure control is dramatic. Typically, intermittent hematology and liver function tests are checked the first 6 to 12 months and later as clinically indicated. Comedications may need adjustment because of known interactions. Obtaining baseline and follow-up serum levels of all AEDs assists in these decisions.

Gabapentin

Gabapentin (GBP) was marketed in the United States in 1994. GBP is a niche AED, showing efficacy against only partial and secondary generalized seizures. Pediatric studies showed efficacy in the treatment of partial seizures, whether refractory or benign. GBP was studied in children as adjunctive therapy in refractory partial seizures and as monotherapy in benign centrotemporal epilepsy of childhood. Two double-blind studies of GBP in childhood absence epilepsy failed to demonstrate efficacy. A single placebo-controlled study of GBP in patients with generalized tonic-clonic seizures did not show efficacy over placebo.

GBP was the first AED to be introduced that was excreted entirely by the kidney. This infers a significant clinical advantage because GBP is neither the cause nor the object of pharmacokinetic interactions. Additionally, GBP is not bound to serum proteins, so it is not displaced by other drugs.

The main side effects during controlled trials were somnolence, dizziness, and ataxia. Infrequently (< 5%), aggressive behavior may occur, especially if there is a prior history of hyperactivity, mental retardation, or underlying behavior disorder. These are readily reversible upon discontinuation of GBP. Increased appetite and subsequent weight gain can be bothersome. However, idiosyncratic fatal side effects have not been attributed to GBP use, making it one of the safest AEDs.

We presently use GBP as initial therapy in the treatment of benign centrotemporal epilepsy in childhood and as adjunctive therapy for children with refractory partial onset seizures. The drug's lack of pharmacokinetic interactions, outstanding safety profile, and ability to rapidly titrate make it one of the new AEDs used early on in the treatment of partial seizures in children. GBP is initiated at 10 to 20 mg/kg/d, given three times daily, and the dose is increased by the same amount every 3 to 7 days to achieve a total daily dose of 35 to 45 mg/kg/d. If seizures persist, the GBP dose can be increased to 60 to 80 mg/kg/d as tolerated. Children younger than 4 years of age may benefit from doses up to 100 mg/kg/d owing to their higher renal clearance of GBP. Adolescents are titrated up to doses of 1,800 to 2,400 mg/d as the first plateau and may be increased to 3,600 to 4,800 mg/d, if needed, to achieve maximal benefit.

Lamotrigine

LTG has been available in the United States since 1995. LTG was demonstrated to be effective, even as monotherapy,

TABLE 26-12. Lamotrigine Dosing

A.	Lamotrigine added to an AED regimen containing VPA:	
	Weeks 1 and 2:	0.15 mg/kg/d in one or two divided doses, rounded down to the nearest whole tablet
	Weeks 3 and 4:	0.3 mg/kg/d in one or two divided doses, rounded down to the nearest whole tablet
	May then increase by 0.3 mg/kg/d every 1 to 2 weeks administered twice daily. Usual maintenance dose 1 to 5 mg/kg/d. (maiximum 200 mg/d).	
B.	Lamotrigine added to EIAEDs (without VPA):	
	Weeks 1 and 2:	0.6 mg/kg/d in two divided doses, rounded down to the nearest whole tablet
	Weeks 3 and 4:	1.2 mg/kg/d in two divided doses, rounded down to the nearest whole tablet
	May then increase by 1.2 mg/kg/d every 1 to 2 weeks. Usual maintenance dose 5 to 15 mg/kg/d (maximum 400 mg/d in two divided doses).	
C.	Lamotrigine added to AEDs other than EIAEDs and VPA:	
	Weeks 1 and 2:	0.3 mg/kg/d in one or two divided doses, rounded down to the nearest whole tablet
	Weeks 3 and 4:	0.6 mg/kg/d in two divided doses, rounded down to the nearest whole tablet
	May then increase by 0.6 mg/kg/d every 1 to 2 weeks. Usual maintenance dose 4.5 to 7.5 mg/kg/d (maximum 300 mg/d in two divided doses).	

AED = antiepileptic drug; EIAEDs = enzyme-inducing antiepileptic drug (carbamazepine, phenytoin, phenobarbital or primidone); VPA = valproate.

in the treatment of partial seizures in adults. Double-blind monotherapy trials compared treatment of new onset partial seizures ± secondary generalization with LTG, CBZ, or phenytoin. No difference in efficacy was noted between the three AEDs, but different side effects were encountered. Controlled studies in children have shown efficacy in treatment-resistant partial seizures, Lennox-Gastaut syndrome, and childhood absence epilepsy. Uncontrolled series have suggested its efficacy against a broad range of seizure types and epilepsy syndromes, including generalized tonic-clonic seizures, juvenile myoclonic epilepsy, infantile spasms, and seizures associated with Rett syndrome and juvenile neuronal ceroid lipofuscinosis. LTG is less effective against myoclonic seizures and, rarely, may worsen the myoclonus.

Adverse effects consist mainly of two types: (1) dose related central nervous system (CNS) toxicity and (2) rashes. Common side effects include somnolence, dizziness, headache, diplopia, nausea, vomiting, and, rarely, insomnia. LTG may have a brightening or energizing effect in some children. In children with an underlying encephalopathy, this may present as acting-out behavior and require discontinuation of the drug. Serious rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis, are the primary concern associated with LTG therapy. Overall, rashes occur in up to 10% of patients, usually during the first 8 weeks. In children, coadministration with VPA and rapid dose escalation increase the risk of rash. As a result, the titration schedule for LTG use has been revised a couple of times, slowing the rate of dose escalation, and this has resulted in a marked decrease in the incidence of serious rashes. The initial titration rates resulted in an estimated 1:100 to 1:200 children being at risk for serious skin rashes, and although no data are available in the United States, post marketing experience in other countries shows that this appears to be decreased several-fold with the current dose schedule (Table 26-12).

In the United States, it is recommended that LTG be stopped in the presence of a rash, unless another specific etiology can be identified with certainty (eg, chickenpox). Rechallenge with LTG in patients who developed a rash after the first exposure has been successful in some patients, although the authors do not advocate this unless all other treatment options have been exhausted. LTG is predominantly metabolized by the liver and has pharmacokinetic interactions with other AEDs, resulting in a complicated dosing schedule. With LTG as monotherapy in children, the elimination half-life is 30 to 33 hours, 7.7 to 14 hours with LTG and enzyme-inducing AEDs (CBZ, phenytoin, phenobarbital, and primidone), and 43 hours with LTG and VPA.

LTG is a broad-spectrum AED that offers an alternative to VPA monotherapy and can be effective as adjuvant therapy to prevent recurrent seizures.

Topiramate

TPM, the next broad-spectrum AED, was approved in the United States in 1997. The efficacy of TPM has been demonstrated in double-blind, placebo-controlled studies in children with new-onset seizures (partial or generalized), intractable partial seizures, Lennox-Gastaut syndrome, primary generalized tonic-clonic seizures, and juvenile myoclonic epilepsy. A recent study showed equivalent efficacy of TPM, CBZ, and VPA when used as initial therapy for the treatment of partial-onset or generalized tonic-clonic seizures in childhood. Uncontrolled studies suggest its efficacy in the treatment of infantile spasms, severe myoclonic epilepsy in infancy, and childhood absence seizures.

Over 50% of TPM is excreted unchanged by the kidneys. The clearance is higher in children than in adults, leading to the need for higher relative daily doses on a mgper-kg basis. The most common side effects are CNS related and include somnolence and fatigue, impaired concentration, word-finding difficulties, and confusion. All the CNS side effects can be significantly minimized by slow dose titration or by use of TPM as monotherapy.

The non-CNS side effects consist primarily of anorexia and weight loss, paresthesias, dysgeusia, and, rarely, nephrolithiasis. The last three side effects are related to TPM's weak carbonic anhydrase inhibition, which is probably also responsible for the asymptomatic metabolic acidosis commonly seen on routine serum chemistries. TPM should cautiously be coadministered to children on acetazolamide, ZNS, or the ketogenic diet because of the increased risk of nephrolithiasis and metabolic acidosis. Rarely, children may experience hyperthermia and oligohydrosis. If oligohydrosis occurs, the clinician and family will have to decide if the degree of seizure control justifies the lifestyle alterations (ie, limiting duration of exposure to warm weather). Encouraging good fluid intake can help minimize the risk of nephrolithiasis. With extensive experience, to date, no severe or life-threatening adverse events have been attributed to TPM.

TPM is used as initial therapy in children with new onset seizures, and as a broad-spectrum AED, especially in young children, in whom greater concerns of VPA side effects exist. It is a potent AED in the treatment of refractory partial seizures. Although it is typically introduced slowly to minimize CNS adverse effects, the author has rapidly titrated TPM in some children without significant problems. Initial monotherapy doses are 25 mg/d given at bedtime, with weekly increases of the same amount to an initial plateau of 50 mg twice daily (or start at 0.5 mg/kg/d and increase by 0.5 mg/kg/d weekly to 2 to 2.5 mg/kg/d given twice daily). Most children on monotherapy are maintained on 100 to 200 mg/d (2.0 to 4.5 mg/kg/d). Initial adjunct doses in children are typically 0.5 to 1.0 mg/kg/d divided two or three times daily, with weekly increases to 6 mg/kg/d. Children < 6 years of age have tolerated doses up to 20 to 30 mg/kg/d, although the typical dose is 12 mg/kg/d given three times daily in this age group. Children aged 6 to 12 years usually achieve maintenance doses as adjunctive therapy of 6 to 9 mg/kg/d and may tolerate twice-daily administration. TPM has joined VPA and LTG as a broad-spectrum agent to be used in children with mixed seizure disorders.

Tiagabine

Tiagabine (TGB) was approved in the United States in the fall of 1997. This is the first licensed AED in the United States that was based on our modern knowledge of brain neurochemistry. TGB is a nipecotic acid derivative that increases extracellular γ-aminobutyric acid (GABA) by inhibiting reuptake of GABA by the neurons and glia.

Double-blind and open-label studies have documented the efficacy of TGB in the treatment of refractory partial onset seizures in children. Uncontrolled studies suggest efficacy as monotherapy in partial-onset seizures and in improvement of spasticity. The GABA-ergic effect of TGB may exacerbate absence seizures.

Although patient exposure is still limited (about 100,000 patients), no potentially life-threatening adverse effects have been attributed to TGB. Side effects noted in clinical trials were all related to the CNS and include dizziness, tremor, inattention, nervousness, somnolence, asthenia, and weakness. Again, the side effects of TGB are all minimized by slow dose escalation, intake with food, and use as monotherapy. TGB, like vigabatrin (VGB), elevates synaptic GABA levels, raising concerns about the possibility of visual field defects. However, the mechanisms for elevating synaptic GABA levels are completely different, and this may explain why the retinal problems encountered with VGB have not occurred with TGB.

The authors prescribe TGB as adjunctive therapy in the child with partial seizures and spasticity (eg, in cerebral palsy). Dosing begins in children at 0.1 mg/kg/d and is increased by this amount weekly to 0.4 to 0.6 mg/kg/d in children who are not taking enzyme-inducing AEDs. Children taking enzyme-inducing AEDs may require doses up to 1.0 mg/kg/d, typically divided three times daily. In young children (age < 24 months) doses up to 3.0 mg/kg/d have been used.

Oxcarbazepine

Oxcarbazepine (OXC) was approved in the spring of 2000 in the United States for the treatment of partial onset seizures with or without secondary generalization. Since then, it has received monotherapy approval for the treatment of partial-onset seizures in children over 4 years of age. OXC is a keto-analogue of CBZ and can be thought of as a prodrug because it is rapidly converted to the monohydroxy derivative. This derivative is responsible for the antiepileptic effect. This design avoids the epoxide metabolite of CBZ, which was shown to be linked to neurotoxicity, especially when CBZ was used with other AEDs. Comparison, double-blind trials have evaluated OXC versus CBZ or phenytoin or VPA in the treatment of pediatric partial seizures. No significant difference in efficacy was noted for any agent. Dose requirements are approximately 50% higher for OXC than for CBZ, and many patients tolerate conversion from one drug to the other.

The adverse effects of OXC in children are somnolence, dizziness, headache, and, rarely, rash. The incidence of rash is less common than with CBZ, and the cross-allergy between CBZ and OXC was found in only about 1 of 3 children. Hyponatremia, although rare, occurs more commonly with OXC than with CBZ, but hematologic changes associated with CBZ have not been seen with OXC.

Treatment with OXC is usually initiated at 5 to 10 mg/kg/d, divided in two doses, and increased by this amount weekly to 20 to 30 mg/kg/d. Some children may benefit from further dose escalation to 40 to 50 mg/kg/d. Recently, a slower initial dose of 5 mg/kg/d has been suggested to minimize CNS side effects.

Zonisamide

ZNS has been available in the United States since the spring of 2000 but for 10 years prior to that in Japan. As a result, more information is available than we have for the other recent AEDs. Efficacy in partial seizures has been found in several controlled studies. Efficacy in infantile spasms, Ohtahara syndrome, Lennox-Gastaut syndrome, absence seizures, generalized tonic-clonic seizures, and the progressive myoclonic epilepsies has been reported.

The most common adverse effects of ZNS are somnolence, ataxia, anorexia, and weight loss. ZNS, like TPM, inhibits carbonic anhydrase and may cause renal stones, dysgeusia, oligohydrosis, and hyperthermia. Potentially, these side effects could be worsened by coadministration with TPM or acetazolamide. This drug is also contraindicated in patients on the ketogenic diet. Simultaneous use of ZNS with stimulant medication may have a synergistic effect on appetite suppression. Serious rashes rarely occur. ZNS has a sulfonamide moiety and should not be used in a child with a prior history of allergic rash to sulfonamide antibiotics.

Therapy with ZNS is initiated at 1 mg/kg/d and increased by this amount weekly to 6 to 8 mg/kg/d, typically administered twice daily. Children under age 2 years may tolerate dose increases to 15 mg/kg/d. Serum levels and clinical response may help guide dosing decisions, especially in young children. There is currently no commercial dose formulation that may be easily given to young children. This may be accomplished by placing the contents of one 100 mg capsule in 30 cc of apple juice. This is stable for 48 hours when refrigerated and should be shaken well before each dose is administered.

Levetiracetam

The United States approved levetiracetam (LEV) in 2000. Approval was based on multicenter, double-blind studies in adults with partial epilepsy. Pediatric studies evaluating the efficacy in partial seizures are completed, and results are pending.

Although the overall exposure is limited, to date LEV has a good safety profile. The most common adverse effects are asthenia, somnolence, dizziness, and nervousness. Hostility, anger, or aggressive behavior occurs in some children, especially if they have an underlying encephalopathy or history of behavior disorders. This is reversible upon discontinuation of the drug.

Currently, the authors use LEV as adjunctive treatment for partial-onset seizures. It may benefit some patients with symptomatic generalized seizures or juvenile myoclonic epilepsy. Therapy is initiated at 10 to 20 mg/kg/d and increased by this amount weekly. Maintenance doses are typically 40 to 60 mg/kg/d, although some children tolerate doses up to 80 or 100 mg/kg/d. This is administered as a two- or three-times-daily dosing.

Vigabatrin

VGB is not approved by the U.S. Food and Drug Administration but is used in the United States. This is the drug of choice for treating infantile spasms secondary to tuberous sclerosis complex and may benefit children with infantile spasms due to other etiologies. Controlled studies have also shown its efficacy in the treatment of partial-onset seizures, but potential visual field defects will relegate VGB to a treatment of last choice in this seizure type. Anecdotal evidence suggests its efficacy in Lennox-Gastaut syndrome and generalized tonic-clonic seizures.

VGB's entry into the U.S. market has been delayed because of concerns over visual field constriction associated with its use. This defect predominantly affects the nasal field bilaterally, is usually asymptomatic, and may persist even after discontinuation of VGB. As a result, the fundamental issue when prescribing VGB is the evaluation of the risk-benefit ratio. When treating infantile spasms, this side effect may be a modest price to pay for seizure control and the potential for a better developmental outcome. Other adverse effects reported are hyperactivity, weight gain, drowsiness, ataxia, and somnolence.

When treating infantile spasms, VGB is initiated at 50 mg/kg/d, given twice daily, and the dose is increased by the same amount after 1 week to a total of 100 mg/kg/d. Some children may benefit from doses up to 200 mg/kg/d. Doses used in the treatment of partial-onset seizures are typically 20 mg/kg/d, administered twice daily, and increased by this amount weekly to 40 to 60 mg/kg/d. After the decision to use VGB has been made, a plan should be in place for visual field testing before starting the medicine. This will serve as a baseline to evaluate possible changes during VGB treatment. In older children, this may consist of a complete ophthalmologic evaluation and formal visual field testing every 4 to 6 months. In the

infant, formal ophthalmologic evaluation, visual evoked potentials, and an electroretinogram may need to be performed periodically. A set protocol for monitoring visual field defects has yet to be developed.

Pregabalin

Pregabalin was approved in 2005 for use in the United States. It has proven to be a safe and highly effective adjunctive therapy for epilepsy, especially in treatment of adult patients with refractory partial seizures, with or without secondary generalization. In addition to use as an anticonvulsant, pregabalin is an effective analgesic for neuropathic pain and an anxiolytic drug used in the treatment of generalized anxiety disorder. The drug has a selectively inhibitory effect on high voltage-gated calcium channels through an associated $\alpha_2\delta$-1 subunit, leading to a decrease in both neurotransmitter release and post-synaptic excitability. Pregabalin does not interact with other AEDs, is not metabolized by the liver, and does not bind to plasma proteins. It is almost completely absorbed (> 90%), exhibits a linear pharmacokinetic profile and is excreted unchanged by the kidneys, with a half-life of about 6 hours. Importantly, dose adjustments are required for patients with renal insufficiency. Pregabalin is well tolerated: adverse effects are dose-related, the most common being somnolence, dizziness and ataxia. Weight gain is seen in a small proportion of patients, and erectile dysfunction has occasionally been reported.

The effective adult dose range for pregabalin is typically 150–300 mg/d up to 600 mg/d given orally in two or three divided doses. Therapy usually begins with 50 mg 3 times a day, increasing to 100 mg 3 times a day within a week depending on effectiveness and tolerability. In children we have used doses that are 30–50% higher on a mg/kg basis (as is true of most other AEDs) to compensate for the increased renal clearance. Although the rate of pregabalin absorption is slowed by concomitant food intake, there is no clinically relevant effect on total absorption, and hence pregabalin may be taken with or without food.

Conclusion

Uncontrolled or recurrent seizures affect a large number of children in the United States. Compliance with medical therapy is a critical component that needs to be addressed when initiating therapy (see Chapter 27, "Discontinuing Anti-epileptic Drugs in Childhood Epilepsy"). If the child continues to have seizures and no other cause is identified, a rational treatment plan should be formulated. This may require further diagnostic testing. If this is done and all available treatment opinions are pursued, the child and the family will achieve the best possible seizure control and quality of life.

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Practitioner and Patient Resources

Epilepsy Foundation
4351 Garden City Drive, Suite 406
Landover, MD 20789
Phone: (800) 332-1000
http://www.epilepsyfoundation.org/
The Epilepsy Foundation is the nonprofit organization representing patients with epilepsy in the United States. Local chapters provide patient education, job training, and advocacy.
The Epilepsy Foundation recommends these books:
Freeman J, Vining E, Pillas D, editors. Seizures and epilepsy in childhood: a guide for parents. Baltimore (MD): The Johns Hopkins University Press; 1990.
Reisner H, editor. Children with epilepsy. A parents' guide. Bethesda (MD): Woodbine House; 1988.

The Epilepsy Research Foundation
PO Box 3004
London W4 1XT
Phone: (+44) 020 8995 4781
E-mail: info@erf.org.uk
http://www.erf.org.uk
The Epilepsy Research Foundation is devoted solely to sponsoring effective research for all who now suffer from epilepsy.

H.O.P.E. Mentoring Program
Phone: (877) HOPE 4 YOU (877-467-3496)
http://www.epilepsyfoundation.org/services/hope.html
H.O.P.E., a part of the Epilepsy Foundation, was created to allow people who live with epilepsy to educate others and to share their experiences. H.O.P.E. trains people with epilepsy to be "patient educators" throughout the epilepsy and neurologic communities.

Epilepsy Information Service (EIS)
Department of Neurology
Wake Forest University School of Medicine
Medical Center Blvd.
Winston-Salem, NC 27157
Phone: (800) 642-0500
http://www.bgsm.edu/neurology/department/diagneuro/neuro1.html
The EIS is a nonprofit resource center that offers a nationwide toll-free information line for people with epilepsy and their families, professionals, and the public. Free educational packets are available to all callers.

Epilepsy.com
11911 Freedom Drive #730
Reston, VA 20190
Phone: (703) 437-9720
http://www.epilepsy.com
Epilepsy.com is an online resource provided by The Epilepsy Project, a nonprofit organization that supports research. Epilepsy.com provides information for children, parents, and professionals.

CHAPTER 27

DISCONTINUING ANTI-EPILEPTIC DRUGS IN CHILDHOOD EPILEPSY

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Fifty percent of children with epilepsy will outgrow the disorder. For those who achieve complete seizure control with medication, a question arises: Is it appropriate to attempt to discontinue medication? After 2 years seizure-free, it almost always is reasonable to taper and stop antiepileptic drug (AED) treatment—success will be achieved 70% of the time.

Why Try to Discontinue Medication?

There is no evidence that AED treatment actually *causes* remission of epilepsy—AED treatment only *suppresses* the symptoms (seizures) and a mysterious form of brain maturation "cures" the seizure tendency. The long-term remission rate appears to be the same whether or not epilepsy is treated with daily medication.

With AED treatment, about 70% of children with epilepsy eventually become seizure-free for several years. About 70% of this privileged group remain seizure-free when AEDs are discontinued. Families often have a very different perception than their physician of how much risk they are willing to take in stopping AEDs. Some are surprisingly worried about further seizures, while others leap at any chance to have their child off medication. If a child has been seizure-free for several years, most families wish to try stopping AED treatment to eliminate possible side effects and having to take medication every day. Once a child is off medication and remains seizure free, many families find the daily anxiety they felt because they feared recurrent seizures vanishes.

Risks of Stopping AED Treatment

There are two concerns about stopping AEDs: (1) injury (ie, physical or emotional) from a recurrent seizure and (2) failure to regain control if seizures recur. Neither of these issues has been well studied.

There should be very little worry of physical injury from a recurrent seizure, although a child's activities need to be taken into account. A teenager's driving privileges, or lake swimming, might be reasonably curtailed. Death from a recurrent seizure, in a child who has been seizure-free for years, is almost unheard of and was not noted in several large population-based studies of death in children with epilepsy. Most recurrences after medication is stopped occur within the first 6 months (and nearly all by 12 months), so full activity does not need to be suspended for long.

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Many neurologists have cared for a child who discontinued AED treatment, developed recurrent seizures, and then never gain regained satisfactory seizure control. It is, of course, unknown whether discontinuing medication was causative; however, this sequence of events is, fortunately, rare. In our cohort of 504 patients with partial or generalized tonic-clonic seizures, 70% were seizure free long enough to attempt to discontinue AED treatment; only 3 of those who stopped developed intractable epilepsy. Bouma, et al. reported a less satisfactory outcome in a selected series of 198 children with epilepsy who discontinued AEDs. Forty recurred and 12/40 did not regain complete seizure control over the next nine years. About In our experience, 40% of the children who have recurrent seizures when AEDs are discontinued will become completely seizure-free again with AED treatment and go on to discontinue treatment for a second time. Of those, 68% will remain seizure-free. Therefore, an initial failed discontinuation does not mean that the child will have lifelong epilepsy.

When to Discontinue AED Treatment

Nearly all studies of the recurrence rate when AEDs are discontinued after a child has been seizure-free for 1 to 5 years have produced similar results—60 to 70% of children will remain seizure-free. Few randomized controlled trials in children have compared different durations of seizure freedom before discontinuing medication. One compared treatment for 3 years versus for 1 year, provided the child was seizure-free for the last 6 months. The recurrence rate in the 3-year treatment group was lower (71% versus 53%). Another study randomly assigned children whose epilepsy came quickly under control to 6 months or 12 months of treatment before stopping AEDs. The success rate for the 6-month group was 45% compared with 52% in the 12-month group. However, 2 years later the rate of remission was 80% in both groups, indicating there was no apparent penalty for stopping earlier. Another study addressed stopping AED treatment after the child was seizure-free for 1 year. All patients were receiving monotherapy and, overall, 60% were successful. A metaanalysis reviewed seven randomized controlled trials that collectively enrolled 924 children and concluded that recurrence risk is greater for those who have been seizure free < 2 years than for those who have been seizure free > 2 years (Sirven, 2001).

In summary, the recurrence rate among children seizure-free for 6 months is about 50%, for 1 year about 40%, and for 2 years about 30%. The chance of recurrence remains about 30% if treatment is continued for 4 or 5 years seizure-free, so little is gained by continuing treatment after a child has not had seizures for 2 years. On the basis of these data, the usual practice of most neurologists is to wait until a child has been seizure-free for 2 years before attempting to discontinue AEDs. Only 30% of such children will experience seizure recurrence. We think that 1 to 2 years of seizure freedom is adequate. Six months appears too short.

Predicting Seizure Recurrence after Stopping AEDS

In a meta-analysis of discontinuation studies, Berg and Shinnar concluded that three factors were independent predictors of recurrence when AEDs are stopped: (1) adolescent onset of epilepsy, (2) continuing electroencephalogram (EEG) epileptic discharge (EEG spikes), and (3) symptomatic (ie, a preexisting brain lesion) versus idiopathic (ie, a presumed genetic etiology in an otherwise normal child) etiology. Patients with one or more of these factors need to know that the chance of successful discontinuation is significantly reduced; however, none of these factors is absolute, and a trial without AED treatment is still usually reasonable. For most patients, the only risk is a single recurrent seizure.

Tapering of AEDs

There is an unproven hunch that sudden discontinuation of AEDs is dangerous and may precipitate status epilepticus. We are unaware of such a case when a child has been seizure-free for 2 years. Tennison and colleagues randomly assigned 133 children who had been seizure-free for about 18 months to discontinue medication either over 6 weeks or 9 months. In the 6-week group, 43% had seizures recur, compared with 36% in the 9-month group (p = NS). Serra, et al, randomized 57 seizure-free patients to a 1-month or 6-month AED taper and found no difference in the rate of seizure relapse. In a nonrandomized study, Todt discontinued AEDs in 433 children, many of whom had been on polytherapy. The rate of taper was a predictor of relapse. Greater caution possibly is warranted for patients on polytherapy; however, there does not appear to be a major advantage in prolonging the taper beyond 6 weeks. A recent Cochrane review determined that there is not enough evidence to determine whether rapid tapering of AED (6 weeks) confers significant advantage or risk when compared to slower tapering (9 months).

Our practice is to taper over 4 to 6 weeks for patients on monotherapy. For those receiving two drugs, we usually taper the first drug over 4 to 6 weeks, then pause for a few months before stopping the second AED.

Contraindications for AED Discontinuation

A few epileptic syndromes are associated with a very high risk of relapse, even though the disorder is typically well controlled with medication. The issue comes up quite often for children with juvenile myoclonic epilepsy (JME)—a lifelong disorder in more than 95%. The seizures are usually convulsive, with an onset in early adolescence, so that by the time a child with JME has been seizure-free for 2 years, he or she may be learning to drive. In our experience, most of these young people choose to continue AED treatment for many more years, especially because they do not want to jeopardize their driver's license.

Practical Tips for Families

These suggestions are for families whose children are about to discontinue AEDs:

1. Learn appropriate first aid for recurrent seizures.
2. Understand whom to call if seizures recur.
3. Decide under what circumstances to go to an emergency department.
4. Keep a few doses of medication available for 6 months after discontinuing AEDs.
5. Know the specific epilepsy syndrome and seizure types, so that information can be conveyed to health practitioners if seizures recur, or simply for a child's information once he or she reaches adulthood.
6. Pay attention to behavioral or cognitive changes after medication has been discontinued. This may affect the choice of medication if seizures recur.
7. Consider how much, if at all, to restrict a child's activities and for how long (a very individual decision).

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Practitioner and Patient Resources

Epilepsy.com
http://www.epilepsy.com
Epilepsy.com is an online resource provided by The Epilepsy Project. Its mission is to inform and empower two groups of patients and their families: those facing newly diagnosed epilepsy and those struggling with epilepsy that has resisted the usual treatments.

Chapter 28

Paroxysmal, Nonepileptic Disorders of Childhood

Robert P. Turner, MD, MSCR

There seems to be never-ending variety to the types of paroxysmal nonepileptic disorders (PNEDs) of childhood. Taking a thorough history is the most crucial part of any evaluation. The misdiagnosis of epilepsy in the case of a PNED may lead to inappropriate and potentially harmful treatments. Thus, distinguishing between epileptic and nonepileptic events simulating seizures in childhood is essential.

Clinical experience dictates that children seem able to exhibit an almost unending range of unusual behavioral episodes that often are mistaken for seizures. Paroxysmal nonepileptic disorders, or PNEDs, are frequently encountered in a pediatric neurology practice, often referred emergently by a primary care practitioner. PNEDs are often mistaken for epileptic seizures. Up to 25% of children (range 10 to 43% at some epilepsy centers; Bye et al 2000) referred with a diagnosis of "epileptic seizures" may have a nonepileptic paroxysmal phenomena.

It is extremely important that PNEDs be diagnosed correctly so that children are not inappropriately placed on antiepileptic medications, while other etiologies go untreated. Encouragingly, most PNEDs self-remit with time, but the evasive and sometimes apparently life-threatening nature of such episodes makes them a frequent reason for lengthy consultations with a pediatric neurologist.

Taking a thorough and accurate history from a witness and/or from the child helps ensure an accurate diagnosis is reached. Subsequent neurodiagnostic testing rarely provides a formal diagnosis. Because PNEDs by definition are intermittent in nature, diagnosis remains challenging. One must remember that diagnostic testing rarely compensates for inadequate or inaccurate history.

Parents or others witnessing the episodes will provide most information, although young children can recount symptoms that may provide diagnostic clues. Some parents may bring videotapes of these events to the physician, which often prove very helpful, because the examination of the child in the office or emergency department is typically normal.

In other cases, documentation of PNEDs with prolonged video-electroencephalograph monitoring may be required and is occasionally diagnostic. It may also reassure the family and clinicians that every effort has been made to eliminate epileptic seizures as a cause. However, neither interictal epileptiform discharges (IEDs) nor a normal electroencephalogram (EEG) should be used for diagnosis or treatment apart from the complete history.

PNEDs are an unrelated group of episodic behavioral and motor phenomena, although some classification is possible if based loosely on pathophysiology. Estimates of incidence and prevalence of PNEDs are virtually impossible owing to their varied and evanescent occurrence. Nevertheless, their relatively frequent presentation to the pediatric neurologist makes knowledge of them essential.

In this review, an etiologic/pathophysiologic classification scheme is used as an approach to overall differential diagnosis. Classification may also be based on the age at which a disorder is most likely to occur, with further division according to its expression during wakefulness or sleep. Thus, PNEDs in children < 5 years old most commonly represent sleep-related or stereotypic movements. PNEDs in children 5 to 12 years old are mostly related to conversion disorders, inattentiveness/daydreaming, stereotypic movements, or sleep-related etiologies. Finally, in children > 12

years old, most common etiologies are similar to those in adults (eg, psychogenic or conversion disorders and cardiovascular disorders).

Cardiovascular Disorders

The main cardiovascular etiologies of PNEDs are syncopal in nature, including cyanotic breath-holding spells (BHS), pallid syncope, and vasovagal syncope.

Cyanotic Infant Syncope

Cyanotic infant syncope, also known as breath-holding, occurs in crying infants who become apneic and lose consciousness secondary to transient cerebral hypoperfusion. The episodes are precipitated in an awake child by pain, fright, or frustration, though the trigger may not be witnessed by a caregiver. Because some breath-holding spells are associated with frustration or anger, a misconception abounds among clinicians, as well as lay people, that all these episodes are "done on purpose" by the child, almost as a self-induced temper-tantrum. Though a tempertantrum may evoke a breath-holding spell, the cascade of events that occurs is far from self-induced by the child.

During a typical event, a child will experience pain, fear, or frustration and begin crying vigorously. End-expiratory apnea occurs with progressive cyanosis and loss of consciousness. Tone may initially be increased, followed by limpness. Such events are terrifying for parents and witnesses and are frequently thought to be a seizure. Some children will experience a brief (< 30 second) tonic-clonic seizure related to relative hypoxia.

Physiologically, it is proposed that vigorous crying leads to the apnea associated with cerebral hypocapnia, compounded by arterial oxygen desaturation. Reduced cardiac output from raised intrathoracic pressure caused by crying may contribute to the events, leading to loss of consciousness.

Consciousness is gradually but often rapidly regained, though the child may be confused and irritable after an episode. This may also lead to confusion with a postictal state. Again, taking a thorough history is the best way to obtain accurate diagnosis and treatment. Accordingly, minimal to no neurodiagnostic investigations are warranted, and families benefit from much reassurance and education regarding the episodes' relatively benign and self-limited nature.

Treatment is uniformly unsuccessful, although occasionally children with iron-deficiency anemia have responded to iron supplementation. Treatment with antiepileptic drugs (AEDs) does not eliminate nonepileptic events and, on the contrary, may sometimes have untoward behavioral side effects, increasing their frequency. The author has now seen two patients with typical cyanotic breath-holding spells that are aborted when the parents blow in their children's faces. Beyond these anecdotal cases, such less invasive treatments would certainly be welcome if shown to have efficacy in a controlled trial.

Pallid Infantile Syncope

The pallid form of childhood syncope, also known as pale breath-holding attacks or reflex anoxic seizures, results from transient cardiac asystole secondary to a hypersensitive cardioinhibitory reflex. In contrast to cyanotic breath-holding spells, the pallid form is rarely associated with crying, apnea, or cyanosis before loss of consciousness. Tonic posturing and a brief tonic or tonic-clonic seizure may ensue before the patient regains consciousness. Again, treatments are typically ineffective, though rare and refractory cases have responded to atropine or cardiac pacing. Ocular compression has been reported to result in asystole in susceptible patients, but this author has never seen this done nor does he recommend its use.

Syncope in Older Children and Adolescents

Vasovagal syncope is not uncommon in the pediatric population. Syncope may also result in falls causing injury that require emergent intervention and, often, neurologic consultation. Again, careful history may indicate presyncopal symptoms of lightheadedness and visual blurring or loss, often helping to distinguish such events from seizures.

Precipitating events, such as prolonged standing, heated environments, or abrupt positional changes (eg, rising from lying to standing) also lend clues to the nonepileptic nature of such events. Autonomic changes often accompany syncope but occur with seizures as well. Pale coloring, diaphoresis, or palpitations may precede syncope, but are rare with seizures. Syncope typically is associated with, at most, brief post-event confusion, with rapid return of consciousness without significant clouding of alertness, as opposed to more prolonged confusion that may follow a seizure. Though incontinence and tongue-biting may occur in association with seizures, they are extremely uncommon in syncope. The distribution of tongue-biting may give a clue to differential diagnosis: laceration of the lateral margin of the tongue is typical of seizures, whereas biting the tip of the tongue is more typical of syncope. Most cases of childhood syncope can be correctly diagnosed on the basis of history alone. Atypical features such as "syncope" while sitting or reclining or chest pain, irregular heart rhythm, or a cardiac murmur on examination should lead to further cardiac investigation for nonvasovagal causes of syncope.

Paroxysmal Movement Disorders

This section describes PNEDs consisting mainly of motor phenomena without significant alteration of consciousness. Disorders are somewhat loosely classified into neonatal/infancy problems, dyskinesias, tic disorders, and miscellaneous phenomena. This broad group of disorders may present diagnostic challenges and may easily be mistaken for seizures.

Jitteriness and Tremor

On occasion, a marked jitteriness in a neonate prompts a pediatric neurology consultation. It may be considered in the spectrum of PNEDs consisting of tremulous movements of the limbs, usually of high frequency and low amplitude. The pathophysiology and etiology are not known, though a history of mild hypoxic-ischemic encephalopathy, hypoglycemia, hypocalcemia, or apparent drug withdrawal from maternal drug abuse are not uncommon. Jitteriness is characterized by irregular but symmetric, rhythmic limb movements of arms and legs, with equal motion in flexion and extension. There is no apparent alteration of consciousness or other movements, such as eye deviation or staring. Passive restraint usually stops the tremulousness or jitteriness, whereas agitation or loud noises tend to increase the movements.

Confusion with neonatal seizures is eliminated by taking a thorough history and examination, often supplemented with video-EEG monitoring. Jitteriness rarely appears beyond the neonatal period in otherwise healthy young infants and tends to diminish gradually over weeks to months.

Tremor is also a common PNED seen in pediatric neurology practice, with benign essential or familial tremor being most prevalent. Though occurring at any age, the most common presentation is between 5 to 10 years. Neurologic evaluation is otherwise normal. A family history, coupled with careful history and examination to eliminate pathologic causes such as neuropathies or metabolic abnormalities, confirms the diagnosis of benign familial tremor. Hands are most commonly involved, with tremor often slightly more evident on the dominant side. Education and assurance are important for the child and family, but symptoms can often be very troublesome and cause difficulties, especially with handwriting and other fine motor activities. Treatment may consist of occupational therapy and pharmacologic intervention (eg, propranolol), but practitioners should be cognizant of potential adverse effects.

Benign Myoclonus of Early Infancy

Benign myoclonus of early infancy most commonly occurs 3 to 8 months after birth, and children who develop the condition will have had a previously normal history and examination. Movements spontaneously remit after weeks or months, and therefore no treatment is required. Myoclonic epilepsies and infantile spasms are often in the differential diagnosis, but the EEG is uniformly normal during and between events. Developmental progression continues unabated and virtually all children outgrow this form of apparently benign myoclonus by the time they are 2 years old.

Paroxysmal Kinesigenic Choreoathetosis

Paroxysmal kinesigenic choreoathetosis (PKC), thoroughly described elsewhere in this text, is characterized by brief episodes of choreoathetotic or dystonic movements. These movements are by definition induced by movement or perhaps fear, although a triggering event may be unclear, blurring the distinction between PKC and paroxysmal dystonic choreoathetosis (PDC). The genetic basis of the condition has yet to be defined, though cases have been reported with a positive family history. Etiology is also yet to be defined, but the clinical picture has been rarely associated with various disorders, including multiple sclerosis, traumatic brain injury, stroke, and hypoparathyroidism associated with basal ganglia calcifications.

The events usually begin in children between the ages of 5 and 15 years who are otherwise healthy, although earlier onset has been reported. The episodes are brief, usually lasting several seconds, although they may persist for several minutes. The movements may be choreoathetotic, dystonic, or ballistic, unilateral or bilateral, although symmetric involvement of the arms is more common than of the legs. During an event, there appears to be no loss of consciousness or other clinical accompaniment, but a child may be unable to speak. Falling has been reported from leg involvement. PKC does not appear to represent an epileptic process and EEGs are uniformly normal. The events may respond to AEDs, with a wide variety reported as effective in the literature.

Paroxysmal Dystonic Choreoathetosis

PDC, or paroxysmal nonkinesigenic dyskinesia (PnKC), probably represents part of the spectrum of choreoathetotic disorders, similar to PKC, but it is not precipitated by movements. Events seen thus far in our case series of seven children occur most commonly while the child is sitting in a car seat, high chair, or baby seat. Triggers appear to be excitement, although other authors have noted fatigue, stress, caffeine, and alcohol. Again, the genetics are far from delineated, but an autosomal dominant form has been linked to chromosome 2q. The events of PDC are similar to those seen with PKC, but usually last much longer (eg, many minutes or hours).

Their onset as well as resolution occurs more gradually than with PKC, and the events occur less frequently.

Spasmus Nutans

Spasmus nutans is a relatively uncommon disorder consisting of the triad of nystagmoid eye movements, head nodding/bobbing, and torticollis. Of unknown etiology, it appears to be benign in most children, with onset before 1 year of age and eventual resolution by age 3 to 5 years. Some children have persistent nystagmus and there has been an unproven clinical suspicion of increased risk of childhood or adult migraine. The head nodding/bobbing is at a low frequency of 2 to 4 Hz and is often the first of the triad to develop. Nystagmus consists of low-amplitude, rapid movements of the eyes, which may be asymmetric, dysconjugate, or monocular. Signs may wax and wane during a day or over weeks, but loss of consciousness is not observed. Spasmus nutans may rarely be mistaken for seizures because of its paroxysmal nature. There is no treatment for spasmus nutans, but because of the constellation of symptoms mimicking tumors of the optic nerves and chiasm, brain neuroimaging is usually warranted.

Benign Paroxysmal Torticollis of Infancy (Spasmodic Torticollis)

Torticollis consists of abnormal posturing of the head and neck. The head is tilted toward the ipsilateral shoulder while the neck is rotated with the chin turned toward the contralateral shoulder. Paroxysmal torticollis, by definition, is intermittent, with clinical events lasting minutes to several days occurring at sporadic intervals. The child, who is normal between events, does not appear ill or in distress, nor is there evidence of alteration of consciousness. Some children experience nausea, vomiting, or pallor at onset, suggesting a relation with pediatric migraine as well as with benign paroxysmal vertigo. Onset of spasmodic torticollis may occur during the first year after birth, with resolution usually by the time a child is 5 years of age. No specific treatment is available for benign paroxysmal torticollis of infancy. Neuroimaging is often warranted because the symptoms suggest brainstem involvement, but in the context of a thorough history and examination the findings are uniformly normal.

Sandifer's Syndrome

Gastroesophageal reflux may present as a PNED, with symptoms of paroxysmal arching or opisthotonic posturing. Events may sometimes be associated with vomiting, agitation, and apparent alteration of consciousness. Children under 1 year of age may exhibit signs of respiratory distress or apnea. Sandifer's syndrome consists of arching without clinical findings of reflux. Rapid onset of head and neck extension with arching of trunk may be confused with the tonic component of a seizure, but clinical observation, at times supplemented with EEG, assists in diagnosis of reflux. Older children may describe discomfort in the abdomen or lower chest and report that the posturing eases the discomfort. Gastrointestinal evaluation is warranted and appropriate treatment of the reflux eliminates the episodes.

Poisoning and Drug Ingestion

The differential diagnosis of acute-onset PNEDs must always include ingestion, especially in a toddler. Clinical presentations may include ataxia, dystonia, and impairment of consciousness. Careful history and examination, often supplemented by urine/serum toxicology screening, may help in making a diagnosis. School-age children and adolescents with repeated episodes of ataxia, slurred speech, drowsiness, or abnormal behavior should be evaluated for drug ingestion, as well as other potential metabolic, endocrine, or neurologic etiologies.

Tic Disorders

Tics consist of sudden, brief, involuntary movements or noises that occur repetitively but that wax and wane. They represent a relatively common PNED referral to a child neurologist. Though etiology is still under investigation, autosomal dominant inheritance has been suggested in large kindreds with family members affected by simple tics, multiple motor tics, and Tourette's syndrome. The clinical spectrum of tic disorders includes the more common and benign transient tic disorders, the less common chronic (eg, present daily for more than 1 year) motor or vocal tics, and Tourette's syndrome.

In children, facial, neck, and shoulder tics are the most common motor tics, but tics of the respiratory tract, consisting of brief snorts or sniffing sounds, also may be diagnosed. Vocal tics usually consist of brief noises (eg, squeaks), utterances, echolalia, or, rarely, coprolalia. Some voluntary suppression of tics is possible by the child, leading to the false impression that they are all self-induced or "in their head." However, this suppression of tics will result in a developing internal urge to express the tic, followed by a certain sense of relief upon doing so.

Benign transient tic disorder may manifest with simple motor tics, though they may vary in their manifestation, giving the impression of a "migratory" tic. Their relatively acute onset not uncommonly results in an emergent consult to the pediatric neurologist for concern of seizures.

Treatment consists most importantly of patient and parent education and the difficult but proverbial "tincture of time," as the transient tics (by definition) spontaneously

remit over weeks to a few months. Medications shown to have some success at suppressing tics are pimozide and haloperidol, but pharmacologic intervention should be reserved for when tics are significantly disabling.

Shuddering Attacks

Shuddering, also known as shivering attacks or benign shudder attacks, is a PNED easily confused with myoclonic seizures that occurs in otherwise healthy children who usually are younger than 3 years old. Events occur only while a child is awake and are most commonly described by parents as a brief "shiver" lasting a few seconds. They usually involve the head (shaking or flexion), trunk, arms, and hands, but are of lower amplitude and faster than myoclonus. There is no loss of tone, whether the child is sitting or standing, and no apparent loss of consciousness, though the brevity of these events makes such assessment difficult. Witnessed by the clinician, either in the office or on home video, such events appear simply as a benign shiver or shudder. They may occur dozens of times per day. They may distress parents but appear not to cause the child any discomfort. The etiology, though nonepileptic, remains unknown and children uniformly outgrow such episodes without sequelae. There is an unproven clinical suspicion that such children may have a higher than expected incidence of later essential tremor.

Stereotypic Movements and Staring

Repetitive, stereotypic movements, or "stereotypie," occur most frequently in children with developmental aberrations involving either physical deficits such as visual or hearing impairment, or language-social abnormalities such as autistic spectrum disorder. Children without apparent neurologic or developmental problems may also rarely manifest stereotypic movements. Events consist of a seeming endless variety of repetitive, apparently purposeless movements, at times performed with intense velocity and magnitude but without loss of consciousness. These movements may consist of hand- or arm-flapping, body rocking, or head shaking, rolling, or banging. Interrupting the child usually stops the movements, helping to eliminate seizures from the differential diagnosis.

Staring without stereotypic movements seems to be a common chief complaint and positive finding. Staring episodes usually occur during a quiet activity, most commonly watching television or listening to a teacher in class. They are frequently mistaken for absence or partial seizures. Their context-specific nature, coupled with the ability to be interrupted, usually helps in confirming the diagnosis, but EEG, with hyperventilation, is sometimes useful to establish the nonepileptic nature of such staring episodes. At times, it may be extremely difficult to determine the true nature of stereotypies and staring episodes by history alone, making video-EEG monitoring very helpful in diagnosis.

Masturbation

Paroxysmal episodes of repetitive rocking/rhythmic motions in a high chair (causing pressure to the suprapubic or pubic area) or tightening of the thighs may occur in infants and young children from masturbation. Such episodes may last many minutes and are often accompanied by apparently altered consciousness, with staring, irregular breathing, and occasional facial flushing and diaphoresis. Such episodes may be easily mistaken for a complex partial seizure, as the thought of childhood masturbation is rarely considered. Though no specific treatment is required, education of parents or caregivers is essential, and distraction should be provided to the child gradually and eventually to break the cycle of masturbation.

Stool Withholding or Constipation

Stool withholding may result in episodic behavior of staring and apparent unresponsiveness. Stool withholding may sometimes result from pain associated with constipation and anal fissures. Children may show a sudden interruption of activity and assume a motionless posture of slight truncal flexion. Such behaviors may be mistaken for absence or partial seizures, especially if the episode is prolonged or soiling of the undergarments is present from stool-leakage around inspissated stool. Treatment of the constipation is effective.

Sleep-Related Disorders (Parasomnias)

Sleep-related PNEDs are relatively common in pediatric neurology practice and are covered in a separate chapter. These consist of four categories: (1) disorders of arousal, (2) disorders of sleep-stage transition, (3) parasomnias usually associated with rapid eye movement (REM) sleep, and (4) other parasomnias. By definition, sleep-related disorders are unpleasant or undesirable behavioral or experiential phenomenon that occur predominately or exclusively during sleep.

Disorders of arousal consist of sleep or night terrors (pavor nocturnus), sleepwalking (somnambulism), and confusional arousals, and in this group sleep terrors are the most common PNED encountered in practice.

Disorders of sleep-stage transition consist of rhythmic movement disorder/head-banging (jactatio capitis nocturna), sleep starts (hypnic jerks), sleep talking (somniloquy), and nocturnal leg cramps. In this group of disorders, rhythmic movement disorder and sleep starts are the most common reason for referral to a pediatric neurologist.

Disorders consisting of parasomnias usually associated with REM sleep include nightmares, sleep paralysis, and REM sleep-behavior disorder. Typically, only nightmares may be referred to a pediatric neurologist involved in the diagnosis of PNEDs.

Disorders categorized as "other parasomnias" consist of sleep bruxism, sleep enuresis, nocturnal paroxysmal dystonia, primary snoring, infant sleep apnea, and benign neonatal sleep myoclonus. Though sleep bruxism and enuresis may be reasons for referral to a child neurologist, benign neonatal sleep myoclonus (BNSM) is one of the more common PNEDs seen in the first months after birth.

The most common parasomnias presenting as PNEDs are night terrors, hypnic myoclonus, and BNSM. Taking a thorough history again usually clarifies the diagnosis and video EEG monitoring of events may be extremely helpful to confirm diagnosis, avoid unnecessary pharmacologic interventions, and provide parent education and assurance concerning their ultimate benign prognosis.

Migraine, Acute Confusional Migraine, and Migraine Equivalents

Migraine in children is relatively common, and the diagnosis is usually easily forthcoming after a history of headaches with symptom-free intervals. The diagnostic criteria for pediatric migraine include auras consisting of visual, sensory, or motor symptoms; recurrent headaches with or without nausea, vomiting, or abdominal pain; unilateral throbbing pain; relief usually with rest or sleep; and a family history of migraine.

Acute confusional migraine, usually associated with some language dysfunction, usually occurs in adolescents. Gradual onset of confusion followed by language deficits may last hours, making other causes of acute confusion such as ingestion, infection, metabolic dysfunction, or postictal confusion important to include in the differential diagnosis. Headache is usually absent and the child often has no memory of the event. Differentiation from status epilepticus (nonconvulsive or complex partial) may be challenging in some patients.

In basilar artery migraine, confusion or even loss of consciousness may occur with occipital headache and other brainstem symptoms. Thus, vertigo, tinnitus, facial pain, diplopia, ataxia, and alternating hemiparesis may occur in basilar artery migraine. Findings of acute or subacute hemiparesis warrant emergent neurologic evaluation and exclude a diagnosis of a PNED.

Migraine equivalents—migraine aura without headache—consist of paroxysmal symptoms of migraine *without* headache. Hemifield scintillating scotomata or focal somatosensory disturbances are the most common auras of migraine to occur without headache. Recurrent abdominal pain and vomiting have been reported as migraine equivalents, such as cyclic vomiting syndrome. Recurrent attacks of nausea, vomiting, and abdominal pain occur on a daily or weekly basis but without clouding of consciousness, often with periods of remission lasting weeks to months. Some children with cyclic vomiting syndrome may later develop migraine, especially those who have a strong family history of migraine, suggesting a genetic link between the two disorders.

Several migraine phenomena represent PNEDs that may be confused with epileptic seizures because of their paroxysmal occurrence and their association with neurologic deficits or alteration of consciousness. Certain visual auras are characterized by a range of simple or complex visual hallucinations, beginning in the peripheral visual field and migrating toward the center. These may be confused with occipital seizures.

Somatosensory symptoms may accompany or follow visual symptoms, but such symptoms typically evolve over a longer time than those that occur with focal sensory seizures. Hemiparesis or hemiplegia may occur in hemiplegic migraine, but the existence of motor movements (myoclonic jerks or focal clonic movements) should suggest a seizure. Differentiation of migraine or migraine equivalents from seizures is sometimes complicated because the EEG may be abnormal in some patients with migraine.

Benign Paroxysmal Vertigo

Population-based studies document overlap between migraine and benign paroxysmal vertigo (BPV), suggesting a relation between the two. Therefore, BPV may also be regarded as an age-dependent migraine equivalent. During an event, the child, often as young as 1 to 2 years, will stop what he or she is doing and remain motionless, often in the supine position, with associated pallor, distress, and occasional nystagmus or emesis. The vertigo may be terrifying for the child, who may cling to their parent. Loss of consciousness does not occur. Upon recovery, a verbal child may be able to recall and detail their event. Events may last seconds to minutes and vary in frequency from daily to monthly. Vestibular function testing may reveal abnormalities between events, but the remainder of general and neurologic examinations is normal. BPV may be mistaken for seizures, especially if accompanied by ataxia or falling. Acute treatment should be undertaken cautiously because antihistamines may worsen symptoms and events often cease before medication has time to take effect. If frequent enough, prophylactic use of low-dose cyproheptadine may be considered.

Psychological and Conversion Disorders

Nonepileptic Seizures

Nonepileptic paroxysmal abnormal behaviors may occur as a manifestation of psychiatric illness or an emotional disorder, such as a conversion disorder in children. Frequently, children referred with a diagnosis of epilepsy have nonepileptic seizures (NES) shown by clinical history and video-EEG monitoring. Gates (2002) has wisely and clearly reviewed this topic, appropriately noting the preferred term "nonepileptic seizure" as opposed to the demeaning and pejorative terms often used in the past (eg, hysterical seizures, hysteroepilepsy, nonepileptic pseudoseizure). Unfortunately, NES may not occur in isolation and the comorbid existence of epilepsy increases the diagnostic acumen required for accurate management.

NES are unusual in children younger than 10 years old but when they do occur they are more common in girls. The event or "seizure" is usually characterized by striking motor activity such as pelvic thrusting, arching of the back, thrashing of the limbs, and even self-injury. The episodes may have a gradual onset with a build-up of motor activity over minutes and usually last longer than a typical epileptic seizure. Respiration often is irregular, with gasping or moaning sounds. An association between such NES and previous or concurrent sexual or physical abuse (or other significant trauma in childhood) has been shown.

NES may manifest as a gradual slump to a motionless supine position with unresponsiveness and closed eyes often with some eyelid flickering, often mistaken for cardiogenic syncope. NES may be a manifestation of a conversion disorder. A deliberate simulation of an epileptic attack may occur in some children with epilepsy in an attempt to manipulate their environment (eg, malingering). School avoidance may often underlie such a situation and detailed psychosocial history is important to investigate.

NES are often initially mistaken for epileptic seizures. History is crucial and a precise description of the attacks by a witness may identify clinical features unusual for epileptic seizures, such as a lack of stereotypic movement between attacks, gradual onset, and prolonged duration. Though an interictal EEG may be repeatedly normal in a patient with NES, it is often necessary to record a typical attack with inpatient video-EEG monitoring.

Spontaneous typical events may not occur during a period of video-EEG monitoring, and therefore it is often necessary to attempt to provoke such an event. Methods include suggestion, hyperventilation, photic stimulation, or administration of an intravenous (IV) "convulsant drug" (saline) or skin patch. Ethical considerations, however, are raised by such practices, with more invasive procedures (eg, IV or a skin patch) seldom being done in today's medicolegal environment and in the era of the Health Insurance Portability and Accountability Act. However, some physicians see a role for these techniques when spontaneous attacks cannot be recorded in patients with suspected NES, and their success in eliciting events, though simply implying suggestibility on the part of the patient, may prevent the patient from taking unnecessary antiepileptic medication.

Finally, serum prolactin elevation can be seen within 30 minutes after a tonic-clonic or complex partial seizure but not after an NES. A baseline serum prolactin must be collected for comparison. Marked elevation of serum creatinine kinase can be seen for 2 to 3 days after a tonic clonic convulsion but not after an NES. However, mild to moderate creatine kinase elevation may occur in response to an extremely vigorous NES.

Discussion of the results of video-EEG monitoring with a patient with NES should be straightforward, compassionate, and truthful. The physician should recommend appropriate psychological or psychiatric intervention, because treatment of NES begins with the identification of underlying psychosocial or psychiatric problems. Also, where a diagnosis of NES is confirmed in a patient taking an AED, medication tapering must be done. Overall, in the pediatric population, the prognosis of NES or conversion disorders appears good, assuming appropriate ongoing treatment of the underlying provoking factors.

Munchausen Syndrome by Proxy

Munchausen syndrome describes repeated self-simulation of illness, leading to numerous investigations and unnecessary and inappropriate treatments. Munchausen syndrome by proxy, extremely difficult to diagnose and painstaking in management, refers to a situation in which caregivers deceptively fabricate illness in their children, leading to frequent, inappropriate investigations and treatments, often provided by many health care workers.

Conversely, because of the difficulty of diagnosing PNEDs, this diagnosis has sometimes been wrongly given to a child or family, leading to serious psychosocial implications. The syndrome of Munchausen by proxy is usually seen with children younger than 6 years of age. Most commonly, the mother, often with some medical or paramedical training, is the individual responsible for the sequence of feigned signs or symptoms in her child. The children are brought to medical attention with various symptoms, as well as fabricated signs, that usually suggest a multisystem disorder.

Fabricated symptoms or signs of bleeding from the gastrointestinal or respiratory tract and paroxysmal loss of consciousness or seizures are among the most common complaints. Additionally, a history of persistent or recurrent

unexplained illness may be given. Possible warning signs include a clinical history that is not in keeping with the child's general health, a temporal relationship between the symptoms and the mother's presence, a mother who is virtually always present with the child, reported inability of the child to tolerate any or all prescribed medicines, and a mother apparently unconcerned in the face of serious signs and symptoms. When a diagnosis of Munchausen by proxy is reached, multispecialty involvement of medical and nursing staff, social services, and psychiatry is warranted. Unfortunately, changing health care providers and simply being "lost to follow-up" are common with Munchausen syndrome by proxy, and as such significant morbidity is common and deaths have occurred.

Conclusions

Children frequently exhibit a wide range of unusual behaviors that often are mistaken for seizures. PNEDs are frequently encountered in pediatric neurology practice and can be mistaken for epileptic seizures. It is essential that PNEDs be diagnosed correctly so children are not placed on AEDs needlessly while other etiologies go untreated. Due to the intermittent nature of PNEDs, diagnosis may be challenging and almost exclusively depends on the clinical history, occasionally supplemented with video-EEG monitoring. Witnessing episodes provides the most information; caregivers and some young children can recount symptoms that may provide diagnostic clues. Videotaping these events may be very helpful; otherwise, documentation with video-EEG may be required. Almost invariably, general and neurologic examinations are normal in children with PNEDs. Diagnostic testing, when indicated, is also almost invariably normal. Thus, treatment, if indicated, must be carried out cautiously while specifically addressing the underlying cause. Thorough communication between patient, family, and clinician and continuity of follow-up are important to ensure the highest standards of clinical care are provided.

Suggested Readings

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Practitioner and Patient Resources

Epilepsy Foundation of America
4351 Garden City Dr., Suite 406
Landover, MD 20785-2267
Phone: (301) 459-3700 or (800) EFA-1000
E-mail: postmaster@efa.org
http://www.epilepsyfoundation.org
The Epilepsy Foundation is a national charitable organization for individuals with epilepsy. It serves to ensure that people with epilepsy are able to participate in all life experiences and tries to prevent, control, and cure epilepsy through research, education, advocacy, and services.

Epilepsy Information Service (EIS)
Department of Neurology
Wake Forest University School of Medicine
Medical Center Blvd.
Winston-Salem, NC 27157
Phone: (800) 642-0500
http://www.wfubmc.edu/neuro/epilepsy/information.htm
The EIS is a nonprofit resource center that offers a nationwide toll-free information line for people with epilepsy and their families, professionals, and the public. Free educational packets are available to all callers.

Chapter 29

The Ketogenic Diet

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The ketogenic diet is a safe, effective, and underutilized therapy for children with difficult-to-control seizures. The diet may be useful for other conditions as well. The ketogenic diet should only be undertaken under medical supervision and under the care of a trained dietician.

Introduction

Since the re-introduction of the ketogenic diet (KD) about 10 years ago, its use has expanded dramatically and become worldwide. The diet is now accepted as a safe and effective therapy for children with difficult-to-control seizures. The major impediments to its use are inexperienced physicians and the lack of well-trained dieticians, who are given insufficient time to adequately educate and assist parents or patients to properly adhere to the ketogenic diet. Tolerance of the diet by parents and children is related to the diet's effectiveness in that specific child. When effective in substantially decreasing seizure frequency, or in allowing a decrease in medications and their side effects, the diet is usually well tolerated. When less effective, it is often discontinued by the families.

Background

The ketogenic diet is very high in fat, adequate in protein and very low in carbohydrate content. It was designed to mimic the biochemical effects of fasting. Numerous old and recent studies document its effectiveness in controlling difficult-to-control seizures of varying types and in children and adolescents of varying ages. There are few studies of the effectiveness of the diet in adults.

Devised in the early 1920's to duplicate the beneficial effects of prolonged fasting on seizures, the diet was utilized until the development of phenytoin in the late 1930's, but then infrequently used. Since the mid to late 1990's the diet has been used with increasing frequency and at an increasing number of centers worldwide. Its efficacy has been well documented and its side effects evaluated.

The Effectiveness of the Ketogenic Diet

The ketogenic diet appears to be more effective in children with difficult-to-control seizures than any of the new anticonvulsant medications and appears to have fewer side effects than these medications. Despite considerable research efforts, and speculation about its mechanism(s) of action, how the diet works remains unclear.

During the 1930's to 1950s, when few anticonvulsant medications were available, many studies (1) showed that roughly 72% of children placed on the ketogenic diet had a greater than 50% decrease in their seizures and fifty-four percent had greater than 90% reduction in seizure frequency.

In the mid 1990's a prospective study of 150 consecutively treated children, averaging 5 years of age, with a mean of 410 seizures per month were reported in the mid 1990s. The seizures were of multiple types, and the children had failed to respond to a mean of 6.2 drugs. Eighty-three percent of those initiating the diet continued for 3 months, and 55% remained on the diet for more than one year. It should be noted that the time a patient remains on a therapy has been used as a measure of tolerability and efficacy.

Outcomes of the Ketogenic Diet
At Johns Hopkins up to 3–6 years after start.

Number initiating	Seizure control and diet status	3 months	6 months	12 months	3–6 years
Total 150	Seizure free	4 (3%)	5 (3%)	11 (7%)	20 (13%)
	90–99%	46 (31%)	43 (29%)	30 (20%)	21 (14%)
	50–90%	39 (26%)	29 (19%)	34 (23%)	24 (16%)
	< 50%	36 (24%)	29 (19%)	8 (5%)	18 (12%)
	Continue Diet	125 (83%)	106 (71%)	83 (55%)	18 (12%)

TABLE 29-1. Outcomes of 150 consecutive children started on the ketogenic diet at Johns Hopkins. The children averaged 410 seizures per month at the time of diet initiation. The seizures were of varying types. Children were followed-up at 3, 6, and 12 months (2) and again at 36–72 months (3) after starting the diet.

Children with this seizure frequency and resistance to drugs would be expected to have far less than a 10 percent chance of responding to any medication. Yet, as shown in Table 29-1 and Figure 29-1 half of the children initiating the diet remained on it for 1 year. By one year, seven percent of those starting the diet were seizure free, and an additional 20% had a 90% or greater decrease in their seizures. Few medications have been assessed for efficacy and tolerability one year after initiation. What is even more surprising is that 13% of this difficult-to-control group were seizure-free 3–6 years after starting the diet and 27% percent had greater than a 90% decrease in their seizures. Outcomes of studies from other centers are similar, although reporting smaller numbers of children followed for less time. Although the diet has never been evaluated in a blinded, crossover fashion, such a study is in progress. Studies of the ketogenic diet, its potential mechanisms of action, and its potential uses other than in epilepsy have recently been summarized.

Who should try the diet?

Although the studies cited above were performed on children who had failed on average more than 6 medications, the diet should not be reserved as the last resort. Individuals with epilepsy who have failed two medications, appropriately used, are said to have only a 10% chance of responding to any other medication. Therefore the effectiveness of the diet would suggest that it be tried in those who have failed two medications. The diet is tolerated if its benefits—seizure control and lack of sedative effects—outweigh the rigidity and the constraints of the diet. Children whose quality of life is not impaired by their seizures or the effects of medication are unlikely to remain on this rigorous diet.

The Hopkins protocol had been to fast the child for 48 hours; however, we now fast for only 24 hours, admitting the child after about 18 hours of fasting. The importance and effectiveness of these periods of fasting have not been studied. However, preliminary evidence from an ongoing study suggests that fasting may play an important role in jump-starting the seizure control. After the fast, a ketogenic eggnog containing 1/3 of the daily caloric allotment is given for breakfast, lunch and dinner, followed the next day by 3 meals with 2/3 of the caloric allotment and then 2 meals of typical solid food, after which the child is discharged. The number of calories and the ratio of fat to protein and carbohydrate in the child's diet are individually assessed depending on the child's age and weight. They are later adjusted depending on the success of the diet and the child's subsequent weights. We utilize the 4 day admission to assure that the child does not become either too hypoglycemic or too acidotic during fasting. We further use this period of hospitalization to assure that the family understands the diet, learns to read labels and is able to manage illness. Our approach seems to be successful. It is not, however, the only approach. Some ketogenic programs do not hospitalize the children at all. Others do not fast children. The MCT diet appears to be as successful as the 4:1 ketogenic diet, although alleged to be less palatable. None of these approaches have been adequately compared or studied.

Fine Tuning the Diet

Initiation of the diet is the easy part; however careful monitoring by an experienced dietician is crucial to the diet's success. Fine-tuning assures that the child approaches and then maintains ideal body weight and is neither losing nor gaining weight excessively. This monitoring assures proper ketosis and adequate seizure control. Once the family learns to read food and medicine labels, to weigh foods, to find the

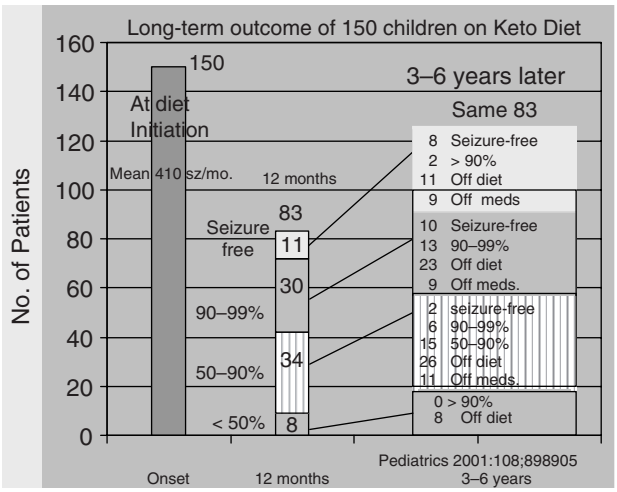

FIGURE 29-1. Outcomes of the 83 children who remained on the diet at 12 months after diet initiation. Note that 20/63 had become seizure-free, 41/83 had a 90% or greater reduction in their seizures, 68/83 had discontinued the diet, and 29 of the 83 were off all medications. (3)

proper foods and cream, and to adjust the diet to the child's food preferences, then they require less support. It is this time-consuming support which, we believe, makes for a successful program. It is the lack of trained dieticians, and the inability to bill for the hours to provide for this support, which impairs more widespread use of the diet.

Side Effects of the Diet

The side effects of the diet are infrequent, usually mild, and infrequently require KD discontinuation. Early-onset side effects associated with diet initiation include acidosis, hypoglycemia, GI distress, dehydration, and lethargy. They are typically transient, easily managed, and are minimized if patients are not fasted. Virtually none require diet discontinuation. Later side effects include: Dyslipidemia, kidney stones, slowing of growth and obesity, bone density, and constipation.

Myth: "If they eat that fat they'll all get heart disease and strokes" - No!!

Dyslipidemia is uncommon. In 141 children prospectively followed on the diet over two years (Figure 29-2). There was an increase in atherogenic apoB-containing lipoproteins, VLDL and LDL and a decrease in the anti-atherogenic HDL cholesterol. Cholesterol increased approximately 130% but then stabilized over the two-year period. The lipid profiles of children on the KD more than 6 years returned toward baseline.

Society seems to have been brainwashed about the lethality of fat ingestion. Although cholesterol and the other lipids increased significantly during the first 6 months on the diet, less marked but still significant changes were seen 12 and 24 months after starting the diet. The biologic significance of these changes is unknown. Children rarely remained on the diet for more than 2 years and then continued on a relatively low fat diet. Rare patients with a family history of familial hyperlipidemia have had marked increase in their triglycerides. These usually respond to a lowering of the diet ratio.

Height and Weight

Height and weight are not problems in carefully supervised children. Children on the diet grow normally over a period of two years on the diet, but the growth of younger children appears to be more affected than that of older children. Those on the diet for more than 6 years often appear to be less than the 10% for height. However, growth appears to increase rapidly after diet discontinuation.

Myth: "If you eat a high fat diet you'll get fat - right?" Wrong!!

The weight gain of children on the diet is carefully controlled by the dietician who adjusts the number of calories ingested to meet the requirements for the child's activity. Weight gain indicates that more calories are being consumed than are being burned. Severely handicapped children often need fewer calories than more active children. Our studies suggest that to achieve optimal seizure control, children must be maintained close to their ideal body weight for their height. Overweight children achieve best seizure control when the diet's caloric content is calculated for them to lose to ideal weight. Underweight children are given sufficient calories to approach ideal body weight.

Kidney Stones

Kidney Stones occur in 6–7 percent of children on the ketogenic diet. These stones are commonly uric acid or calcium/uric acid. Low urine pH and decreased fluid intake may lead to precipitation from urine supersaturated with uric acid and calcium and thus to stone formation. Maximizing fluid intake and the addition of polycitrate (Polycitra-K, 2 mEq/kg/day divided bid) to maintain pH greater than 6.5 solubleizes the uric acid and may prevent or even dissolve stones. The prophylactic use of polycitrate appears to have significantly decreased the incidence of kidney stones. An elevated urinary calcium/creatinine ratio may indicate a predisposition to stones and warrant liberalization of fluids and the use of polycitrate. The occurrence of the stones does not appear to be increased by the use of carbonic acid

inhibiting anticonvulsant medications. Stones can be managed and the diet rarely needs to be discontinued.

Bone density may be adversely affected by the KD. A higher risk of skeletal fractures in children on the KD has been reported. Prevention with calcium supplementation, pamidronate, or lower ketogenic diet ratios remains unproven.

Constipation is a common side-effect of the diet. The bowel habits of a child on the diet are different than prior to the diet since the amounts of food are small. There is also decrease in bulk, but small stools are not constipation. Straining, abdominal discomfort and hard stools indicate constipation. The fluid restrictions of the diet may contribute to the condition and fluid can be liberalized. Using group A vegetables (see book-8) instead of group B may increase the bulk since group A vegetables have less carbohydrate per unit of bulk. Adding a small amount of medium chain triglyceride oil (MCT) (which must be calculated to replace a portion of the fat) may also help. Stool softeners such as Epsom salts, Miralax (1 tbsp/day), and aloe vera have been found useful. Enemas are a last resort. **Constipation should never be a reason for discontinuing the diet.**

Myth: No child will stick to that kind of diet. Untrue!!

Behavior problems on the diet

Behavior problems on the diet may include food stealing and food refusal. These can usually be managed without altering the diet if the parents have the will and the anticipatory advice. They are discussed in our paper on maintenance of the diet and in our book.

Make the diet appealing. Creative parents can make the diet very attractive and appealing. Cookies can be made with egg white and cottage cheese. They can be colored with carbohydrate-free food coloring and crumbled to make "cold cereal" for breakfast. Cookies or special muffins can be taken to parties at school. Cheesecake for a birthday party and exchanging Halloween candy for money are but a few of the many creative ways to make the diet more acceptable to a child. If a parent thinks the diet is unpalatable, or forces the child to eat separately from the rest of the family, the diet is likely not to be continued. If the diet is portrayed as a "special" meal for the child so that they can rid themselves of seizures and medication, then there are fewer problems. If the diet is effective, it is usually acceptable to the child and the parents.

We usually ask parents to try the diet for three months in order to allow the parents to adjust to preparing the meals and find the child's preferences. It takes time for the child to adjust to the restrictions. Working parents often will set aside some time on the weekend to prepare a week's worth of meals, label and freeze them so that meals do not have to be weighed and measured during the busy week. We have found that for some children the diet must be very precise. For example, some children who are fed dinner early (around 5 p.m.) and eat nothing else before going to bed, may have insufficient fuel to maintain ketosis and may have early morning seizures. A late snack or a later dinner may correct that problem. We have seen a snack of 3 macadamia nuts be well tolerated, whereas 7 macadamia resulted in a return of the seizures, Even carbohydrate-containing toothpaste, or sorbitol-containing suntan lotion, may lead to a recurrence of seizures.

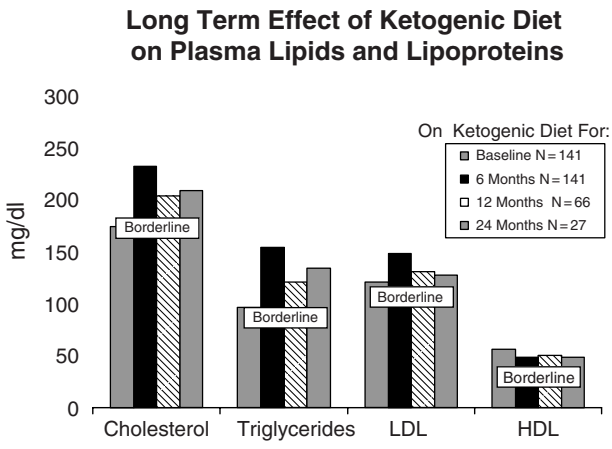

FIGURE 29-2. Changes in the plasma lipids while on the ketogenic diet. (10) The changes from baseline seen at 5 months after initiating the diet were virtually all statistically significant, but less marked changes were seen at 12 and 24 months. The biologic significance of these changes in children who usually discontinued the diet after two years is unknown.

Discontinuing the diet

The diet is usually continued for two years, although this duration is arbitrary. Having a finite time limit does, however, help the family and the children understand that the dietary restrictions are not forever. We originally ask the parents to try the diet for at least three months. As can be seen in Table 29-1, eighty-three percent continue the diet for 3 months, 71% continued for 6 months and 55% remained on the diet at one year. The primary reason for discontinuing the diet is because it is ineffective in sufficiently controlling the seizures. The other reason is because it is too difficult. We believe that these are two sides of the same coin. The diet is not too difficult if it is controlling the seizures or allows a decrease in the medications. It is too difficult if these goals are not achieved. The classical way to discontinue the diet is to decrease the

ratio from 4:1 to 3:1 for a number of months, then to 2:1 for several months, then to stop. We have successfully tapered the diet by maintaining the calculated diet as prescribed but switching from cream to regular milk which maintains the diets' rigidity, but decreases its ratio to about 2.5:1. If the seizures do not recur within a week or two we substitute skim milk for the regular milk. The ratio is now about 1.5:1. If the seizures do not increase then the diet may be stopped. If in the course of this taper seizures increase, then we resume the heavy cream. We have had occasional families, usually those with severely handicapped children who have maintained the diet for many years without ill effects.

Other Interesting facts about the diet

1. The diet has been used successfully in children with infantile spasms who have failed ACTH and or Vigabatrin.
2. There are suggestions that the Atkins high-protein-low carbohydrate diet may control seizures in both children and adults with difficult-to control seizures.
3. The ketogenic diet improves the developmental quotient, and improves the child's behavior, attention, and social skills.

The mechanisms underlying the anticonvulsant effects of the diet are unknown. It is neither the acidosis nor the fluid restriction. Whether it is the degree of ketosis, the beta-hydroxy butyric acid level, or amount of acetone in the blood is unclear. Some feel that it may be the caloric restriction or carbohydrate restriction of the diet. Others are investigating the levels of specific fatty acids. These and other possible mechanisms of action are currently under active investigation.

Summary

- The diet is effective in controlling difficult-to-control seizures.
- The ketoacidosis associated with the ketogenic diet is not unhealthy and is quite different than the ketoacidosis associated with uncontrolled diabetes.
- A high fat diet with caloric restrictions is compatible with a normal active life, with some dyslipidemia.

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CHAPTER 30

EPILEPSY SURGERY AND CORTICAL STIMULATION

SUSAN KOH, MD

Epilepsy surgery is usually the last resort for many patients with intractable epilepsy and the only effective treatment for childhood catastrophic illness such as hemimegalencephaly or Rasmussen's encephalitis. In addition, vagal nerve stimulation and transcranial magnetic stimulation provide alternative treatments that are helpful for patients who cannot undergo resective surgery.

Epilepsy surgery has been well established as an effective treatment for intractable epilepsy in adults. In children, epilepsy surgery relieves intractable seizures, which helps them reach developmental milestones. This is especially true for children with catastrophic illnesses occurring at a young age. In this chapter, we discuss improvements in the selection and evaluation of patients who are potential candidates for surgery and describe advances in surgical techniques.

In addition, technological advances in vagal nerve stimulation (VNS) or transcranial magnetic stimulation (TMS) have been achieved in the past few years. Chronic stimulation provides an effective treatment for children who have intractable epilepsy and are not candidates for surgery. Accordingly, we also describe the efficacy of VNS and TMS.

Candidacy for Epilepsy Surgery

The lifetime risk of developing epilepsy is 3.2%. It is thought that at least 60% of all seizures are partial seizures arising from a single location in the cortex. In addition, approximately 5 to 10% of patients with new onset seizures eventually develop intractable epilepsy. Many of these intractable partial seizure patients are not referred to epilepsy surgical centers. It is estimated that as many as 5,000 new patients annually in the United States may benefit from epilepsy surgery, but only a third receive treatment. Much of this is related to the fact that many primary physicians have not received the training necessary to properly identify and refer patients who might benefit from epilepsy surgery. This is especially true for pediatric epilepsy patients because many pediatric neurologists are concerned about surgical risks and, therefore, are reluctant to send patients to epilepsy surgery centers.

Many benefits are associated with epilepsy surgery, such as less morbidity and mortality due to intractable epilepsy and status epilepticus, less use of antiepileptic drugs, improved quality of life, and improved cognition and development. Complications associated with surgery include bleeding, risk of infection, cranial nerve dysfunction, increased intracranial pressure, and stroke. These complications are more prevalent in children because of their smaller body volume as well as the extensive types of surgeries that are performed, such as hemispherectomy.

For some patients, especially in those undergoing temporal lobectomies, surgery is thought to be curative if the epileptogenic focus is localized to an easily accessible area that is not involved in critical function. However, many times a patient has diffuse areas of involvement that cannot be fully resected. This is especially true for mentally retarded children, in that the dysfunction involves both hemispheres. With these children, palliative surgery decreases seizure frequency but does not eliminate them. For example, patients who have drop attacks may benefit from corpus callosotomy, where the risk of head injury is lessened, although other seizures will not stop.

Whether surgery is performed for palliative reasons or for curative reasons, medical intractability of seizures is important to establish. Many children are thought to have intractable epilepsy, but further evaluation, such as long-term videotelemetry, shows these children have nonepileptic events. Children who are the best surgical candidates have partial onset seizures. Medical intractability for partial seizures should include a substantial trial of antiepileptic drug therapy. This includes trying at least three antiepileptic drugs, one of which includes a newer antiepileptic drug, such as felbamate, lamotrigine, topiramate, zonisamide, or levetiracetam. Children who are surgical candidates frequently have at least one seizure per month, although recurrent status epilepticus or regression in cognitive skills may justify surgery even if seizures are less frequent. Finally, if a patient has a disorder where the prognosis for cognition and seizure control is poor, then surgery should be considered at an earlier, stage. Such disorders may include Rasmussen's encephalitis, severe Sturge-Weber syndrome, gross cortical dysplasia, and hemimegalencephaly.

Contraindications for surgery include seizure disorders, such as benign rolandic epilepsy or childhood absence, that have a natural tendency to abate. In addition, some believe surgery is contraindicated for patients who have a neurodegenerative illness, such as Batten disease, as the procedure would not improve the dire outcome. Noncompliance with medications is also a contraindication, as medical intractability has not been established.

There are some controversial contraindications as well, such as intercurrent psychiatric illness. Some reports indicate surgery worsens psychiatric illness, such as psychosis, depression, and mania. However, other reports in the literature suggest surgery may improve these conditions. Other practitioners believe mental retardation may be a contraindication for surgery because diffuse involvement of both hemispheres is implied. However, in many children with mental retardation, surgery is effectively used as palliative therapy for disabling seizures. Finally, some believe a lack of social support may be a contraindication because the child might not be able to participate in the intensive rehabilitation required after some surgeries, such as a hemispherectomy.

Evaluation

Epilepsy surgery evaluation includes long-term videotelemetry, high-resolution magnetic resonance imaging (MRI), and functional neuroimaging such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT). These studies assist with localization of the epileptic focus. At least two of the three modalities need to map to the same brain region for a child to be considered an epilepsy surgery candidate. Other tests can be performed to corroborate a single epileptogenic focus.

Scalp Electroencephalography

Videotelemetry is preferred over routine scalp electroencephalography (EEG) to establish whether an event is actually a seizure and to interpret the semiology that determines seizure origin. The interictal background as well as the ictal onset of at least two typical seizures should be captured. If mesial temporal lobe sclerosis is considered, then sphenoid electrodes or cheek electrodes should be placed. In addition, the timing of the seizure electrographically as well as its semiology can aid in determining whether the seizure starts in a deep focus (where there are EEG changes before the clinical event). In children, the ictal onset is often more subtle than in adults, so electroencephalographers should have considerable pediatric experience.

With recent advances in neuroimaging, including stronger magnet strength and improved computerized sequences, more abnormalities are now detected on MRI. A high resolution MRI is the preferred neuroimaging tool for epilepsy surgery evaluation. However, CT is still used occasionally as an adjuvant imaging modality, especially in etiologies noted for calcifications, such as tuberous sclerosis, cysticercosis, or Sturge-Weber syndrome. The MRI should include fluid-attenuated inversion recovery (FLAIR) sequences and T2 coronal sequences with thin cuts (1 mm) through the temporal lobe to see mesial temporal lobe sclerosis. Most children suffer from cortical dysplasia, with subtle changes noted on neuroimaging such as gyral thickening and gray-white matter junction blurring. These are difficult to differentiate unless there is a neuroradiologist who has experience in interpreting films for epilepsy surgery. In addition, some MRI scans (especially T2 and FLAIR sequences) are placed on a surgical navigational system where the MRI is coupled with an operative microscope; the surgeon can determine his intraoperative orientation and location in relation to the lesion through the wand. This allows for a more complete resection of a deep lesion.

Functional Neuroimaging

In many children with subtle cortical dysplasias suspected on MRI, functional neuroimaging such as PET or SPECT can provide valuable information on the extent of cortex affected.

PET Imaging

PET is a nuclear medicine scan that uses radioactive tracers to find the epileptic zone. PET is especially useful for temporal lobe seizures in adults. Epileptic cortex typically shows decreased uptake of fluorodeoxyglucose

(FDG). The PET scan's sequences are based on interictal background pattern and, therefore, will have poor reliability if a patient has a seizure. Therefore, we obtain PET imaging concurrently with EEG. If a seizure occurs within 5 minutes of the injection, the study is considered an ictal study. Other tracers such as α-methyl-L-tryptophan (AMT) may be more effective in evaluating conditions such as tuberous sclerosis, but AMT is less readily available than FDG. There are now newer techniques where the PET interictal scan is superimposed onto a MRI scan (called PET-MRI fusion) which gives better resolution of abnormalities.

SPECT is also a nuclear medicine study, and hexamethylpropyleneamine oxime (HMPAO) is injected to evaluate cerebral blood flow. At the onset of a seizure, cerebral blood flow increases. Thus, the HMPAO injection must ideally occur within 30 seconds of seizure onset.

Magnetoelectroencephalography

A magnetoelectroencephalograph (MEG) detects and measures magnetic fields generated by electrical activity using superconducting quantum interference devices (SQUIDs). Magnetic fields form dipoles parallel to the cortical surface and are picked up by SQUIDs. Unlike EEG, MEG is unaffected by overlying tissue or bone that attenuates electrical potentials between cortex and scalp. MEG arises from intracellular currents in active neurons and, therefore, also offers greater spatial resolution than EEG. Therefore, MEG is helpful as another evaluation tool when the EEG ictal onset is too broad or unclear. MEG is often superimposed on an MRI image and, therefore, is easier for nonelectroencephalographers to read. It is especially advantageous in surgical planning in cases where there is a previous resection, because it shows location of dipoles relative to the original resection site. Also, MEG is useful in identifying offending foci in conditions with multiple cortical anomalies (eg, tuberous sclerosis). Finally, MEG is beneficial in comparing the epileptogenic zone with the motor, visual, or language areas because MEG uses evoked potentials to find these areas. MEG may provide help in localizing where subdural grid electrodes can be placed for more accurate recordings during intraoperative monitoring. Also, MEG is useful in multifocal etiologies like tuberous sclerosis where there are several tubers; it may determine which of these tubers is the epileptogenic tuber. Finally, MEG is beneficial in comparing the epileptogenic zone with the motor, sensory, auditory, visual or language areas since MEG utilizes evoked potentials in order to locate these areas. MEG has also been shown in some studies to detect dominance in language and might substitute for the Wada procedure in some cases. However, MEG is costly and is unavailable in many locations. EEG source imaging is similar to MEG, except it is EEG superimposed onto MRI scans. It is easier to apply in younger or developmentally delayed children requiring sedation. However, there are problems due to the electrodes not able to sample basal temporal or frontal areas in detail.

Other Neuroimaging Techniques

Other modes of evaluation include proton magnetic resonance spectroscopy (MRS) and blood oxygen level dependent (BOLD) functional MRI. MRS is not commonly used in children, because it is mainly helpful for temporal lobe epilepsy patients. Affected cortical regions have decreased *N*-acetyl aspartate, a neuronal marker.

Functional MRI uses rapid scanning techniques to find areas with low deoxyhemoglobin concentration, which correlates with increased cerebral blood flow. Ictal onset can be determined because blood flow increases in areas where the seizure starts. It also can be used for localizing frequent interictal spiking if performed with concurrent EEG. Finally, functional MRI demonstrates eloquent cortical regions subserving motor or language functions. Technical considerations of functional MRI include limited cooperation of patients and variable results when using current language testing paradigms.

SPECT, PET, and MEG all have benefits and disadvantages. SPECT and PET are similar in resolution and quality of study and require a trained reader to interpret the results. The main difference between the two is that SPECT requires a dedicated technician who is willing to inject the patient during an electrographic or clinical seizure. PET is an interictal study, although the procedure is more costly than SPECT. In addition, SPECT is useful for seizures lasting longer than 30 seconds, because the tracer has time to reach the area of origin. In contrast, PET does not have this time requirement because it is an interictal study.

MEG is helpful when either SPECT or PET do not detect lesions or when the EEG is nonfocal or difficult to interpret. MEG determines the dipole location in relation to a previous surgery site or if there are multiple foci seen on MRI (such as tuberous sclerosis). Finally, MEG can also determine where motor or vision is located relative to dipole area. However, MEG is costly and is not widely available.

Neurocognitive testing

Neurocognitive testing can localize the area damaged by the epileptogenic site as well as assess the state of the surrounding brain tissue. A neuropsychologist can sometimes predict what deficits a child might have with surgery and removal of the epileptogenic zone. In addition, she or he can also anticipate whether the surrounding tissue may be able to take on some of the functioning of the removed area.

Invasive Procedures

After localizing the epileptogenic zone at surgery, other invasive studies are performed to confirm the location or to further tailor the resection. In addition, if there is a concern that the epileptogenic focus is involved in critical function such as motor or language, functional mapping is also executed.

Electrocorticography

In this procedure, the skull and dura are removed and subdural electrodes are placed on the area most suspected as a focus. An interictal background is recorded, which means that seizure onsets are sometimes not captured. Anesthesia is usually weaned off to increase the yield for interictal abnormalities and provoke seizures. Interictal spike discharges are not as revealing as the slowing and attenuation in the background. Somatosensory evoked potentials are performed before electrocorticography to localize the motor strip. Depth electrodes are rarely used in children, because most children do not have mesial temporal lobe sclerosis but neocortical epilepsy, which is easily accessed by grid.

Subdural Grid Monitoring

Chronic subdural grid recordings are another option in children. The patient is implanted with subdural grid electrodes in suspected cortical regions and then monitored in the pediatric intensive care unit for seizure onset and mapping of the critical cortex. Subdural grids provide accurate information for children, especially in cases where other evaluations such as scalp EEG is nonlocalizing or vague or if neuroimaging is nonlesional. Also, if surgical evaluations provide noncongruent results, then subdural grid monitoring can provide more accurate information. A grid is used when multiple foci are seen, such as in tuberous sclerosis. Finally, grids can provide vital information on language and motor function localization relative to seizure focus localization. Problems with subdural grid electrodes in children include the need for sedation, so children do not attempt to remove the leads. As with all implants, there is a risk of infection and bleeding.

Functional Mapping

Functional mapping is used for both language and motor cortex and is often performed simultaneously with subdural grid monitoring. Here, the subdural electrodes are directly stimulated while the patient is talking or reading (to see if there is a pause) or observed for movements. In children, there are usually higher thresholds found compared with adults for an after discharge or for a functional response. In addition, both the duration and intensity of stimulation needs to be increased for a response to be provoked.

Wada testing

Wada testing involves performing a cerebral angiogram, and then sodium amytal is injected into the cerebral artery numbing one side of the brain. This provides a small window of time in order to test whether language and memory is dominant in that hemisphere. Wada is helpful in cases of language and memory testing, especially for temporal lobe epilepsies. However, the limitations are significant in the pediatric population. Children need to remain awake and cooperative during this invasive procedure which is very difficult to do in small children. Antiepileptic medications such as topiramate and zonisamide will interact with the sodium amytal and therefore, larger amounts of sodium amytal will need to be injected to see whether there is an effect. Sleepiness and transient visual field deficits are common with this procedure. Differences in what anesthestic agent is used (sodium amobarbital and sodium methohexital) can alter the findings. Finally, findings of verbal memory may differ if the stimuli is nonverbal (ie, a picture) rather than verbal. In some pediatric centers, functional MRI is used for language mapping rather than Wada, although there are few studies validating this substitution. In addition, there have been some preliminary studies suggesting that MEG and language mapping may supersede a Wada test, especially in children.

Types of Surgery

Temporal Lobectomy

Temporal lobe seizures are less common in children than in adults. If they occur, they tend to be neocortical rather than mesiotemporal. Therefore, temporal lobectomies are often more extensive in children. Additional problems with extensive temporal lobectomies include superior quadrantanopsia due to resection of Meyer's loop in the temporal white matter, transient anomies due to swelling, and memory difficulties. In addition, there can be language complications based on whether the temporal lobe resected is dominant for language or memory. Usually, if operating on the dominant language, the surgeon will take less tissue (4–5 cm compared to 7cm from the tip). Therefore, neurocognitive testing and Wada testing is important in most temporal lobe resections.

Extratemporal Lobectomy

Extratemporal seizures such as frontal, parietal, and occipital seizures are more common in children than in adults; frontal seizures are most prevalent. Extratemporal lobectomies are typically needed in older children rather

than in younger children, who have multilobar epilepsy. However, extratemporal lobectomies carry a greater risk of affecting language and motor functions. There can be temporal mutism or motor apraxia with removal of the supplementary motor area, abulia in frontal resections, neglect in parietal resections or visual loss in occipital resections. Extratemporal lobe resections may have less long term seizure freedom rates than in temporal lobe resections. In some cases, the surgery will need to be performed while the patient is awake since critical cortex for language or motor may be involved.

Multilobar Hemispherectomy

Multiple lobe involvement is the most common epilepsy surgery for young children with catastrophic illnesses, which tend to involve diffuse areas. Multilobar resections often carry more surgical complications due to bleeding and potential for neurologic deficits. Temporal–occipital–parietal resections are performed but are less effective than hemispherectomy. Hemispherectomy, characterized by two predominant types, involves the removal of an entire hemisphere. With anatomic hemispherectomy (AH), the entire hemisphere is removed, but the basal ganglia is spared. Functional hemispherectomy (FH) involves removal of the temporal and/or parietal lobes with disconnection of the white matter tracts between the frontal and occipital lobes. AH is performed less frequently than FH because of increased risks of bleeding, subdural hematomas, increased intracranial pressure requiring ventriculoperitoneal shunting, and more long-term side effects, such as siderosis. After hemispherectomy, dense hemiparesis and visual field loss occurs. However, in children who receive intense rehabilitation, the hemiparesis is primarily restricted to fine motor movements of the fingers, and truncal control remains intact. The patient can still run with a hemiparetic gait and use the affected arm as a helper hand. There is potential for incomplete disconnection of white matter tracts because of the difficulties involved with the surgery, especially in very young patients. Therefore, patients may start having seizures again that require a reoperation.

Corpus Callosotomy

Corpus callosotomy is performed as a palliative procedure because it is only helpful for drop attacks and not for other types of seizures. The anterior two-thirds is disconnected, as removal of the entire corpus callosum will cause deficits in children with intact language; this is called split-brain phenomena, characterized by problems with communication of visual information, such as in reading. Transient acute postoperative disconnection syndrome also can occur where there is mutism, hemineglect or hemiparesis. Sometimes, a corpus callosotomy may make an epileptogenic focus become more evident and therefore, a focal resection afterwards can be performed.

Multiple Subpial Transections

This procedure entails sweeping a probe along the pial surface perpendicular to the long axis of the gyrus and disconnecting the horizontal fibers while leaving the vertical fibers intact. Theoretically, this will prevent seizures from spreading but will leave the function of the area intact. Therefore, it is often used where there is involvement of eloquent cortex. In practice, it does not effectively eliminate seizures in many patients, especially in cortical dysplasia. In addition, there have been complications described, such as temporal mutism due to edema postoperatively, or stroke due to excessive bleeding.

Cortical Stimulation Devices

Many patients are not candidates for surgical resection because of the diffuse nature of their illness. Therefore, chronic stimulation is an option for these patients with intractable seizures. Although stimulation is beneficial because it is easy to reverse, there are problems concerning safety of the stimulation on cortical structures.

Vagal Nerve Stimulation

VNS was first performed in 1988 by Penry and colleagues in 15 adults with partial seizures who were implanted with a stimulator in the left chest wall and bipolar platinum electrodes in the left vagus nerve. Five of 14 patients had at least a 50% reduction in seizures, and two of these patients became seizure-free. Other studies revealed that rapid cycling of 7 to 30 seconds on and 30 seconds off improved seizure control for patients who were initially resistant to VNS. Long-term studies have shown improvements up to 18 months after the start of stimulation. Results from use of VNS in children are similar to those in adults. In addition, there have been case reports describing the use of VNS in patients with juvenile myoclonic epilepsy, Lennox-Gastaut syndrome, absence seizures, and generalized myoclonic seizures for whom there was better seizure outcome compared with outcomes after other approaches were tried. VNS has also been used in patients with tuberous sclerosis, refractory status epilepticus, and hypothalamic hamartomas.

The most common side effects of VNS are hoarseness and tingling in the neck. Coughing can improve after changing the parameters of the stimulation. Surgical complications include hardware failure and deep infections that required removal of the device. Other problems may include torticollis and vocal cord paralysis from surgery.

Patients have not had pulmonary, heart, or gastrointestinal complications, which was initially a concern because the vagus nerve has efferent projections to these systems. It is not known how vagal nerve stimulation works, but some believe it is the afferent projections to the amygdala and hippocampus that may be important.

There was a recent abstract by De Giorgio (2006) concerning the use of the trigeminal nerve stimulator in 7 adults where these adults wore electrodes on their face and were transiently stimulated during the day. There was 50% or greater improvement in seizures in 4 of the 7 patients with tingling of the teeth and forehead as the main side effect.

Other Types of Chronic Stimulation

Other centers of stimulation include cerebellar, caudate, and thalamus. There have not been many studies on humans and no clear efficacy has been found.

Transcranial Magnetic Stimulation

Unlike the other stimulation studies listed above, TMS does not require surgery. A circular water-cooled stimulation coil is placed on the area where the seizure is thought to originate from, and low-frequency stimulation is used. TMS has been used for writer's cramp, depression, and cerebellar ataxia. One published study of TMS for cortical dysplasia demonstrated that 100 stimuli given biweekly at 0.5 Hz at 5% below motor threshold for 4 consecutive weeks while simultaneous EEG was recorded led to a 70% reduction in the frequency of seizures and a 77% reduction in the frequency of interictal spike. TMS was thought to be potentially more effective for neocortical foci than for mesiotemporal epilepsy. Adverse effects include pain at the stimulated site on the scalp, induction of seizures if using high-frequency stimulation, and nausea if used on the posterior fossa. No children have been studied so far and, therefore, the risks specific to them are unknown.

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Practitioner and Patient Resources

Epilepsy Foundation of America
4351 Garden City Dr. Suite 406
Landover, MD 20785-2267
Phone: (301) 459-3700 or 1-800-332-4050
E-mail: postmaster@efa.org
http://www.epilepsyfoundation.org
The Epilepsy Foundation of America is the national organization that works for people affected by seizures through research, education, advocacy, and service. It is an organization of volunteers committed to the prevention and cure of epilepsy and a positive quality of life for everyone who lives with seizure disorders. Current strategic goals include broadening and strengthening of research, providing individuals and families with easy access to reliable information, and ensuring access to appropriate medical care for those affected by seizures.

American Epilepsy Society
842 N. Main St.
West Hartford, CT 06117-2507
Phone: (860) 586-7505
E-mail: info@aesnet.org
http://www.aesnet.org
The American Epilepsy Society promotes research and education for professionals dedicated to the prevention, treatment, and cure of epilepsy.

Chapter 31

Pediatric Epilepsy: Comorbidity and Quality of Life

Robert P. Turner, MD, MSCR

Those involved in the care of children with epilepsy know well the truth of the statement, "There's much more to it than the seizures." In other words, the total absence of seizures does not necessarily indicate completely successful treatment. If the management and impact of epilepsy were simply a matter of mere seizure counts, treating patients with pediatric epilepsy would be rather simple. However, the daily management of epilepsy in children becomes far more challenging, complicated by multiple confounding factors that are often hard to describe or quantitate, whether in clinical or research settings.

The Burden of Epilepsy

The worldwide burden of epilepsy is estimated to be 1% (1.6% in children) of the total burden of disease, and this burden is felt both on an individual basis and on the worldwide population as a whole. This impact and burden crosses every geopolitical and socioeconomic barrier, yet it is thought to be a conservative estimate because it does not take into account (1) the effects on family members who have a relative with epilepsy, (2) the stigma of having epilepsy, or (3) the social exclusion of those with epilepsy.

Coincident with the burden of epilepsy, many, if not most, people with epilepsy function without apparent problems over and above their otherwise well-controlled seizures. Most, for example, are of normal intelligence and some function with superior cognitive abilities. On the other side of the spectrum, the significant and often progressive impact of refractory epilepsy on the lives of children is well known.

Why, then, are there often problems reported in the daily lives of many children with epilepsy?

Is it epilepsy or one epileptogenic process itself? Is it the cumulative effect of seizures? Is it the untoward effects of antiepileptic drugs (AEDs)? Is it the psychosocial adjustment of living with epilepsy? Is it the societal stigma of living in a world with such pervasive misinformation about epilepsy and people with epilepsy?

Answers to these and other questions are not simple or straightforward, nor likely to be conclusively answered in the near future, either at the bedside or in the laboratory. To evaluate where we are with current concepts of the epilepsy comorbidities and quality of life issues, we must understand the more recent history of evolution of ideas about the nonseizure aspects of epilepsy.

History: Out of the Shadows

The history of epilepsy dates back thousands of years. Clinical descriptions and etiologic hypotheses have existed for centuries. Currently, research discoveries of the electrophysiologic and genetic nature of epilepsy are increasing exponentially. Yet, in this twenty-first century, with the newer emphasis on curing epilepsy, we seem to be still just applying a Band-Aid to the management of epilepsy and related disorders.

Complicating this problem is the apparent pervasive nature of epilepsy, as well as misinformation from the past, which has led toward an international focus to bring

epilepsy out of the shadows and into the clinical and research disciplines.

The current methods of treating those suffering from seizures centers around what I have classified as the three "D"s: Drugs, Diets, and Dissections. *Drugs* have been the mainstay of treatment since the discovery of antiseizure efficacy of bromide of potassium in 1857 by Sir Charles Locock. Recent research is focusing on the newer concept of antiepileptic (vs anticonvulsant) substances, for example, the ability to abort or reverse the epileptogenic process (Schachter, 2002). *Diets* have been an effective individual and adjunctive treatment with the use of the ketogenic diet and more recently in trials with the Atkins diet. *Dissections*, or epilepsy surgery, including vagal nerve stimulation, have dramatically increased in efficacy with the development of specialized epilepsy centers around the world. In addition, there are increasingly more possible interventions in the arena of complementary and alternative medicine (CAM).

The goal for the treatment of children with epilepsy remains "No seizures. No side effects. As soon as possible." Many have been rendered seizure-free by the interventions of drugs, diets, or dissections. Yet, there are times when we seem to be dramatically ineffective, even counterproductive, in treating or reversing the effects of epilepsy. To quote Michael Trimble:

> It seems likely that in the far-off future, people will look at our primitive treatments for many medical conditions with mirth and scoffing, as we do now (inappropriately) at the attempts of our 18th and 19th century predecessors. Drugs will be recognized as the poisons they are, and crudely administered. Why bombard the whole body with a toxin to get to a relatively small area of malfunctioning neurons in the brain?

What are we doing today that may seem folly to future generations? We must devise plans for the comprehensive management of the immediate and remote effects of seizures and epilepsy, even in the midst of an ever-increasing body of literature of the adverse effects of antiepileptic drugs and epilepsy surgery. We must follow the maxim "primum non nocere," or "First, do no harm," with our patients.

Trends over the past century have focused on better schema of classification and terminology when dealing with diseases and their consequences.

Universal classification systems have been developed by the World Health Organization (WHO), exemplified by the most recent *International Classification of Diseases* (ICD-10). Initially formalized in 1893 as the Bertillon Classification or International List of Causes of Death, such classifications have, by necessity, been revised over the decades. This has certainly helped in our understanding, classification, and discussions of epilepsy.

With the improved classification of diseases, as well as the growing knowledge of the effects of various disease states, classifications of consequences of diseases became necessary. In 1980, WHO launched the International Classification of Impairments, Disabilities, and Handicaps (ICIDH).

Experience with ICIDH led to clarification of the effects of diseases on the individual, resulting in the International Classification of Functioning, Disability, and Health (ICIDH-2), or ICF (available at http://www.who.int/icidh). ICF incorporates the transition from an emphasis on disease (eg, "*consequence of disease*" classification) to a focus on health and health-related states (eg, "*components of health*" classification). Instead of the treatment of comorbidities in relation to diseases, this classification incorporates quality of-life measures (QOLM) in relation to health.

The ICF aim is to "provide a unified and standard language and framework for the description of health and health-related states," though not specific for epilepsy. The International League Against Epilepsy (ILAE) is ever striving for improvements in such classification and terminology, including the new diagnostic scheme using five Axes: Axis 1: Ictal phenomenology, Axis 2: Seizure type, Axis 3: Epilepsy syndrome, Axis 4: Etiology, and Axis 5: Impairment. Axis 5, dealing with impairments, was initially called an "optional, but often useful, additional diagnostic parameter." We are in a time, however, when incorporation of impairments and impacts related to epilepsy are crucial in the overall management of patients.

Pediatric neurologists have been adept in incorporating Axes 1 through 4, but only recently has there been more widespread discussion regarding impairments related to epilepsy. Current management of these impairments, an issue even more challenging than their mere classification, will be discussed later in this chapter.

Though still not modified for specific description of the health status of people with epilepsy, ICF nonetheless provides a framework with which to describe those impairments, or comorbidities, affecting the lives of children and their families. After discussion of epilepsy comorbidities, the interrelationship of these impairments within the larger context of quality-of-life (QOL) issues will be reviewed.

Comorbidities: It's More than the Seizures

"Epilepsy is a cruel disorder that has given my son broken bones, hospitalizations, blood clots, and secondary infections. Socially, he has missed over 2 years of accumulated days from school since kindergarten." These words, echoed by parents all over the world, were spoken at the July 2003 Living Well with Epilepsy II Conference in Baltimore by Linda Warner, immediate past chairwoman of the Epilepsy Foundation Board of Directors and mother of a teenage

son, Eric, who has had epilepsy since childhood (see http://www.EpilepsyFoundation.org/epilepsyusa/living well2.cfm).

Three aspects are critical to any discussion of the impact and comorbidities of epilepsy: (1) where do they come from, (eg, *etiology)*; (2) what are they, (eg, *classification)*; and (3) what do we do about them, (eg, *management)* (discussed elsewhere in this chapter).

Etiology

Regarding etiologies, the perplexing issue centers around the perpetual "chicken and the egg" paradox: what are true comorbidities (eg, *intrinsic*—associated with the epilepsy, or *extrinsic*—present at the diagnosis of epilepsy, but unrelated) versus what are consequences (eg, progressive effects) of seizures or epilepsy. Researchers are diligently studying the underlying anatomic and neurochemical changes associated with epilepsy, including the catastrophic pediatric epilepsies. However, definitive answers as to etiology are still unavailable.

Certainly, potential side effects of AEDs and epilepsy surgery should be diligently sought at every patient encounter. Side effects of AEDs, adverse events of treatments, and issues of overtreatment in epilepsy are important over and above comorbidities, but are beyond the scope of this chapter.

What are the more common impairments or comorbidities associated with epilepsy? Obviously, impairments present in children with epilepsy are dependent, at least in part, upon the etiology of and specific type of epilepsy or epilepsy syndrome. Children with refractory epilepsy (≥ one-third of children with epilepsy) suffer from far more than intractable seizures, including neurobiochemical circuitry changes, cognitive decline, psychosocial dysfunctions, restricted lifestyles, and increased mortality risk. Such impairments, often leading to a "downward spiraling quality of life," have led to theories that refractory epilepsy is its own separate, multifactorial condition.

Classification

More common comorbidities are encountered across the spectrum of patients with epilepsy and can be classified using the two ICF domains: (1) health domains and (2) health-related domains. A *domain* is defined as a practical and meaningful set of related physiologic functions, anatomic structures, actions, tasks, or areas of life. *Health domains* include seeing, hearing, walking, learning, and remembering. *Health-related domains* include transportation, education, and social interactions (see http://www.who.int/icidh).

The following tables (Tables 31-1 and 31-2), developed by the author as an integration of the ICF classification and the Review of Systems, may be used during the history portion of the patient encounter to help with the management of epilepsy in children. More common comorbidities, present even among some children with well-controlled epilepsy, are listed in the second column of each table.

Among the most commonly reported pediatric epilepsy comorbidities, independent of AED effects, are cognitive and learning impairments (including transient cognitive impairment due to interictal epileptiform discharges) and mental health dysfunction or psychopathology (including higher prevalence of emotional and behavioral problems, attentional or attention-deficit hyperactivity disorder

TABLE 31-1. Pediatric Epilepsy Comorbidities in Health Domains (Internal Factors)

Body Functions or Structures	Impairments or Disabilities
1. Constitutional/general health systems	Accidents from seizures
2. Eye systems, including seeing function	
3. Ear, nose, and throat systems	ENT infections
4. Cardiovascular system	SUDEP; 2–3 times the standardized mortality ratio
5. Respiratory system	Aspiration risk
6. Gastrointestinal and digestive system	Constipation
7. Genitourinary and reproductive systems	Polycystic ovarian syndrome
8. Musculoskeletal and movement systems	Fracture risk
9. Dermatologic or skin and related systems	Drug rashes; photosensitivity
10. Nervous and sensory system functions	Cognitive and memory impairments, migraine, and sleep impairments
11. Psychiatric system and mental functions	Mental health impairments, including depression, ADHD, anxiety, behavior problems
12. Endocrine and metabolic systems	Bone demineralization (AED effects)
13. Hematologic and lymphatic systems	Abnormal CBC indices (AED effects)
14. Immunologic and allergies systems	Increased susceptibility to illnesses

ADHD = attention-deficit hyperactivity disorder; AED = antiepileptic drug; CBC = complete blood count; ENT = ear, nose, and throat; SUDEP = sudden unexplained death in epilepsy.

TABLE 31-2. Pediatric Epilepsy Comorbidities in Health-Related Domains (External Factors)

Activities or Participations	Limitations or Restrictions
Neurologic	
Learning and applying knowledge	Cognitive limits
General tasks and demands	Memory limits
Communication	Speech/language limits
Self	
Mobility	Accidents; driving
Self-care and self-efficacy; successful coping	Fear or uncertainty of having a seizure; repeated loss of control
Lifestyle and relationships	
Domestic life	Interference with daily life
Interpersonal interactions and relationships	Psychosocial and relationship problems
Society	
Major life areas (school, employment)	Academic limits; employment limits and absence
Community, social, and civic life	Stigma; misunderstanding

difficulties, depression, anxiety, and relationship difficulties). Other valid comorbidities, though less common, include increased illnesses and increased standardized mortality ratio (SMR).

Another significant comorbidity, involving both health and health-related domains, relates to accidents. Although reportedly "mild" according to literature surveys, accidents most commonly result in contusions, wounds, fractures, abrasions, and brain concussions.

Health-Related Quality of Life: The Pervasive Nature of Epilepsy

The pioneering work of Karnofsky and Burchenal in the 1940s brought quality of life issues toward the forefront as they demonstrated that medical outcome (eg, tumor bulk and months alive) was not the sole determinant of outcome. During this same decade, the WHO began recognizing health as a state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity (see http://WhqLibDoc.who.int/Hist/Official_Records/Constitution.pdf).

With the growth of qualitative research in QOL, the need for adequate QOLMs has increased. Currently many QOLMs are available, while many others are undergoing development and validation studies. Crucial to the development of adequate QOLMs is the input of children and adults with epilepsy—what factors they feel are important to their QOL.

However, no matter where one practices pediatric neurology in the world, cross-cultural differences influencing QOL are important to understand, as patients from many ethnolinguistic and sociocultural backgrounds are encountered. QOL issues have been documented from many countries outside the United States of America, but common threads are seen inherent to the diagnosis of epilepsy (van den Broek et al, 2004; Ronen et al, 2003, and Camfield et al, 2001).

One preference is classifying common QOL issues according to (1) individual factors, (2) family factors, and (3) societal factors.

The key individual factors influencing QOL in children with epilepsy are the severity of epilepsy and AED side effects. Confounding factors, more difficult to analyze, relate to socioeconomic status and gender-specific issues.

Family adjustment to the diagnosis of epilepsy, frequency of and reactions to seizures, fear of seizure occurrence, and general attitudes toward epilepsy are all important factors contributing to QOL.

Many, if not most, people with epilepsy and their families, have (or have had) a major concern that their epilepsy or seizures could have fatal consequences. The uncertainty and fear of having a seizure and sudden unexplained death in epilepsy and studies showing an increased SMR ranging from 1.9 to 3.6 contribute to this legitimate concern.

The stigma inappropriately attributed to persons with epilepsy is still a major problem throughout the world, reflecting long-standing bias and a lack of awareness and misunderstanding of seizures, epilepsy, and people with epilepsy. Organizations and associations worldwide are attempting to increase public awareness and education to eventually eliminate the stigma that accompanies epilepsy, as reflected by the "Out of the Shadows" campaign by the WHO.

Increased use of medical services by people with epilepsy, as compared with those without epilepsy, is well-documented.

Improving QOL for all patients with epilepsy should remain one of the major goals of practitioners. Many clinical measurement tools are currently available to assist in obtaining and using QOL measures to optimize outcomes in patients with epilepsy.

Empowerment: Taking Charge of Epilepsy

Management of such complex issues clearly requires a team approach that involves the patient, family members, and professionals, including social workers, educational and vocational specialists, psychologists or neuropsychologists, medical personnel (nurses and nurse practitioners, neurophysiology technicians, and primary care and specialty physicians), and support groups.

For people with newly diagnosed epilepsy, seizure control as early as possible, education into management strategies, discussion of possible comorbidities, and

information about current research trends, including work toward the cure for epilepsy, are important factors to maintain an emphasis on health and health-related outcomes.

The demand for medical services, mental health needs, and information or education about epilepsy are growing for children and their families with epilepsy. A positive and healthy attitude toward a seemingly uncertain future is an essential component of management that should be in the armamentarium of every practitioner.

Management strategies that focus solely on seizure reduction are incomplete as they fail to assess the needs of the whole child and his or her family. Effective support systems and communication for the family are essential, yet such practices are often quite time consuming. Maintaining the highest QOL for children with epilepsy requires time, commitment, empathy, and compassion on the part of the pediatric neurologist. We must continue to heed the ethic of "primum non nocere" and take charge of epilepsy management with our patients.

Suggested Readings

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van den Broek M, Beghi E, RESt-1 Group. Morbidity in patients with epilepsy: type and complications: a European cohort study. Epilepsia 2004;45:71–6.

Practitioner and Patient Resources

International League Against Epilepsy (ILAE)
342 North Main Street
West Hartford, CT 06117-2507
Phone: (860) 586-7547
Fax: (860) 586-7550
http://www.ilae-epilepsy.org
The ILAE is the world's preeminent association of physicians and other health professionals working toward a world where no person's life is limited by epilepsy. Its mission is to provide the highest quality of care and well-being for those afflicted with the condition and other related seizure disorders.

World Health Organization: International Classification of Functioning, Disability, and Health
20 Avenue Appia
1211 Geneva, Switzerland
E-mail: ustunb@who.int
http://www.WHO.int/ICIDH
As a new member of WHO Family of International Classifications, ICF describes how people live with their health condition. ICF is a classification of health and health-related domains that describe body functions and structures, activities, and participation. The domains are classified from body, individual, and societal perspectives.

Epilepsy Foundation of America
4351 Garden City Drive, Suite 406
Landover, MD 20785-2267
Phone: (301) 459-3700 or 800-332-1000
E-mail: postmaster@efa.org
http://www.epilepsyfoundation.org
The Epilepsy Foundation is a national charitable organization for individuals with epilepsy. It serves to ensure that people with epilepsy are able to participate in all life experiences and will try to prevent, control, and cure epilepsy through research, education, advocacy, and services.

Chapter 32

Psychosocial Challenges of Epilepsy in Adolescence

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David Griesemer, MD

This chapter outlines a practical approach to successful care of adolescents with epilepsy during this critical time in their social and intellectual development. Participatory decision making and quality of daily life are as important as adequacy of seizure control and freedom from medication side effects.

Adolescence is a time of significant growth and development across physical, cognitive, social, and emotional domains. Adolescents rely less on their parents and more on their peers in establishing self-identity. Peer pressure, emergence of abstract thinking, and changes in physical development can lead to the potential for risky behavior, such as sexual activity and substance abuse. However, adolescents still desire and need close family relationships, even as parents struggle to facilitate independence while providing appropriate supervision and continued guidance. Cooperative effort of adolescent and parent to balance autonomy and supervision is required for healthy adaptation through these developmental changes.

Chronic illness such as epilepsy can threaten successful adaptation. Epilepsy poses many challenges given its potential central nervous system (CNS) effects on social, emotional, and cognitive functioning and its impact on quality of life. The Epilepsy Foundation of America (EFA) emphasizes the importance of diagnosing and treating psychiatric or behavioral problems that often accompany pediatric epilepsy. Additionally, clinicians, researchers, and advocacy groups have highlighted the necessity of addressing family needs, fostering independence, and improving access to mental health for adolescents with epilepsy.

Challenges for the Adolescent

Seizures in adolescents are associated with neuropsychological impairments, including social deficits, internalizing symptoms, such as anxiety and depression, externalizing symptoms, such as conduct problems and impulsivity, and cognitive deficits. The perceptions and abilities of adolescents to analyze various situations may therefore be compromised and thus not age appropriate. Even though these symptoms are often subthreshold, they can still cause significant impairment. Adolescents with epilepsy also face stigma and report social isolation as their peers often know little about epilepsy and discriminate against them. In addition, nonepileptic seizures (NES) may complicate the picture (Table 32.1).

Additionally, adolescents' perceptions of epilepsy, including "seizure self-efficacy" and "attitudes toward epilepsy," have a significant impact on adjustment to epilepsy. Seizure self-efficacy or the belief adolescents have about taking care of themselves and their seizure condition can be a critical point of intervention. Similarly, teens' attitudes toward epilepsy, or their positive and negative feelings about having a seizure condition, are also key factors to address. Finally, caregiver attitudes and stress management influence adolescent adjustment.

TABLE 32-1. Symptoms and Behaviors

Internalizing	Externalizing
Anxiety	Conduct behaviors
Depression	Attention deficit hyperactivity disorder
Cognitive	**Risk Taking Behaviors**
Learning disorder	Substance use/abuse
Mental retardation	Sexual activity
Neuropsychological deficits (memory, speed of processing, executive function)	Irresponsible driving
Conversion	
Nonepileptic seizures	

Challenges for Caregivers

Raising an adolescent in today's world is a difficult task, and coping with a chronic illness may compromise attempts at successful parenting. Parents often feel anxious, frustrated, and guilty about the teens' diagnosis and their changing role. Because of uncertainty about when seizures occur, it is difficult for parents to allow increased physical and/or emotional independence and personal responsibility for self-management of epilepsy. In a majority of cases, there is no clear etiology for the seizures, and long-term outcome is unclear. For some parents whose children have significant cognitive limitations or other disabilities, caregiving is a full-time commitment.

The impact of epilepsy extends beyond the teen-caregiver relationship. The financial and emotional strain of epilepsy can threaten a marriage and relationships within a family. Frequent medical appointments, complex seizure treatment regimens, educational obstacles, psychologic intervention, monthly prescription refills, and struggles over insurance coverage are exhausting. Healthy siblings, who experience the stress and impact of epilepsy, may exhibit attention seeking behavior or overcompensate for other family stressors. Indeed, every member of the family is faced with potential changes in family dynamics, financial status, and daily routines and must learn new ways to cope.

Challenges for Health care Providers

Epilepsy encompasses more than just seizures, and adolescence is more complex than just hormonal changes. In providing comprehensive care, the physician and epilepsy team must balance the needs of the adolescent with those of the family. The adolescent should be encouraged to take ownership in the plan of care, learn about all aspects of epilepsy and available treatments, and make contributions to decisions about therapy. Caregivers have a significant role in the office visit; however, it is critical for the adolescent to have "alone" time with the epilepsy provider to discuss risky behaviors that can occur with the increased freedom of adolescence. There should be confidential discussion about the potential impact of these behaviors on seizures and seizure treatment; adolescents should be counseled about sex, pregnancy, consideration of family planning in advance, possible fertility issues, use of alcohol, illicit drugs, and cigarettes, sudden unexplained death in epilepsy, and the issue of stigma in epilepsy. Limits to confidentiality should also be discussed with adolescents. Because of pressures to shorten office visits, it may take several sessions to cover all the important issues.

Both adolescents and parents should be educated about potential increase or changes in seizure activity caused by hormones. Such changes may require an adjustment in medication or change in treatment plan. Parents and teens should also be educated about disclosure of the seizure diagnosis required by schools, camps, athletic teams, traveling school clubs, potential employers, and Department of Motor Vehicles. It is important for families to understand why this information is needed, and issues related to disclosure should be discussed. Driving laws and disability laws may vary in different jurisdictions; this information is also important to share with the teen and his/her caregivers.

Psychiatric symptoms increase in adolescence, and adolescents with seizures are at greater risk than healthy peers. Therefore, epilepsy health care providers should routinely screen for these symptoms. Given the complexity of CNS involvement in patients with seizures, psychiatric symptoms in adolescents with epilepsy often fail to mirror typical diagnostic classifications. Symptoms may be subthreshold for clinical psychiatric disorders but may significantly impair the adolescent. Often it is difficult to distinguish seizure activity (aura, aggressive behaviors, and emotional lability) and psychiatric symptoms that occur between seizures. The picture may be further complicated by NES, which can be mistaken as epileptic but may instead represent psychologic disturbance. A final challenge involves limited access to mental health care, especially to providers with expertise in adolescents with epilepsy. Nevertheless, the presence of significant psychiatric symptoms and/or neuropsychological deficits requires referral to a psychiatrist or psychologist for further assessment and continued care.

Implications for Clinical Practice

Treating epilepsy in adolescents is more comprehensive than just controlling the seizures or attributing mood swings to adolescence. Assisting teens in developmentally appropriate management of seizures will promote self-efficacy, which influences positive adjustment to epilepsy and increases

adherence. The following recommendations are provided to assist the epilepsy team in promoting optimal seizure management, quality of life, and comprehensive care for adolescents with epilepsy and their families.

1. Facilitate communication and coordinated planning by all professionals who participate in the care of the adolescent—physicians, nurses, psychologists, social workers, and others. Focus should be on the teen's overall function and performance not just on the frequency and severity of seizures.
2. Educate teens and caregivers regarding the treatment plan and seizure management. Use clear and concise language to facilitate understanding and to promote knowledge about epilepsy.
3. Build trust and rapport with the teen in order to enhance communication. Allow the teen opportunities to speak with you in confidence, and listen to the teen. It is important for him or her to contribute to the plan of care and take responsibility.
4. Do not avoid the tough issues such as sex, smoking, substance use, but instead address them openly. Provide education on the interactions of illicit substances and anti-seizure medications, as well as the potential impact of illicit drugs on seizures. Discuss the implications of pregnancy.
5. Discuss limits to driving and state driving regulations for persons with epilepsy.
6. Screen for behavioral, cognitive, and emotional disorders. There are a variety of self- and caregiver-report checklists available for use as screening instruments, including the Pediatric Symptom Inventory <http://www.dbpeds.org/pdf/psc.pdf> and the Vanderbilt Rating Scales <http://www.help4adhd.org/en/treatment/scales>. If longer screening tools for the assessment of depression are not available, two recommended questions can be used as follows:
    1. During the past month, have you often been bothered by feeling down, depressed, or hopeless?
    2. During the past month, have you often been bothered by having little interest or pleasure in doing things?

    If a patient and/or caregiver answers either question with a "yes," then further assessment for the presence of depression is required. If depressive symptoms are endorsed, assess for suicidal ideation.
7. When screening necessitates, refer to a mental health provider, preferably one with specialized training in pediatric epilepsy. There is promise for the effectiveness of cognitive-behavioral interventions in youth with epilepsy, and preliminary guidelines exist for the use of psychopharmacologic agents in adolescents with epilepsy.
8. Be aware of stigma toward teens with epilepsy. Promote use of the EFA website <http://www.efa.org>, state epilepsy foundations, and local support groups.
9. Encourage the teen to participate in extracurricular activities to promote peer interaction, meaningful friendships, and mastery. Also encourage the teen to consider giving back to the community by helping others. Such activities will enhance self-confidence.
10. Address caregiver worries and needs; encourage them to seek help when appropriate from other professionals and to use resources for national, state, and local organizations for epilepsy. Caregivers should be made aware of laws regarding education and employment and be referred to the appropriate advocacy agencies if needed.
11. Address impact of epilepsy on the family. Encourage caregivers to continue setting limits and assigning to their teens developmentally appropriate responsibilities. Also, promote caregiver habits that are healthy, such as stress management, exercise, positive interactions with other family members, and support networks. Refer the family for appropriate interventions as indicated (eg, behavior management, family therapy).
12. Communicate with the school nurse, teacher, and other education personnel regarding classroom accommodations, safety, and epilepsy knowledge. Also, discuss potential future goals, which may include formal education or vocational training.

Conclusion

Epilepsy provides increased stress for teens and their families due to the potential unpredictability of seizures, CNS effects of epilepsy, adverse epilepsy treatment effects, psychiatric symptoms, financial issues, marriage and family strain, and social stigma. However, teens and caregivers can be encouraged to take control of epilepsy instead of allowing it to control them. "Living well with epilepsy" should be the ultimate goal for teens, caregivers, and health care providers. Improving self-efficacy for seizure management and attitudes toward epilepsy will enhance control and quality of life for teens and their caregivers.

Suggested Readings (*highly suggested readings)

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Wagner JL, Smith G. Psychosocial interventions in pediatric epilepsy: a review of the literature. Epilepsy Behav 2006;8:39–49.

Patient and Practitioner Resources

Epilepsy Foundation
8301 Professional Place
Landover, MD 20785-7223
(800) 332-1000
<http://www.efa.org>
The Epilepsy Foundation is the national voluntary agency solely dedicated to the welfare of the over 3 million people with epilepsy and their families in the United States. The organization works to ensure that people with seizures are able to participate in all life experiences and to prevent, control, and cure epilepsy through research, education, advocacy, and services. In addition to programs conducted at the national level, epilepsy clients throughout the United States are served by local Epilepsy Foundation offices in nearly 100 communities.

Epilepsy.com online
<http://www.epilepsy.com>
Epilepsy.com is an online resource provided by the Epilepsy Therapy Development Project. Its mission is to inform and empower two groups of patients and their families: those facing newly diagnosed epilepsy and those struggling with epilepsy that has resisted treatment.

National Institute of Mental Health
Public Information and Communications Branch
6001 Executive Boulevard, Room 8184, MSC 9663
Bethesda, MD 20892-9663
1-866-615-6464 (toll-free)
<http://www.nimh.nih.gov>
The National Institute of Mental Health's mission is to reduce the burden of mental illness and behavioral disorders through research on mind, brain, and behavior. The website provides information about mental health issues and mental illness and how to seek help.

Parents Against Childhood Epilepsy Inc
A Research and Education Fund
7 East 85th Street Suite A3
New York, NY 10028
(212) 665 - (PACE) 7223
<http://www.paceusa.org>
Parents Against Childhood Epilepsy is a not for profit corporation formed in 1996 to battle the devastating and far-reaching disease of epilepsy. It was founded by a group of parents in response to their experiences in caring for the medical, physical, social, educational, developmental, and emotional needs of their children who suffer from epilepsy and severe seizure disorders. Fund-raising supports advances in medical research of epilepsy. Information and supports are also provided to many families with similar needs with telephonic networking, email systems, and seminars.

Citizens United for Research in Epilepsy
730 N. Franklin Street Suite 404
Chicago, IL 60610
(312)255-1801
<http://www.cureepilepsy.org>
Citizens United for Research in Epilepsy is a nonprofit organization dedicated to finding a cure for epilepsy by raising funds for research and by increasing awareness of the prevalence and devastation of this disease. The organization was formed by parents of children with epilepsy.

Health Care Provider Resources
Bright Futures at Georgetown University
Box 571272
Washington, DC 20057-1272
(202) 784-9772
<http://www.brightfutures.org>
Bright Futures is a national health promotion initiative dedicated to the principle that every child deserves to be healthy and that optimal health involves a trusting relationship between the health professional, the child, the family, and the community as partners in health practice.

Developmental Pediatrics Online
<http://www.dbpeds.org>
This site is aimed at professionals interested in child development and behavior, especially in the medical setting, and is closely associated with the American Academy of Pediatrics Section on Developmental and Behavioral Pediatrics.

CHAPTER 33

EPILEPTIC ENCEPHALOPATHY

BRIAN G.R. NEVILLE

Epileptic encephalopathy (EE) consists of impairments that include cognitive deficits, behavioral problems, and coordination deficits directly attributable to epilepsy. This chapter reviews the diagnostic approach and management of common EEs.

"Additional impairments" are very common in babies and children with epilepsy and are broadly separated into those directly caused by any primary pathology and those which are directly attributable to the epilepsy. This latter category is now known as an epileptic encephalopathy (EE). These impairments include selective and global cognitive deficits, a wide range of behaviors, and coordination problems. The mechanisms by which children with epilepsy fail to gain or lose skills or show deviant development are poorly researched, but risk factors for this process have emerged. It is particularly a feature of a group of early onset epilepsies that have been variously described as malignant or catastrophic epilepsies. These include as follows:

1. Dravet syndrome (severe myoclonic epilepsy of infancy)
2. West syndrome (infantile spasms)
3. Early onset lesional temporal lobe seizures
4. Lennox-Gastaut syndrome and a group of related disorders with multiple seizure types and regression but without satisfying the strict EEG criteria for Lennox-Gastaut syndrome.
5. Landau-Kleffner syndrome
6. Early onset seizures with hemimegalancephaly
7. Sturge-Weber syndrome

The detailed diagnostic and management aspects of these disorders are dealt with in childhood epilepsy texts. Although these conditions are described in a classical form, it is everyone's experience that EE occurs commonly in atypical presentations. The major investigatory feature of EE is a high rate of subclinical seizure activity particularly in sleep leading to the main hypothesis that such activity in the developing brain disrupts higher cognitive learning and recently acquired skills. The timing and style of regression in the above group of disorders shows some specific characteristics.

In Dravet syndrome, development continues through the early seizures with fever, but marked cognitive regression usually occurs in the onset of multiple afebrile seizures around the age of 12 months.

In West syndrome, with a peak age of onset at 4 to 5 months, either before or at the time of onset of spasms, the baby shows loss of visual responsiveness, vocalization, and sometimes of head control. In some, early development is slow representing the impact of the causative pathology, and in others, early development is normal.

With early onset partial seizures associated with dysembryoplastic lesions particularly of the temporal lobe, regression may occur as plateauing of development not loss of skills. In all the above, the appearance of autism spectrum disorders is common.

In tuberous sclerosis, severe regression is confined to those with early onset seizures particularly West syndrome supporting the pathogenic theory outlined above. Lennox-Gastaut syndrome occurs somewhat later but may develop following an earlier syndrome, eg, West syndrome, and may show plateauing, regression, and fluctuation of functioning. It is also a condition in which the patient may lapse into a groggy state in which they are ataxic and regressed and show atypical absence, and myoclonic jerks may be seen or felt in the limbs. This state of minor epileptic status may respond rapidly to treatment.

Landau-Kleffner syndrome is described as acquired auditory agnosia following a period of normal speech development. However, as the diagnosis is reported in literature, it includes all types of aphasia, global regression, and behavioral and motor regression, and these were

interestingly reported in the original description. When looking at this literature and that of epileptic status in slow sleep (ESES) and continuous spike-wave in slow wave sleep, it becomes clear that there is a major overlap of these conditions. Within this group, there are patients who have shown massive regression with few or no clinical seizures.

The specific feature of early onset seizures with hemimegalancephaly is that although usually first recognized in the neonatal period, the encephalopathy is often well established by that time strongly suggesting an intrauterine onset.

The encephalopathy of Sturge-Weber syndrome is unique with acute episodes of seizures, hemiplegia, and cognitive loss with evidence of cortical ischemia. The unusual feature is of progressive cortical atrophy and calcification. This encephalopathy is not therefore a pure EE.

The above encephalopathies may show some possibility of reversal by treatment but much of what is lost can never be recovered and represent some of the most disabled and problematic children that we see. Not all encephalopathies are severe, and it is now recognized that so-called benign Rolandic epilepsy is associated with a selective problem of language processing.

Review of the progress of children at school shows that over 50% have problems with academic progress and/or behavior (Lambeth study, unpublished). The issue of how much of these impairments are primary and what is secondary to epilepsy and thus an encephalopathy is unresolved, but it indicates a very high rate of additional impairments that require management in children with epilepsy.

Diagnosis

From the above discussions, it is clear that a number of epilepsy syndromes involve concurrent developmental plateauing and regression; thus, an encephalopathy should be anticipated. One should also look out for similar trends in children with less easily characterizable syndromes that resemble the recognized malignant epilepsies.

The general clues to the presence of EE are as follows:

1. Regression of skills previously gained particularly stepwise or fluctuating.
2. The appearance of unusual features, eg, motor disorder or autism spectrum disorder. These can be difficult if the disorder starts early in life.
3. Plateauing of development, meaning lack of the expected progress in development. This, however, requires standardized assessments of cognition, attention, language, and social development. Since promoting developments is one of the major aims of epilepsy management, there is a good case to be made for screening all children with epilepsy for these areas of functioning and for formal review of progress.

Sometimes in the investigation of a child with progressive disease, a severe epileptic EEG abnormality is found, which gives a lead to an EE. However, the EEG and particularly the EEG in sleep is usually required to support the diagnosis although arbitrary figures for the proportion of slow sleep occupied by epileptic activity are unhelpful.

Sometimes a trial of treatment with the main stream drugs used, ie, benzodiazepines or corticosteroids results in dramatic improvement, which clarifies the diagnosis.

It is important to exclude progressive diseases of the nervous system, eg, Rasmussen's syndrome, ceroid lipofuscinosis, Menke's disease, and the progressive myoclonus epilepsy syndromes. The clue to these is relentless progression, lack of correlations between epilepsy severity and decline, changes in magnetic resonance imaging, falling away of head growth, and the appearance of new neurological signs. Sometimes static pathology, eg, Rett syndrome and Angelman syndrome behave as if there is an EE, and indeed, in the latter, there may well be a combination of primary impairments and an acquired EE.

Treatment and Management

The various syndromes of epilepsy need to be treated with appropriate antiepileptics as described elsewhere, but overt seizure response to treatment may not reflect the underlying encephalopathy response. In fact, stopping ESES is often very difficult, and regular monitoring of the process with developmental/cognitive assessment and sleep EEG records is required. In general, benzodiazepines and corticosteroids have been found to be most useful because of the long lasting nature of the group of disorders it may often be necessary to follow short courses of corticosteroids with weekly pulsed prednisolone. It is advisable that if this course of action is taken to ensure varicella immunity and use ranitidine to reduce the chance of gastric erosion. Ketogenic diets may also prove helpful if behavior is not prohibitive.

Cognitive and Behavioral Management

Children with this group of epilepsy have a very high rate of problems in these areas and practically never do their impairments conform to a psychiatric diagnosis. They commonly have features of global cognitive regression, attention deficit hyperactivity disorder (ADHD), and autism spectrum sometimes with quite violent behavior,

usually out of keeping from their earlier developmental state. Many also have obvious motor coordination problems. In general, such children through presenting serious problems are poorly assessed and managed but clearly require multidisciplinary care.

The overall message of the available evidence is that pharmacological management of ADHD does not reduce seizure control and is sometimes an essential prerequisite to epilepsy and cognitive assessment.

ASD is very commonly overlooked and must be positively assessed, and management particularly educational should be appropriate. There has been a tendency to neglect these aspects of childhood epilepsy with mental health services often feeling unable to intervene. In most parts of the world, there is no alternative but that those concerned with childhood epilepsy should have some training in the identification and management of the common behavior disorders. Although the cognitive impairments are commonly global, there may be highly selective problems of language or memory, which must be carefully explored by psychological assessment. Educational management must recognize the phenomenon of fluctuating cognitive and behavioral functioning.

This medical management should be multidisciplinary and integrate with school and home management. It should be recognized that the burden of care for families can be huge and in-house support may be necessary.

Suggested Readings

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Practitioner and Patient Resources

Epilepsy Foundation
8301 Professional Place

Landover, MD 20785

Phone: (800) 332-1000

<http://www.epilepsyfoundation.org/>

The Epilepsy Foundation pledges to always bring you accurate and up-to-date information about epilepsy, its treatment, and the impact it has on daily life.

Chapter 34

Current Pharmacotherapy for Pediatric Seizures and Epilepsy

Bernard L. Maria, MD, MBA

Shannon Drayton, PharmD

There are many seizure types, etiologies, and epileptic syndromes. The best first-choice antiepileptic drug (AED) depends on the type of epilepsy, the special circumstances of every child and family, and, more often than not, the experience of the prescribing physician.

Pharmacotherapy for Febrile Seizures

Daily antiepileptic drugs (AEDs) should not be prescribed for febrile seizures. However, in the 2 to 5% of the population that have febrile seizures, abortive therapy with rectal diazepam (Diastat®) should be considered. Caregivers are grateful to have something at home they can administer to stop a prolonged recurrent febrile seizure, and that gives them time to seek a medical evaluation of the fever. Because the great majority of seizures stop within 5 minutes without medication, administering diazepam (Diastat®) is not recommended unless the seizure lasts longer than 5 minutes. After administration of diazepam, the seizure typically stops within 3 minutes. Because of sedative effects associated with the use of diazepam, one must be cautious about the possibility of masking signs of meningitis. However, many children who are younger than 1 year of age with onset of febrile seizures will predictably have more events with common viral illnesses and fever. Because 20 to 30% of patients have recurrent febrile seizures within 24 hours of onset, one of the major additional benefits of diazepam (eg, Diastat®) has been the fact that it can be effective for hours after administration. Diazepam has also been a valuable adjunct for families living in remote areas with more limited access to emergency services.

An Approach to First-Line Pharmacotherapy

After a single unprovoked seizure, many practitioners initiate AEDs, despite the fact that such practices are not evidence-based. In addition, oral phenobarbital or phenytoin are still prescribed as first-line therapy, even though other AEDs are safer, better tolerated, and more effective. It has been said that phenobarbital is a "good drug for the doctor" because it is easy to prescribe and monitor and is inexpensive; however, in patients discharged from the hospital on phenobarbital after a single prolonged seizure, we wean the drug over a few weeks time. Phenytoin is poorly absorbed through the child's gut and has 0-order kinetics, which complicates its use in children; phenytoin is associated with gingival hyperplasia, hirsutism, and academic underachievement.

One argument offered by child neurologists who initiate AEDs *before* epilepsy is diagnosed is that "the electroencephalogram (EEG) was abnormal", "events were underreported", or that "the first seizure was prolonged and atypical." However, a significant minority of children with a first unprovoked seizure and abnormal EEG will not have a second event. Thus, use of daily AEDs should be postponed until a second unprovoked seizure has been

clearly documented. In managing such patients, we emphasize education and reassurance. When caregivers are particularly anxious about recurrence, rectal diazepam can be prescribed for use in the unlikely event that a recurrent seizure will last more than 5 minutes.

When the diagnosis of epilepsy has been made and the risk of seizure recurrence is high, it is important to strive for seizure freedom. In most forms of epilepsy, 70 to 75% of patients will be free of seizures and side effects when the proper AED and dose are prescribed. Children with recurrent seizures must be fully evaluated clinically before carefully considering a first-line AED. Some AEDs or faulty treatment exacerbate seizures, as discussed by Dr. Wheless in Chapter 26, and a number of factors must be considered in choosing an AED, including the proper classification of the epilepsy and the fact that the majority of patients outgrow the needs for AEDs within a couple of years (Figure 34-1).

In child neurology practice over the years, one develops a level of comfort with a few select AEDs. The decision to adopt a new AED is more art than science, because so few head-to-head studies compare AEDs for a given type of epilepsy. It has also been our experience that "only babies like to be changed"; a longstanding practice of using a particular AED as first-line therapy may be very difficult for some practitioners to change. Familiarity with a given AED is important to quality care as long as safety and efficacy data on a new or different AED are not that compelling. An example of inappropriate resistance to switching would be the continuous use of phenobarbital or phenytoin as first-line oral therapy in children with localization-related epilepsies. On the other hand, switching to another firstline AED should be carefully considered because switching costs can be high (seizure recurrence, nonadherence, doctor shopping, drug costs) with relatively limited benefit to patients and caregivers. It is appropriate to consider switching a patient who is receiving immediate-release carbamazepine to extended-release carbamazepine or oxcarbamazepine to decrease potential deleterious side effects.

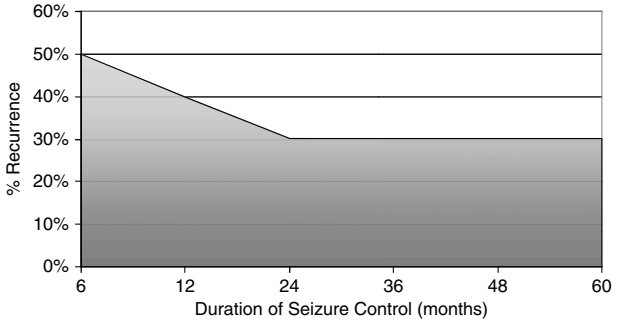

FIGURE 34-1. Risk of seizure recurrence after discontinuation of Antiepileptic Drug Therapy.

Pharmacotherapy for Partial Epilepsy

In the past few years, our first-line therapy for partial epilepsy has switched from extended-release carbamazepine (Carbatrol®) to oxcarbazepine (Trileptal®) to avoid the epoxide metabolite of carbamazepine. The old adage with carbamazepine to "start low and go slow" (10 mg/kg/d, building up to 20 mg/kg/d in 3 to 7 days) also applies to oxcarbazepine (10-15 mg/kg/d divided b.i.d., building slowly to a median dose of 30 mg/kg/d in a couple of weeks). One exception to the rule of using oxcarbazepine or carbamazepine as first-line therapy in partial epilepsy is in the treatment of benign rolandic epilepsy (BRE), for which gabapentin (Neurontin®) is a logical drug of choice because it is effective and very well tolerated.

Pharmacotherapy for Generalized Epilepsy

In generalized idiopathic epilepsies, valproate (Depakote®) continues to be our first-line drug of choice [except in infants where topiramate (Topomax) is a drug of choice] because it is effective in a broad array of seizure types, although many child neurologists would rather first prescribe ethosuximide (Zarontin®) or lamotrigine (Lamictal®) for childhood absence epilepsy. Our primary concern with ethosuximide is that it may be ineffective in atypical absence, and that it can trigger a generalized tonic-clonic seizure in such cases. Lamotrigine is effective in absence, though it often takes longer to achieve seizure control. Valproate can cause hepatotoxicity, pancreatitis, and dose-related thrombocytopenia; however, valproate provides excellent antiepileptic coverage for typical and atypical absence, and the occasional partial epilepsy masquerading as absence. In infantile spasms, adrenocorticotropic hormone (ACTH) (20 to 30 international units daily) is our drug of choice unless tuberous sclerosis is found. In tuberous sclerosis, an additional challenge for caregivers is obtaining highly effective vigabatrin, because it is not sold in the United States. In Lennox-Gastaut syndrome, valproate is our first-line drug of choice.

In summary, the first-line armamentarium of AEDs includes five core drugs: (1) diazepam (intermittent rectal use for febrile seizures or at-home availability after first unprovoked or recurrent seizures), (2) ACTH (for infantile spasms), (3) valproate (for all generalized epilepsies except infantile spasms or generalized seizures in infants (topiramate)), (4) oxcarbazepine (for all partial epilepsies except BRE), and (5) gabapentin (BRE). Table 34-1 provides detailed information about AEDs, with emphasis on common drug interactions. Because of the vast array of drugs with similar indications, it has become common practice (in contrast to the 1980s and 1990s), after recurrent seizures, to taper off the first-line AED while

TABLE 34-1. Antiepileptic Pharmacotherapy

Generic Name	Trade Name	Web Site	Dosage Forms	Usual Doses	Mechanisms of Action	Indications
Carbamazepine	Tegretol®, Tegretol-XR®	www.pharma.us.novartis.com/product/pi/pdf/tegretol.pdf	Suspension 20 mg/mL; tablets 200 mg; chew tablets 100 mg; extended-release tablets 100 mg, 200 mg, 400 mg	10–40 mg/kg/d divided bid for extended release; tid to qid for immediate release; usual adult dose 200–600 mg PO bid	Modulation of sodium channels	Simple partial, complex partial, generalized tonic-clonic
	Carbatrol®	www.carbatrol.com	Extended-release capsules 100 mg, 200 mg, 300 mg			
Clonazepam	Klonopin® C-IV	www.rocheusa.com/products/klonopin	Tablets 0.5 mg, 1 mg, 2 mg	0.01–0.3 mg/kg/d divided tid or given qhs; 0.5 mg PO tid for adults; max 20 mg/d	Enhance GABA	Myoclonic, Lennox-Gastaut syndrome, atonic, absence
Diazepam (rectal)	Diastat® C-IV	www.diastat.com/full_presc.pdf	Pediatric rectal gel 2.5 mg, 5 mg; adult rectal gel 10 mg, 15 mg, 20 mg	age 2–5 y: 0.5 mg/kg; age 6–11 yr: 0.3 mg/kg; age >12 yr: 0.2 mg/kg	Enhance GABA	Acute repetitive seizures
Ethosuximide	Zarontin®	www.pfizer.com/download/uspi_zarontin_capsules.pdf	Capsules 250 mg, solution 50 mg/mL	15–40 mg/kg/d divided bid; adult dose 250–750 mg PO bid	Reduces current in the T-type calcium channels	Absence
Felbamate	Felbatol®		Tablets 400 mg, 600 mg; suspension 120 mg/mL	15–45 mg/kg/d (or 1,200–3,600 mg) divided tid–qid; usual max 60 mg/kg/d	Blocks glycine binding to the NMDA receptors	Lennox-Gastaut syndrome, complex partial
Gabapentin	Neurontin®	www.pfizer.com/download/uspi_neurontin.pdf	Capsules 100 mg, 300 mg, 400 mg; tablets 600 mg, 800 mg; solution 50 mg/mL	Initiate at 10–20 mg/kg/d divided tid–qid; titrate up to 40–60 mg/kg/d; usual max 90 mg/kg/d	Not known	Partial with or without secondary generalized tonic-clonic
Lamotrigine	Lamictal®	http://us.gsk.com/products/assets/us_lamictal.pdf	Tablets 25 mg, 100 mg, 150 mg, 200 mg; chew tablets 2 mg, 5 mg, 25 mg	200–500 mg/d divided bid; 5–15 mg/kg/d; start dose slowly at 50 mg qid for adults (see Table 26-12)	Blocks sodium channels and blocks release of glutamate	Simple partial, complex partial, generalized tonic-clonic, Lennox-Gastaut syndrome, absence
Levetiracetam	Keppra®	www.keppra.com/images/pdf/LatestPI.pdf	Tablets 250 mg, 500 mg, 750 mg; solution 100 mg/mL	Initial 10 mg/kg PO divided bid or 500 mg PO bid, increase every 2 weeks to 40–60 mg/kg/d or 3,000 mg/d	Inhibits propagation of seizure by unknown mechanism	Partial onset
Lorazepam	Ativan® C-IV		Tablets 0.5 mg, 1 mg, 2 mg; solution 2 mg/mL; injection 2 mg/mL, 4 mg/mL	0.05–0.1 mg/kg/dose, 4 mg/dose maximum, may repeat in 10–15 min	Enhance GABA	Status epilepticus
Oxcarbazepine	Trileptal®	www.pharma.us.novartis.com/product/pi/pdf/trileptal.pdf	Tablets 150 mg, 300 mg, 600 mg; suspension 60 mg/mL	Adult: initiate at 300 mg PO bid, increase weekly to usual maintenance dose of 1,200–2,400 mg/d; child: initiate at 10 mg/kg/d, titrate to 30–60 mg/kg/d	Modulation of sodium channels	Partial onset
Phenobarbital	generic C-IV Luminal®		Elixir 4 mg/mL; tablets 15 mg, 16.2 mg, 30 mg, 32.4 mg, 60 mg, 64.8 mg, 90 mg, 100 mg; injection 30 mg/mL, 60 mg/mL, 65 mg/mL, 130 mg/mL	2–6 mg/kg/d divided qd to bid (high end of range for infants/young children)	Enhance GABA	Generalized tonic-clonic, simple partial, complex partial, myoclonic

TABLE 34-1. Antiepileptic Pharmacotherapy (continued)

Generic Name	Trade Name	Web Site	Dosage Forms	Usual Doses	Mechanisms of Action	Indications
Phenytoin	Dilantin®, Cerebyx® (fosphenytoin)	www.pfizer.com/download/uspi_dilantin_kapseals.pdf	Injection* 50 mg/mL (fosphenytoin is 50 mg/mL phenytoin equivalent); suspension 25 mg/mL; chew tablets 50 mg; capsules* 30 mg, 100 mg	4–12 mg/kg/d divided bid—tid for children getting PO, qid–bid for adults getting PO, divided q6h for IV dosing	Modulates sodium channels	Generalized tonic-clonic, complex partial, simple partial
Primidone	Mysoline®	http://www.choosemysoline.com/XcelMysolPI_18913.pdf	Tablets 50 mg, 250 mg	10–25 mg/kg/d divided bid–tid; max 2 g/d	Enhances GABA	Generalized tonic-clonic, simple partial, complex partial
Tiagabine	Gabitril®	www.gabitril.com	Tablets 2 mg, 4 mg, 12 mg, 16 mg, 20 mg	Adult: 32–56 mg/d divided bid–qid (start with 4 mg PO qd, adjust weekly); child: 0.1 mg/kg/d divided tid, increase to 0.6 mg/kg/d (1 mg/kg/d with enzyme inducers)	Inhibits neuronal and glial uptake of GABA	Partial onset
Topiramate	Topamax®	www.orthomcneil.com/products/pi/pdfs/tpamax.pdf	Tablets 25 mg, 50 mg, 100 mg, 200 mg; sprinkles 15 mg, 25 mg	Children: 1–3 mg/kg/d divided bid; usual dose is 5–9 mg/kg/d divided bid–tid; Adult: 200–400 mg/d divided bid, initiate slowly with 25–50 mg qhs, increase weekly	Blocks sodium channels, enhances GABA activity, and antagonizes the kainate subtype of the glutamate receptor	Partial onset, Lennox-Gastaut syndrome, generalized tonic-clonic, juvenile myoclonic epilepsy
Valproic acid/ Divalproex	Depakene®		Solution 50 mg/mL; capsules 250 mg	15–60 mg/kg/d divided bid–tid	Unknown (may enhance GABA)	Generalized tonic-clonic, absence, myoclonic, partial onset
	Depakote®, Depakote ER®	www.rxabbott.com/pdf/depakote.pdf	Sprinkles 125 mg; tablets 125 mg, 250 mg, 500 mg; extended-release tablets 250 mg, 500 mg			
Vigabatrin (not available in the United States)	Sabril®		Tablets 500 mg; oral powder for solution 500 mg, 1 g, 2 g, 3 g	Adult: 2–4 g/d divided bid; children: 1–2 g/d or 40–100 mg/kg/d	Inhibits GABA-transaminase (preventing GABA metabolism)	Infantile spasms due to tuberous sclerosis
Zonisamide	Zonegran®	www.eisai.com/pdf_files/ZonegranPI.pdf	Capsules 25 mg, 50 mg, 100 mg	Adult: 200–400 mg/d PO bid (max 600 mg), initiate with 100 mg PO qd and adjust every 2 weeks; children: initiate at 1 mg/kg/d, adjust every 2 weeks (max 15 mg/kg/d)	Modulates sodium and T-type calcium channels	Partial onset, generalized, absence, myoclonic, Lennox-Gastaut syndrome, infantile spasms

Generic Name	Absorption	Volume of Distribution (L/kg)	Protein Binding (%)	Elimination	Half-Life	Usual Target Range
Carbamazepine	70–90% bioavailable, peak dependent on dosage form	0.79–1.4	60–85%	Hepatic metabolism, active metabolite	Initial 20–50 h, then 5–14 h; induces own metabolism over first 2 weeks	4–12 μg/mL
Clonazepam	Peak 1–4 h, > 90% bioavailable	1.8–4.4	85%	Hepatic metabolism	20–40 h	20–70 ng/mL
Diazepam (rectal)	90% bioavailable rectally		99%	Hepatic metabolism	30–60 h	Not applicable
Ethosuximide	Peak 1–4 h, > 90% bioavailable	0.6–0.7	< 10%	Hepatic metabolism	10–20% unchanged in urine	30–60 h 40–100 μg/mL
Felbamate	Peak 2–6 h, > 90% bioavailable	0.7–1	20–25%	50% renal, 50% hepatic metabolism	14–23 h	30–100 μg/mL
Gabapentin	35–60% bioavailable, dose-dependent absorption, peak 1–3 h	0.8	0	100% renal	5–9 h	4–20 μg/mL
Lamotrigine	Peak 1–4 h, > 98% bioavailable	0.9–1.4	55%	Metabolism	12–50 h, up to 70 hours with valproic acid	3–20 μg/mL

Continued on next page

TABLE 34-1. Antiepileptic Pharmacotherapy (continued)

Generic Name	Absorption	Volume of Distribution (L/kg)	Protein Binding (%)	Elimination	Half-Life	Usual Target Range
Levetiracetam	Peak 1–2 h, > 90% bioavailable	0.7	< 10%	33% nonhepatic metabolism, 67% excreted renally unchanged	Adult: 7 h	5–50 μg/mL
Lorazepam	Peak 0.5–3 h	1.3	85%	Hepatic metabolism	12 h	50–240 ng/mL
Oxcarbazepine	Peak 4.5 h, > 95% bioavailable	0.75	40%	Hepatic metabolism, active metabolite	Parent 1–2.5 h, metabolite 12 h	12–30 μg/mL for the monohydroxy derivative
Phenobarbital	> 90% bioavailable, oral peak 1–6 h	0.5–1	45%	Hepatic metabolism, 25% renal	40–140 h	15–40 μg/mL
Phenytoin	> 90% bioavailable, peak 2–12 h	0.75–1	88–93%	Hepatic metabolism	5–34 h	10–20 μg/mL total, 1–2 μg/mL free (for patients with ↓ protein binding)
Primidone	> 90% bioavailable, peak 2–4 h	0.4–1	20–30%	Metabolism—two active metabolites: phenobarbital and phenylethylmalonamide (PEMA)	3–7 h (PEMA t½ 30–36 h)	5–12 μg/mL, consider phenobarbital levels
Tiagabine	Peak 0.5–3 h, > 90% bioavailable	1.4	96%	Hepatic metabolism	4–9 h	Not established
Topiramate	> 80% bioavailable, peak 2 h	0.6–0.8	13–17%	60% excreted unchanged in urine, hepatic metabolism 40–70%	21 h	Not established
Valproic acid/ Divalproex	> 90% bioavailable, peak 1–8 h	0.13–0.19	90%	Hepatic metabolism	7–20 h	50–150 μg/mL
Vigabatrin	50–65% bioavailable, peak 0.5–2 h	0.8	Minimal	Excreted unchanged in urine	7 h	Not established
Zonisamide	Peak 2–6 h, 85% bioavailable	1.45	40%	50–70% hepatic metabolism, 30–50% renal	27–60 h	20–30 μg/mL

Generic Name	Dose-Related Side Effects	Idiosyncratic Side Effects
Carbamazepine	Double or blurred vision, lethargy (reduced by slow dose titration)	Agranulocytosis (1:575,000), fluid retention, bone marrow suppression, SIADH, Stevens-Johnson syndrome
Clonazepam	Drowsiness (50%), ataxia (30%), behavioral disturbances (25%), movement disorders, slurred speech, hypersecretion	
Diazepam (rectal)	Sedation	
Ethosuximide	GI distress, drowsiness, hiccups, sedation	Headache, liver, lupus, hematologic, Stevens-Johnson syndrome
Felbamate	Anorexia, weight loss, vomiting, insomnia, headache, somnolence, rare cases of aplastic anemia (25:100,000) and liver failure (8:100,000)	
Gabapentin	Somnolence, dizziness, ataxia, nystagmus, weight gain, nausea, vomiting, blurred vision, tremor, slurred speech, peripheral edema, dyspepsia, hiccups	
Lamotrigine	Fatigue, drowsiness, ataxia, dizziness, headache, nausea, vomiting, double or blurred vision, nystagmus	Rash with possible development of Stevens-Johnson syndrome (1:1,000 adults, 1:100 children), alopecia, abdominal pain
Levetiracetam	Somnolence (14.8%), asthenia (14.7%), coordination difficulties (3.4%), dizziness, nervousness, behavioral problems, ↓ blood counts	
Lorazepam	Sedation with risk of respiratory depression, amnesia, abnormal behavior, withdrawal reactions	
Oxcarbazepine	Headache, drowsiness, fatigue, nausea, dizziness, hyponatremia (hematologic toxicity not observed to date), psychomotor slowing, ataxia, tremor, visual changes	
Phenobarbital	Sedation, mental dullness, cognitive impairment, hyperactivity, ataxia, respiratory depression	Hyperactivity, rash
Phenytoin	Nystagmus, ataxia, lethargy, propylene glycol in IV preparation can cause myocardial depression, bradycardias, other ECG changes, hypotension	Gingival hyperplasia, ↑ body hair, coarsening of facial features, acne, folate deficiency, rash
Primidone	Same as phenobarbital	
Tiagabine	Sedation, dizziness, weakness, memory impairment, inattention, emotional lability, headache, abdominal pain, anorexia, tremor	

TABLE 34-1. Antiepileptic Pharmacotherapy (continued)

Generic Name	Dose-Related Side Effects	Idiosyncratic Side Effects
Topiramate	Speech and language problems, difficulty with concentration and attention, confusion, fatigue, paresthesias, weight loss	Psychomotor slowing, somnolence, urolithiasis, diarrhea, hyperthermia, acute myopia and secondary angle closure glaucoma, hyperchloremic metabolic acidosis, oligohydrosis with hyperthermia
Valproic acid/ Divalproex	GI upset, tremor, lethargy, changes in menstrual cycle, thrombocytopenia	Weight gain, nausea, alopecia, hepatitis, pancreatitis, bruising, polycystic ovarian syndrome Risk of hepatotoxicity in child < 2 yr old on polytherapy—1:500–800 Risk of hepatotoxicity in child > 2 yr old on monotherapy—1:45,000–117,000
Vigabatrin	Drowsiness, fatigue, ataxia, behavioral changes, weight gain, psychosis (in predisposed patients and upon abrupt withdrawal), hematologic, visual field problems	
Zonisamide (contraindicated with sulfa allergy)	Drowsiness, psychosis (2%)Nephrolithiasis (4%), ↓ GFR (8%), dizziness, confusion, ataxia, memory impairment, paresthesias, nystagmus, diplopia, tremor, anemia, leukopenia, nausea, vomiting, anorexia, weight loss, rash, oligohydrosis with hyperpyrexia (especially important in children)	

Generic Name	Added Drug ↓ Original AED	Added Drug ↑ Original AED or ↑ Active Metabolite
Carbamazepine (carbamazepine can decrease the efficacy of oral contraceptives; decrease levels of cyclosporin, doxycycline, theophylline, thyroid and warfarin; and increase the potential for acetaminophen toxicity in overdose or frequent dosing)	Felbamate, lamotrigine, phenobarbital, phenytoin, primidone	Cimetidine, clarithromycin, diltiazem, erythromycin, felbamate (↑ epoxide metabolite), isoniazid, lamotrigine (↑epoxide metabolite), valproic acid (↑ epoxide metabolite), verapamil
Clonazepam (combination with valproic acid may increase absence status)	Carbamazepine, phenytoin, phenobarbital, primidone	? oral antifungals
Diazepam (rectal) (phenobarbital and diazepam in combination increase the risk of respiratory depression)	Not of concern with acute use	Not of concern with acute use
Ethosuximide	Carbamazepine, phenytoin, phenobarbital, primidone	? isoniazid, ? valproic acid
Felbamate	Carbamazepine, phenytoin	Erythromycin
Gabapentin (20% decreased absorption if taken with antacids)	None known	None known
Lamotrigine	Acetaminophen, carbamazepine, oxcarbamazepine, phenytoin, phenobarbital, primidone	Valproic acid
Levetiracetam	None known	None known
Lorazepam (other drugs with CNS depressant effects can potentiate sedation or respiratory depression)	Phenytoin	Probenecid, oral contraceptives, valproic acid
Oxcarbazepine (can decrease efficacy of oral contraceptives)	Carbamazepine, phenobarbital, phenytoin, primidone, valproic acid, verapamil	
Phenobarbital (can decrease efficacy of antiretroviral agents, oral contraceptives, theophylline, verapamil, warfarin, and quinidine, decrease vitamin D and folic acid, and increase the potential for acetaminophen toxicity in overdose)	Phenytoin	Dexmethylphenidate, methylphenidate, primidone, phenytoin, valproic acid
Phenytoin (can decrease efficacy of oral contraceptives, tacrolimus, teniposide, theophylline, thyroid, warfarin, quinidine, and decrease vitamin D and folic acid; and increase the potential for acetaminophen toxicity in overdose)	Antacids/tube feedings, sucralfate, phenobarbital, vigabatrin	Amiodarone, cimetidine, chloramphenicol, felbamate, fluoxetine, fluconazole, isoniazid, itraconazole, oxcarbamazepine, topiramate, valproic acid (↑ free)

Continued on next page

TABLE 34-1. Antiepileptic Pharmacotherapy (continued)

Generic Name	Added Drug ↓ Original AED	Added Drug ↑ Original AED or ↑ Active Metabolite
Primidone (phenobarbital can decrease efficacy of oral contraceptives, theophylline, verapamil, warfarin, quinidine; decrease vitamin D and folic acid; and increase the potential for acetaminophen toxicity in overdose or frequent dosing)	Carbamazepine (↑ phenobarbital), phenytoin (↑ phenobarbital), valproic acid (↑ phenobarbital)	
Tiagabine	Carbamazepine, phenobarbital, phenytoin	None known
Topiramate (can decrease efficacy of oral contraceptives)	Carbamazepine, phenobarbital, phenytoin, valproic acid	None known
Valproic acid/divalproex	Carbamazepine, lamotrigine, phenobarbital, phenytoin, primidone, topiramate	Felbamate, isoniazid, salicylates (↑ free)
Vigabatrin	None known	None known
Zonisamide	Carbamazepine, phenobarbital, phenytoin, valproic acid	None known

*Injection and capsules are 92% phenytoin, dose listed is phenytoin sodium. AED = antiepileptic drug; CNS = central nervous system; ECG = electrocardiogram; GABA = γ-aminobutyric acid; GFR = glomerular filtration rate; GI = gastrointestinal; SIADH = syndrome of inappropriate diuretic hormone.

simultaneously starting a second AED. Although "doing two things at once" can complicate clinical decision-making when seizures recur— was it the taper, an ineffective new drug, a drug interaction, or a subtherapeutic new drug?—the benefits of monotherapy in terms of cognition still far outweigh the incremental benefits of polypharmacy on seizure control. Additional questions that will need to be answered in coming years that will affect the choice of first-line AEDs are as follows:

- Should topiramate supplant valproate as a first-line broad-spectrum AED beyond infancy?
- Should lamotrigine replace valproate as an equally potent but significantly more benign anticonvulsant, especially in non-urgent cases (eg, absence) where there is time for titration?
- Is there any advantage of oxcarbamazepine over extended-release carbamazepine, as both are useful in reducing side effects?
- Should topiramate, zonisamide, or valproate supplant ACTH as first-line treatment for infantile spasms?
- Should levetiracetam be used instead of oxcarbazepine or extended-release carbamazepine as first-line therapy for partial seizures in children?

Suggested Readings

Camfield P, Camfield C. Epileptic syndromes in childhood: clinical features, outcomes, and treatment. Epilepsia 2002;43 (Suppl 3):27–32.

Jarrar RG, Buchhalter JR. Therapeutics in pediatric epilepsy. Part 1: the new antiepileptic drugs and the ketogenic diet. Mayo Clinic Proc 2003;78:359–70.

Shinnar S, Berg A, O'Dell C, et al. Predictors of multiple seizures in a cohort of children prospectively followed from the time of their first unprovoked seizure. Ann Neurol 2000; 48:140–7.

Practitioner and Patient Resources

See the available Web sites listed for each drug in Table 34-1.

Chapter 35

Neurologic Assessment of Behavioral Disorders

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Pediatric neurologists are often consulted about children and adolescents with significant behavior problems where the referring pediatrician or psychiatrist is concerned that there is an underlying neurologic abnormality. This chapter deals with the neurologic history, examination, investigations, and management, which may be considered in this situation. Other chapters cover attention deficit disorder, developmental delay, autism spectrum disorders, depression, and conversion disorders, so these will not be specifically addressed here.

The most common presenting issues are aggressive behavior outbursts, deterioration in school performance, and a variety of bizarre behaviors, which the referring doctor is unable to classify but usually considers not organic. In the author's practice, these issues were the presenting problem in 16 of 100 consecutive office-based referrals.

Aggressive Behavior Outbursts

Common neurologic conditions that may be implicated include complex partial seizures, migraines, anticonvulsant medications, daytime somnolence, and an acquired aphasia epilepsy disorder.

Aggressive behavior outbursts are rarely associated with temporal lobe epilepsy, but this is often at the forefront of the family's concerns. A thorough history will usually establish that these are not seizures because the episodes are triggered by a frustrating incident for the child, there is no loss of consciousness, ie, the child remains verbally responsive and often abusive during the episode, there is no stereotyped pattern, and no sleep is required after the episode. Viewing a videotape of a typical episode may be useful to rule out epilepsy, although for parental reassurance an electroencephalography (EEG) and possibly a magnetic resonance imaging (MRI) scan may be required.

In preschool-aged children, iron deficiency can lead to irritable outbursts, so a blood count and iron studies may be indicated. Specific inquiries should also be made about head trauma, particularly episodes that were severe enough to cause loss of consciousness.

In school-aged children and adolescents, the aggressive outbursts may signify an inability to cope with the school or home environment, so a more detailed history focusing on general medical health, the undisclosed use of drugs, sleep disorders, and external stress should be obtained. It is very unusual for aggressive outbursts caused by an underlying neurologic condition to only occur in one environment, eg, if the child's behavior is good at school but quite difficult at home, then a psychologic problem is much more likely.

Medications are frequently implicated in causing deterioration in behavior, especially anticonvulsants. In a study of 216 children and adolescents with epilepsy, significant side effects requiring discontinuation of an anticonvulsant occurred in 15% of drug exposures. Behavioral changes were responsible for almost 50% of these, ie, 7%, with irritability, aggression and hyperactivity were most commonly encountered. Global developmental delay or an intellectual disability were present in 67 patients, and 27 (40%) of these experienced significant side effects compared with 30 (20%) of the group with normal cognition. This difference was principally due to the higher incidence of behavioral side effects in the intellectually disabled group, 28% versus 6% for the normal cognition group. Even allowing for the higher drug exposure in the intellectually disabled group due to their epilepsy being more difficult to control, those with an

intellectual disability were still three times more likely to have significant behavioral side effects from anticonvulsants than those with normal development. This has implications for the choice of anticonvulsant medication in those with global developmental delay or an intellectual disability, ie, choose a medication that is less likely to be associated with behavioral side effects in this group.

In the above study, phenobarbitone and the benzodiazepines were most likely to be associated with significant behavior problems while lamotrigine was least likely. Using slow release forms of anticonvulsants is also likely to reduce the incidence of behavioral side effects. If daytime drowsiness is contributing to irritability, then rearranging the doses to use a smaller dose in the morning and a larger dose at night may alleviate the problem.

Adolescents with aggressive outbursts may attribute these to frequent headaches, but may not recognize that these are migraines as the headache may be frontal or generalized rather than unilateral. In addition, the pain may be perceived as moderate rather than severe, but it is the frequency of these headaches rather than their severity, which interferes significantly with day to day functioning and consequently behavior. Usually, the presence of photophobia, nausea, and phonophobia is sufficient to establish the diagnosis, whereas subsequent treatment with preventative medication such as propranolol has the dual benefit of reducing the frequency of the migraines and aggressive outbursts.

Prolonged episodes of agitation with aggressive behavior can occur in a confusional migraine, and the headache may be absent or mild in this state. The main differential diagnoses include complex partial seizures and an acute encephalopathy, but these may be difficult to determine if no previous episodes have occurred. A urine drug screen, blood glucose level, EEG, and MRI scan are likely to be required if this is the first episode.

Aggressive outbursts with irritability may be due to excessive daytime somnolence although this may not be recognized by teachers or parents unless specifically asked. Obstructive sleep apnea in a child who has prominent snoring is usually well recognized, but other rarer causes of an obstructive sleep pattern include retroposition of the mandible or a long, soft palate. Sleep apnea is also characteristic of a Chiari type I malformation and there may be no long tract signs of spasticity, so a MRI scan is indicated where no other cause of sleep apnea is found.

Daytime somnolence is a cardinal feature of narcolepsy, but this condition is underdiagnosed in children and adolescents. The characteristic pattern of sleepiness in narcolepsy is that it occurs despite adequate nocturnal sleep and the inappropriate situation in which the sleep occurs, eg, while eating, playing, or even walking. The child may be irritable or aggressive as a direct result of drowsiness or as a reaction to criticism by teachers or parents about the daytime somnolence. Children may even be hyperactive as a strategy to overcome excessive sleepiness.

TABLE 35-1. Rare Neurologic Conditions in Which Aggressive Outbursts or Irritability Occur with Previous Normal Development in School-aged Children

Acquired aphasia epilepsy (Landau-Kleffner Syndrome)
Ceroid– lipofuscinosis
GM2 gangliosidosis
Hypothalamic hamartoma
Krabbe's disease
Metachromatic leukodystrophy
Niemann- Pick disease type C
Porphyria– acute intermittent
Rett syndrome (late variant)
Wilson's disease

Rare neurologic conditions that may have aggressive outbursts as a presenting symptom are detailed in Table 35-1. In the acquired aphasia epilepsy syndrome (Landau-Kleffner), there may be no history of seizures, and the loss of language function results in significant aggressive behavior outbursts due to the child being frustrated at not being able to communicate as well as not understanding instructions. If there is a definite loss of speech skills and the EEG in the waking state is normal, then a sleep EEG will be required. Treatment usually involves prednisolone in addition to an anticonvulsant.

Having excluded an underlying neurologic cause for the behavior outbursts, management initially involves counseling by a child psychologist or psychiatrist. In a study of 129 children and adolescents referred to a psychiatry unit with serious aggressive behavior outbursts, Turgay found that underlying psychiatric diagnoses were very common. An oppositional defiant disorder was present in 93%, attention deficit hyperactivity disorder in 88%, and a conduct disorder in 38%.

Treatment of the underlying psychiatric disorder was, therefore, most important in reducing the aggressive outbursts.

In addition to alleviating environmental stressors such as bullying at school, psychoeducational approaches targeting social skills, conflict resolution, and anger management are often used. However, medication is frequently required for severe aggressive outbursts. Studies have shown that stimulant medication, particularly the long acting forms are effective, whereas neuroleptics such as risperidone are recommended for severe and persistent aggressive behavior when the child presents an acute danger to themselves and others. Tiredness and weight gain may be significant side effects of the neuroleptics although both stimulants and risperidone can be safely given as a combination. Risperidone is particularly useful

in children with an intellectual disability, autism, or other pervasive developmental disorders.

If there is a significant underlying problem with a mood disorder, then divalproex sodium has been shown to reduce explosive tempers, aggressive behavior, and mood lability. Concurrent depression or anxiety may also require specific medications.

In a longer term study of 63 children with autism aged 5 to 17 years, risperidone at a mean dose of 2 mg daily was persistently effective in reducing temper tantrums, aggressive outbursts, and self-injurious behavior over a period of 6 months. Discontinuation after 6 months resulted in a rapid return of disruptive and aggressive behavior in most subjects.

Deterioration in School Performance

Although deteriorating school performance may signal the early stage of a rare regressive condition such as adrenoleukodystrophy or subacute sclerosing panencephalitis, it is much more likely to be a sign that the child is stressed, depressed, or lacks motivation. Clinical clues to a neurologic cause for the deterioration include a decline in cognitive functioning, seizures, or a change in coordination, ie, the child becomes clumsy in gross or fine motor skills. Clinical evidence of a cognitive deterioration includes poor short-term memory for subjects that the child is really interested in and slowness to respond to simple questions. Neurologic examination may show subtle coordination difficulties or more obvious spasticity.

When there is no doubt about a decline in cognitive functioning, a full IQ test by a psychologist is an essential investigation. This may reveal a previously unrecognized borderline low IQ or mild intellectual disability, which has only become apparent because the academic work at school has become too challenging in a higher grade. In this situation, investigations will be similar to those of a younger child with developmental delay, including chromosomes and molecular genetics testing for Fragile X. An IQ test will also serve useful as a baseline for future analysis when it is unclear whether there has been a real cognitive decline.

Neurologic conditions that may have cognitive deterioration and apathy/depression as a presenting symptom are detailed in Table 35-2. In the presence of a normal neurologic exam, but definite cognitive decline, then an EEG, metabolic tests, and MRI scan are indicated. Other more extensive investigations such as a lumbar puncture or skin biopsy may be considered after follow up in 2 to 3 months if a regressive disorder becomes more obvious.

TABLE 35-2. Neurologic Conditions in Which Apathy/Depression and Neurologic Regression Occur in School-aged Children

Adrenoleukodystrophy
5–10 methylenetetrahydrofolate reductase deficiency (MTHFR)
Vitamin E deficiency
Ceroid lipofusciniosis
Choreo–acanthocytosis
Gauchers disease
GM2 gangliosidosis
Lafora body disease
Metachromatic leukodystrophy
Subacute sclerosing panencephalitis

Bizarre Behavior or Symptoms

Bizarre behaviors or symptoms that fluctuate in time may be due to an unrecognized neurologic disorder but not recognized as such by nonneurologists. Typical neurologic conditions that may be misdiagnosed as a psychologic disorder include diurnal dystonia, diurnal weakness, motor or vocal tics, complex partial seizures, migraine equivalents, and cataplexy. Nonneurologic conditions that are frequently classified as epilepsy include stereotypies such as gratification phenomenon, behavioral mannerisms, shuddering attacks, and night terrors.

Stereotypies can be defined as involuntary, patterned, coordinated, repetitive, nonreflexive movements that occur in exactly the same way with each repetition. There is disagreement about whether these are goal directed or purposeless, but their repetitive nature suggests that they do serve a purpose for the individual who may have a sensory rather than motor function, eg, the hand rubbing movements in Rett Syndrome.

Stereotypies frequently occur in children with autism, intellectually disability, sensory deprivation, or neurodegenerative disorders. However, these movements can also occur in otherwise normal individuals when they are termed physiologic stereotypies. Behavioral management interventions have been successful, but a follow-up investigation of 81 children aged 7 months to 21 years who had bilateral, repetitive, fixed, involuntary, readily suppressible movements of the arms, hands, and fingers found that these features were frequently chronic and rarely resolved completely, contrary to the usual advice given to parents that the child "will grow out of them" (suggested reading 4).

Paroxysmal dystonia is usually familial and may be misdiagnosed as epilepsy due to excellent responses seen with small doses of anticonvulsants such as carbamazepine or lamotrigine. The adolescent with myasthenia gravis may not recognize that fatigability as the day progresses is a neurologic symptom.

Motor or vocal tics are usually well recognized but may need differentiation from more subtle myoclonic jerks.

Other periodic behaviors such as gratification phenomena or shuddering attacks may require a video with concurrent EEG monitoring to rule out complex partial seizures. Fortunately, these behaviors usually occur frequently enough that the EEG with video does not require prolonged monitoring, and often, review of a home video is enough to establish the diagnosis.

Rare forms of complex partial seizures may be misinterpreted as psychogenic behavior, eg, gelastic (laughing) seizures, or reflex seizures induced by eating, chewing, or brushing teeth, particularly when the seizures do not evolve to focal clonic or secondarily generalized tonic clonic seizures. Some clinical clues to epilepsy include the stereotyped pattern, unresponsiveness during the episode even to noxious stimuli, and loss of memory for events that have occurred during the seizure although some retained consciousness can occur. If the episodes are infrequent, prolonged video EEG monitoring may not be feasible, but an EEG in the sleep deprived state is likely to increase the chance of finding an abnormality.

Just as headaches are often not recognized as migraines, a variety of paroxysmal symptoms due to a migraine equivalent, ie, the aura phase of a migraine without the headache phase, are also often unrecognized by nonneurologists. The commonest of these is benign paroxysmal vertigo but rare forms include a variety of visual distortions attributed to parietal lobe dysfunction such as the "Alice in Wonderland" syndrome where objects seem much bigger or smaller than their usual size.

Cataplexy is frequently misinterpreted as clumsiness, especially if the link between emotional triggers such as laughter and a sudden fall have not been recognized. Although cataplexy is a cardinal feature of narcolepsy, it may also occur in lesions of the ponto-medullary region and in Niemann-Pick type C disease. Another clinical feature of Niemann-Pick type C disease includes excessive daytime drowsiness, making the distinction from narcolepsy difficult. In a study by Challamel and colleagues, 12 of 97 cases of narcolepsy in children were subsequently diagnosed with Niemann-Pick type C. Other clinical features of this disorder include progressive ataxia, episodic dystonia, and defective downgaze.

Adult studies have shown that there are typical characteristics of psychogenic movement disorders many of which are applicable to children and adolescents (Table 35-3). The authors of this study also found that a significantly higher proportion with psychogenic movements had either a family history of neurologic disease or other exposure to neurologic disease. This may be difficult to confirm whether the exposure to a neurologic disorder occurs via the internet or television. In contrast, the frequency of false positive diagnoses of a motor conversion disorder including paralysis range from 5 to 15%.

TABLE 35-3. Factors Suggesting a Movement Disorder is Inconsistent With Organic Disease (Adapted from Shill and Gerber[6])

False weakness or sensory signs
Movement disorder is inconsistent over time, eg, disappears when the patient is not aware of being observed
Distractibility
Abrupt onset
Atypical stimulus sensitivity
Selective disability
Persistent relief by psychotherapy, suggestion or placebo
Atypical response to a pharmacologic agent

In most cases of behavioral abnormalities in children and adolescents, there is no specific underlying neurologic cause. However, a thorough history, complete neurologic exam, and possibly limited further investigations such as an EEG and MRI scan may be required to reassure the child's family and enable the psychiatrist or therapist to embark on an appropriate management program.

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Chapter 36

Clinical Evaluation of Attention Deficit-Hyperactivity Disorder

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Attention deficit hyperactivity disorder (ADHD) occurs in 5 to 8% of children and 4 to 5% of adults, necessitating that clinicians be thoroughly acquainted with its clinical evaluation. Guidelines for doing so are provided in this chapter, but clinicians are further advised to familiarize themselves with the current practice guidelines for ADHD issued by the American Academy of Pediatrics and the American Academy of Child and Adolescent Psychiatry.

This chapter presents an overview of the clinical assessment and diagnosis of attention-deficit hyperactivity disorder (ADHD) in children. The most important components to a comprehensive evaluation of the client with ADHD are as follows: (1) the clinical interview, (2) the completion and scoring of behavior rating scales, (3) psychological testing to rule out comorbid learning disabilities or intellectual delay, (4) consultation with school personnel, in the case of school-age children, and (5) the medical exam. When feasible, clinicians may wish to supplement these components of the evaluation with objective assessments of ADHD symptoms, such as with direct behavioral observations of classroom behavior and academic performance. Other tests of attention and inhibition, such as continuous performance tests, may be used but are not essential to reaching a diagnosis or to treatment planning, although they may yield additional information about the presence and severity of cognitive impairments associated with some cases of ADHD.

The Nature of ADHD

ADHD comprises deficits in behavioral inhibition, sustained attention and resistance to distraction, and the regulation of one's activity level to the demands of a situation (hyperactivity or restlessness). The disorder occurs in 5 to 8% of children and 4 to 5% of adults. Symptoms of the disorder often emerge by 3 to 5 years of age, especially if hyperactive-impulsive behavior is present, and certainly by 12 years of age in the case of attentional problems. Those attention problems have recently been shown to be related to deficits in the larger domain of executive functioning, thus implying that the attention problems evident in ADHD may arise more from impaired executive functioning and self-regulation than from inattention. The male: female ratio is typically 3:1 in community samples and higher in clinic-referred samples. The disorder is more likely to be found in families in which others have the disorder or where depression is more common. It is also more likely to occur in children with conduct problems and delinquency, tic disorders or Tourette's syndrome, learning disabilities, childhood bipolar disorder, or those with a history of prenatal alcohol or tobacco-smoke exposure, premature delivery or significantly low birth weight, or significant trauma to the frontal regions of the brain. Research suggests those with ADHD, particularly the subtypes associated with impulsive behavior (see below), may also have difficulties in the following areas of neuropsychological functioning:

- *Remembering to do things, or nonverbal working memory*. Working memory refers to the capacity to hold

information in mind that will be used to guide one's actions, either now or at a later time. It is essential for remembering to do things in the near future.

- *Delayed development of internal language and rule following, or verbal working memory*. Recent research suggests children with ADHD experience significant delays in the development of internal language, the private voice inside one's mind that we employ to converse with ourselves, contemplate events, and direct or command our own behavior. This private speech is absolutely essential to the normal development of contemplation, reflection, and self-regulation.
- *Difficulties with self-regulation of emotions, motivation, and arousal*. Children and adults with ADHD often have problems inhibiting their emotional reactions to events as well as do others of their age. It is not that the emotions they experience are inappropriate, but that those with ADHD are more likely to publicly manifest the emotions they experience. They seem less able to "internalize" their feelings, to keep them to themselves, and even to moderate them when they do so, as others might do. Consequently, they are likely to appear less emotionally mature, more reactive with their feelings, and more hotheaded, quick-tempered, and easily frustrated by events. Coupled with this problem with regulation of emotion are difficulties in generating intrinsic motivation for tasks that have no immediate payoff or appeal. This incapacity to create private motivation, drive, or determination often makes them appear to lack willpower or self-discipline, as they cannot stay with things that do not provide immediate reward, stimulation, or interest to them. Their motivation remains dependent on the immediate environment for how hard and how long they will work, whereas others develop a capacity for intrinsically motivating themselves in the absence of immediate rewards or other consequences.
- *Diminished planning and problem-solving ability in pursuing long-term goals*. This refers to the capacity to problem-solve while engaged in goal-directed activities. Individuals must be capable of quickly generating various options, considering their respective outcomes, and selecting those most likely to enable them to surmount the obstacle. People with ADHD find such hurdles more difficult to overcome. They often give up their goals in the face of obstacles and fail to take time to think through other options that could help them succeed.
- *Greater than normal variability in their task or work performance*. It is typical of those with ADHD, especially those with subtypes associated with impulsive behavior, to show wide swings in the quality, quantity, and even speed of their work over time. They typically fail to maintain a relatively even pattern of productivity and accuracy in their work from moment to moment and day to day.

ADHD symptoms are often developmentally stable. Although the absolute level of symptoms does decline with age, this is true of the inattentiveness, impulsiveness, and activity levels of normal individuals as well. Although the behavior of those with ADHD may improve, they typically remain chronically behind others of their age in their capacity to inhibit behavior, sustain attention, control distractibility, and regulate their activity level. Research suggests that of those children clinically diagnosed with the disorder in childhood, 50 to 80% will continue to meet the criteria for the diagnosis in adolescence, and up to 66% may continue to do so in adulthood.

Developmental Risks

Fifteen to 34% of those with ADHD ultimately outgrow the disorder. Over the course of their lives, a significant minority of those with ADHD are at greater risk for developing oppositional and defiant behavior (50%), conduct problems and antisocial difficulties (25 to 45%), learning disabilities (25 to 40%), anxiety (10 to 25%), and depression (25%). Approximately 5 to 10% of those with ADHD may develop more serious mental disorders, such as manic-depression or bipolar disorder. Between 10 and 22% may develop antisocial personality disorder by adulthood, and most of these patients also will have substance abuse problems. Overall, approximately 10 to 25% develop difficulties with overuse or dependence upon or even abuse of legal (ie, alcohol, tobacco) or illegal (eg, marijuana, cocaine, illicit use of prescription drugs) substances, with this risk being greatest among those who had conduct disorder or delinquency as adolescents. Most people with ADHD experience problems with school performance, with as many as 30 to 50% having been retained in their school grade at least once and 25 to 36% never completing high school.

As adults, those with ADHD are likely to be undereducated relative to their intellectual ability and family educational background. They are also likely to experience difficulties with work adjustment and may be underemployed in their occupations relative to their intelligence and educational and family backgrounds. They tend to change jobs more often than others do, sometimes out of boredom or because of interpersonal problems in the workplace. They also tend to have a greater turnover of friendships and dating relationships and seem more prone to marital discord and even divorce. The risk of involvement in a teen pregnancy is nearly 10 times greater than normal (40% versus 4%) and risk

for sexually transmitted disease four times greater (16% versus 4%). Speeding while driving is relatively commonplace, as is receiving more traffic citations and, in some cases, having two to three times as many motor vehicle accidents as others are likely to experience in their driving careers. Thus, they are more likely to have had their driver's license suspended or revoked.

Subtypes

Since 1980, it has become possible to categorize those with ADHD into several subtypes, depending upon the combinations of symptoms they experience. The *Diagnostic and Statistical Manual for Mental Disorders* (DSM-IV) currently recognizes three subtypes. Those who have difficulties primarily with impulsive and hyperactive behavior and not with attention or concentration are now referred to as having the *predominantly hyperactive-impulsive type*. Individuals with the opposite pattern, significant inattentiveness without being impulsive or hyperactive, are called the *predominantly inattentive type*. However, most individuals with the disorder will manifest both of these clinical features and so are referred to as the *combined type* of ADHD. Research on those with the combined type suggests that they are likely to develop their hyperactive and impulsive symptoms first, usually during the preschool years. At this age, then, they may be diagnosed as having the predominantly hyperactive-impulsive type. However, most of these children eventually develop difficulties with attention span, persistence, and distractibility within a few years of entering school, and the diagnosis is revised to combined type.

There is considerably less research on the predominantly inattentive type of ADHD, or what used to be referred to as attention-deficit disorder without hyperactivity. What research does exist suggests that 30 to 50% of cases so classified are characterized by some qualitative differences in attention problems, chiefly sluggish cognitive tempo. This subset of cases manifests greater difficulties with daydreaming, passiveness, and sluggishness and with focused or selective attention (ie, filtering important from unimportant information), slow processing of information, mental fogginess and confusion, social passivity or apprehensiveness, hypoactivity, lethargy, and inconsistent retrieval of information from memory. It is also considerably less likely to be associated with impulsiveness (by definition) as well as oppositional/defiant behavior, conduct problems, or delinquency. Evidence suggests a poorer response to stimulant medication for this subset of children but a greater response to psychosocial treatments such as social skills training and behavioral parent training. Should further research continue to demonstrate such differences, there would be good reason to view this subgroup as a separate and distinct disorder from that of ADHD.

Etiologies

ADHD has very strong biologic contributions to its occurrence. Although precise causes at the molecular level of physiology have not yet been identified, there is little question that heredity or genetics and neurologic factors make the largest contribution to the expression of the disorder in the population. The heritability of ADHD averages 80%, meaning that genetic factors account for 80% or more of the differences among individuals in this set of behavioral traits. For comparison, this figure rivals that for autism and bipolar disorder and is just shy of the genetic contribution to human height. Several genes associated with the disorder have been identified (*DRD4-7* repeat, *DAT1*, *DBH Taq* 1). Undoubtedly, more will be revealed, given that ADHD represents a set of complex behavioral traits and so a single gene is unlikely to account for the disorder.

In instances where heredity does not seem to be a factor, difficulties during pregnancy, prenatal exposure to alcohol and tobacco smoke, premature delivery and significantly low birth weight, excessively high body lead levels, and postnatal injury to the prefrontal regions of the brain have all been found to contribute to the risk for the disorder in varying degrees. Research has not supported popularly held views that ADHD arises from excessive sugar intake, food additives, excessive viewing of television, or poor child management by parents. Some drugs used to treat seizure disorders in children (eg, phenytoin, phenobarbital) may increase symptoms of ADHD in some children, but these side effects are reversible.

Assessment

The major goals of the clinical evaluation are to do as follows:

- Determine the presence or absence of ADHD as well as other childhood psychiatric disorders. This differential diagnosis requires extensive clinical knowledge of these other psychiatric disorders. In any evaluation, it may be necessary to draw on measures that are normed for the individual's ethnic background, if such instruments are available, to preclude the over diagnosis of minority children when diagnostic criteria developed on white American children are extrapolated to other ethnic groups. Very helpful in this regard are the well-normed child behavior rating scales, such as the *Child Behavior Checklist, Behavioral Assessment System for Children, ADHD-IV Rating Scale,* and *Conners' Rating Scales.*

- Begin delineating the types of interventions needed to address the psychiatric disorders and psychological, academic, and social impairments identified in the course of assessment. These may include individual counseling, parent training in behavior management, family therapy, classroom behavior modification, psychiatric medications, and formal special educational services, to name just a few.
- Identify the conditions that often coexist with ADHD and the manner in which these conditions may affect prognosis or treatment decision-making. For instance, the presence of high levels of physically aggressive behavior by a child with ADHD may indicate that a parent training program is contraindicated, at least for the time being, because such training in limit setting and behavior modification could temporarily increase child violence toward parents when limits on noncompliance with parental commands are established. Or consider the presence of high levels of anxiety specifically and internalizing symptoms more generally in children with ADHD. Research shows such symptoms may be a predictor of poorer responses to stimulant medication. Similarly, the presence of high levels of irritable mood, severely hostile and defiant behavior, and periodic episodes of serious physical aggression and destructive behavior may be early markers for later bipolar disorder (manic-depression) in children. Oppositional behavior is almost universal in juvenile onset bipolar disorder. Such a disorder is likely to require the use of several psychiatric medications in conjunction with a parent-training program.
- Catalog the child's psychological strengths and weaknesses as well as family and community resources and consider how these may affect treatment planning. It is important to assess parents' own abilities and motivation to carry out the treatment program as well as the family's social and economic circumstances and the treatment resources that may or may not be available within their community and cultural group. Some determination also must be made as to the child's eligibility for special educational services within his or her school district for eligible disorders, such as developmental delay, learning disabilities, or speech and language problems.

Parent Interview

The parent (often maternal) interview, although often criticized for its unreliability and subjectivity, is an indispensable part of the evaluation of children and adolescents presenting with concerns about ADHD. No adult is more likely to have the wealth of knowledge about and history of interactions with a child than a parent. Whether wholly accurate or not, parent reports provide the most ecologically valid and important source of information concerning a child's difficulties. It is the parents' complaints that often lead to the referral of the child, will affect the parents' perceptions of and reactions to the child, and will influence the parents' adherence to the treatment recommendations to be made. I do not typically have the child in the same room when we conduct the parental interview. Other clinicians, however, choose to do so. The presence of the child raises thorny issues to which the examiner must be sensitive. Some parents are less forthcoming about their concerns and the details of a child's specific problems when the child is present, whereas others fail to recognize the potential problems posed for their child by this procedure, making it even more imperative that the examiner review these issues with them before beginning the evaluation.

The interview is designed to formulate a diagnosis and to develop treatment recommendations. Although diagnosis is not always considered necessary for treatment planning (a statement of the child's developmental and behavioral deficits is often adequate), the diagnosis of ADHD does prove useful in predicting developmental course and prognosis for the child, determining eligibility for some special educational placements, and predicting potential response to medication.

The interview covers the following topical areas:

- The major referral concerns of the parents, including specific nature, frequency, age of onset, and chronicity of the problematic behaviors.
- Potential problems that might exist in the developmental domains of motor, language, intellectual, academic, emotional, and social functioning to aid with different diagnosis. Many children with atypical pervasive developmental disorders, such as Asperger's syndrome, or with early bipolar disorder may be viewed by their parents as having ADHD, as the parents are more likely to have heard about the latter disorder than the former ones and will recognize some of the qualities in their children. Questioning about inappropriate thinking, affect, social relations, and motor peculiarities may reveal a more seriously and pervasively disturbed child. Inquiry also must be made as to the presence or history of tics or Tourette's syndrome in the child or in the immediate biologic family members. When these disorders are noted, the cautious use of stimulant drugs in the treatment of ADHD is recommended. Lower doses than typically prescribed may be used to preclude exacerbation of the child's tic disorder. Alternatively, atomoxetine (a nonstimulant approved for ADHD by the FDA in 2003) may be of benefit in these instances as it

does not exacerbate and may even treat comorbid anxiety, and does not contribute to problems with insomnia or exacerbation of tics.

- The family history, including a discussion of potential psychiatric difficulties in the parents and siblings, marital difficulties, and any family problems centered around chronic medical conditions, employment problems, or other potential stress events within the family.
- History of prior treatments received by the child and his or her family for these presenting problems.
- School history year by year, starting with preschool. Gathering a reliable school history gives the clinician two crucial pieces of the diagnostic puzzle. First, is there evidence of symptoms or characteristics of ADHD in school before adolescence? Second, is there evidence of impairment in the child's academic functioning as a result of these characteristics?
- Peer relationships.
- Functioning in community group activities (eg, sports, Scouts, church).
- Symptoms of the major child psychiatric disorders likely to be seen in ADHD (eg, use DSM-IV in some semistructured or structured way). Use care in the evaluation of ethnic minorities to avoid over diagnosing psychiatric disorders simply by virtue of ignoring differing cultural standards for child behavior. Should the parent indicate that a symptom is present, one means of precluding over identification of psychopathology in minority children is to ask if the child is considered to be a problem compared with other children of the same ethnic or minority group. Only if the parent answers "yes" is the symptom to be considered present for purposes of psychiatric diagnosis.
- ADHD diagnostic criteria, which should be reviewed in detail. Diagnosis is based on the criteria in the current version of the DSM, presently the 4th edition (Table 31-1).
- Consider that in some cases adjustments may need to be made to these diagnostic criteria:
- The cutoff scores on both symptom lists (6 of 9) were primarily based on children aged 4 to 16 years in the DSM-IV field trial, making the extrapolation of these thresholds to age ranges outside those in the field trial of uncertain validity. ADHD behaviors tend to decline in frequency within the population over development, again suggesting that a somewhat higher threshold may be needed for preschool children (aged 2 to 4 years).
- The majority of the children studied in the DSM-IV field trial were boys. Studies reliably demonstrate that parents and teachers report lower levels of the behaviors associated with ADHD in girls than in boys. It is possible, then, that the cutoff points on the DSM-IV symptom lists, based as they are mainly on findings in boys, are unfairly high for girls. Some latitude should be granted to girls who are close to but may fall short of the diagnostic criteria by a single symptom.
- The specific age of onset of 7 years is not particularly crucial for identifying children with ADHD. The field trial for the DSM-IV found that ADHD children with various ages of onset were essentially similar in the nature and severity of impairments as long as their symptoms developed before ages 10 to 12 years. Thus, stipulating an onset of symptoms in childhood is probably sufficient for purposes of clinical diagnosis.
- The criterion that duration of symptoms be at least 6 months was not specifically studied in the field trial and was held over from earlier editions of the DSM, primarily out of tradition. Some research on preschool children

TABLE 36-1. Summary of DSM-IV Criteria for ADHD

Developmentally inappropriate levels of at least six of more of the following symptoms of inattention that have persisted for at least 6 months:

(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
(b) often has difficulty sustaining attention in tasks or play activities
(c) often does not seem to listen when spoken to directly
(d) often does not follow through on instructions and fails to finish school work, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
(e) often has difficulty organizing tasks and activities
(f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort such as schoolwork or homework
(g) often loses things necessary for tasks or activities (eg, toys, school assignments, pencils, books, or tools)
(h) is often easily distracted by extraneous stimuli
(i) is often forgetful in daily activities

And/or developmentally inappropriate levels of six or more of the following symptoms of hyperactive-impulsive behavior must likewise be present for 6 months:

(a) often fidgets with hands or feet or squirms in seat
(b) often leaves seat in classroom or in other situations in which remaining seated is expected
(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
(d) often has difficulty playing or engaging in leisure activities quietly
(e) is often "on the go" or often acts as if "driven by a motor"
(f) often talks excessively
(g) often blurts out answers before the questions have been completed
(h) often has difficulty awaiting turn
(i) often interrupts or intrudes on others (eg, butts into conversations or games)

Other diagnostic criteria include the presence of some inattention or hyperactive-impulsive symptoms prior to age 7 years and in two or more settings (home and school, for instance) with these symptoms resulting in impairment in major life activities (family, school, peers, community) and not being easily attributable to other mental disorders. The inclusion of the age of onset of 7 years has been challenged as without scientific foundation and can probably be ignored in favor of the more general criterion that the disorder develop during childhood (eg, onset before puberty, ages 12–16 years).

suggests that a large number of 2- to 3-year-olds may manifest the symptoms of ADHD as part of that developmental period and that these symptoms may remain present for periods of 3 to 6 months or longer. Children whose symptoms persisted for at least 1 year or more, however, were likely to remain deviant in their behavior pattern into the elementary school years.

To assist clinicians with the differential diagnosis of ADHD from other childhood mental disorders, a list of differential diagnostic tips appears in Table 36-2. Under each disorder are listed those features that would distinguish this disorder, in its pure form, from ADHD. However, many ADHD children may have one or more of these disorders as comorbid conditions with their ADHD; thus, the issue here is not which single or primary disorder the child has but which other disorders besides ADHD are present and how they affect treatment planning.

Child Interview

Some time should always be spent directly interacting with the referred child. The length of this interview depends on the age, intellectual level, and language abilities of the children. For preschool children, the interview may serve merely as a time to become acquainted with the child, noting his or her appearance, behavior, developmental characteristics, and general demeanor. For older children and adolescents, this time can be fruitfully spent inquiring about the children's views of the reasons for the referral and evaluation, how they see the family functioning, any additional problems they feel they may have, how well they are performing at school, their degree of acceptance by peers and classmates, and what changes in the family they believe might make life for them happier at home. As with the parents, the children can be queried as to potential rewards and reinforcers they find desirable, which will prove useful in later contingency management programs. Examiners must be cautious not to overinterpret

TABLE 36-2. Differential Diagnostic Tips for Other Disorders Compared with ADHD

ADHD, Predominantly Inattentive Type with Sluggish Cognitive Tempo
- Lethargy, staring, and daydreaming more likely than in ADHD, combined type
- Sluggish cognitive tempo/slow information processing
- Lacks impulsive, disinhibited, or aggressive behavior
- Possibly greater family history of anxiety disorders and learning disabilities
- Makes significantly more errors in academic work
- No elevated risk for Oppositional Defiant or Conduct Disorder

Oppositional Defiant Disorder and Conduct Disorder
- Lacks impulsive, disinhibited behavior
- Defiance primarily directed toward mother initially
- Able to cooperate and complete tasks requested by others
- Lacks poor sustained attention and marked restlessness
- Resists initiating demands, whereas ADHD children initiate but cannot stay on task
- Often associated with parental child management deficits or family dysfunction
- Lacks neuromaturational delays in motor abilities

Learning Disabilities
- Has a significant IQ/achievement discrepancy (+1 standard deviation)
- Places below the 10th percentile in an academic achievement skill
- Lacks an early childhood history of hyperactivity
- Attention problems arise in middle childhood and appear to be task or subject specific
- Not socially aggressive or disruptive
- Not impulsive or disinhibited

Anxiety/Affective Disorders
- Likely to have a focused not sustained attention deficit
- Not impulsive or aggressive; often overinhibited
- Has a strong family history of anxiety disorders
- Restlessness is more fretful, worrisome behavior not the "driven," inquisitive, or overstimulated type
- Lacks preschool history of hyperactive, impulsive behavior
- Not socially disruptive; typically socially reticent

Atypical Pervasive Developmental Disorder, Asperger's Syndrome, or Thought Disorders
- Show oddities/atypical patterns of thinking not seen in ADHD
- Peculiar sensory reactions
- Odd fascinations and strange aversions
- Socially aloof, schizoid, disinterested
- Lacks concern for personal hygiene/dress in adolescence
- Atypical motor mannerisms, stereotypies, and postures
- Labile, capricious, unpredictable moods not tied to reality
- Poor empathy, cause–effect perception
- Poor perception of meaningfulness of events

Juvenile-Onset Mania or Bipolar I Disorder
- Characterized by severe and persistent irritability
- Depressed mood exists more days than not
- Irritable/depressed mood typically punctuated by rage outbursts
- Mood swings often unpredictable or related to minimal events
- Severe temper outbursts and aggression with minimal provocation (thus, oppositional defiant disorder is often present and severe)
- Later onset of symptoms than ADHD (but comorbid early ADHD is commonplace)
- Press of speech and flight of ideas often present
- Psychotic-like symptoms often present during manic episodes
- Family history of bipolar I disorder more common
- Expansive mood, grandiosity of ideas, inflated self-esteem, and high productivity (goal-directed activity periods) often seen in adults with bipolar disorder are usually not present; children more often have the dysphoric type of disorder
- Requires that sufficient symptoms of bipolar disorder be present after excluding distractibility and hyperactivity (motor agitation) from bipolar symptom list in DSM-IV before granting bipolar I diagnosis to a child with symptoms of ADHD
- Suicidal ideation is more common in child (and suicide attempts more common in family history)

any informal observations of the child's behavior during this clinic visit. The office behavior of ADHD children is often far better than that observed at home.

Children younger than 9 to 12 years of age are not especially reliable in their reports of their own disruptive behavior. The problem is compounded by the frequently diminished self-awareness and impulse control typical of defiant children with ADHD. Because of this tendency of ADHD children to underreport the seriousness of their behavior, particularly in the realm of disruptive or externalizing behaviors, the diagnosis of oppositional defiant disorder or ADHD is never based on the reports of the child. Nevertheless, children's reports of their internalizing symptoms, such as anxiety and depression, may be more reliable and thus should play some role in the diagnosis of comorbid anxiety or mood disorders.

Parent Self-Report Measures

Child behavioral disorders, their level of severity, and their response to interventions are, in part, a function of factors affecting parents and the family at large. Family studies of children with ADHD clearly demonstrate an increased prevalence of ADHD among the parents of these children (15 to 20% of mothers and 25 to 30% of fathers). Parental disorder can interfere with compliance with treatments for the child's disorder. Separate and interactive contributions of parental psychopathology and marital discord affect the decision to refer children for clinical assistance, the degree of conflict in parent–child interactions, and child antisocial behavior. Assessing the psychological integrity of parents, therefore, is an essential part of the clinical evaluation of children with ADHD, of the differential diagnosis of their prevailing disorders, and of the planning of treatments stemming from such assessments. The DSM-IV symptom list for ADHD has been cast in the form of two adult behavior rating scales, one for current behavior and the other for recall of behavior during childhood, which can be useful for quickly screening parents for ADHD (Barkley and Murphy, 1998). If elevated scores are apparent, consider referring the parent for further evaluation and, possibly, for treatment.

The Pediatric Medical Examination

Most aspects of an adequate medical interview are identical to those described previously for the parental interview. However, greater time will clearly be devoted to a more thorough review of the child's genetic background, pre- and perinatal events, and developmental and medical history, as well as the child's current health, nutritional status, and gross sensory-motor development. The time to listen to the parents' story and the child's feelings and to explain the nature of the disorder is one of the most important things a physician can offer a family. In this way, the evaluation process itself can often be therapeutic. One major purpose of the medical interview that distinguishes it from the psychological interview noted previously is its focus on differential diagnosis of ADHD from other medical conditions, particularly those that may be treatable In rare cases, ADHD may have arisen secondary to a clear biologically compromising event, such as severe Reye's syndrome, an hypoxic–anoxic event such as near drowning or severe smoke inhalation, significant head trauma, or a central nervous system infection or cerebrovascular disease. The physician should obtain details of these surrounding events as well as the child's developmental, psychiatric, and educational status before the event and significant changes in these domains of adjustment since the event. The physician should also document ongoing treatments related to such events. In other cases, ADHD may be associated with significant lead or other metal or toxic poisonings, which will require treatment in their own right.

It is also necessary to determine whether the child's conduct or learning problems are related to the emergence of a seizure disorder or are secondary to the medication being used to treat the disorder. As many as 20% of epileptic children may have ADHD as a comorbid condition and up to 30% may develop ADHD or have it exacerbated by the use of antiepileptic drugs such as phenobarbital or phenytoin (Wolf and Forsythe, 1978). In such cases, changing to a different antiepileptic drug may greatly reduce or even ameliorate the attentional deficits and hyperactivity of such children.

A second purpose of the medical exam is to thoroughly evaluate coexisting conditions that may require medical management. In this case, the child's ADHD is not seen as arising from these other conditions but as being comorbid with them. ADHD is often associated with higher risks not only for other psychiatric or learning disorders but also for motor incoordination, enuresis, encopresis, allergies, otitis media, and greater somatic complaints in general. A pediatric evaluation is desirable or even required for many of these comorbid conditions. For instance, the eligibility of the child for physical or occupational therapy at school or in a rehabilitation center may require a physician's assessment and written recommendation establishing the need.

Although most cases of enuresis and encopresis are not an effect of underlying physiologic disorders, all cases of these elimination problems should be evaluated by a physician before beginning nutritional and behavioral interventions. Even though many of these cases are "functional" in origin, medications may be prescribed to

aid in their treatment, as in the use of oxybutynin or imipramine for bedwetting. Children with significant allergies or asthma require frequent medical consultation and management of these conditions, often by specialists who appreciate the behavioral side effects of medications commonly used to treat them. Theophylline, for example, is increasingly recognized as affecting children's attention span and may exacerbate a preexisting case of ADHD. For these and other reasons, the role of the physician in the evaluation of ADHD should not be underestimated, despite over whelming evidence that by itself attention span is inadequate as the sole basis for a diagnosis of ADHD.

A third purpose of the medical examination is to determine whether physical conditions exist that are contraindications for pharmacologic treatment. For instance, a history of high blood pressure or cardiac difficulties warrants careful consideration about a trial on a stimulant drug, given the known presser effects of these drugs on the cardiovascular system. Some children may have a personal or family history of tic disorders or Tourette's syndrome, which would dictate caution in prescribing stimulants in view of their greater likelihood of bringing out such movement disorders or increasing the occurrence of those that already exist. These examples merely illustrate the myriad medical and developmental factors that need to be carefully assessed in considering whether a particular child with ADHD is an appropriate candidate for drug treatment.

In the course of the physical examination, height, weight, and head circumference require measurement and comparison to standardized graphs. Hearing and vision, as well as blood pressure, should be screened. Findings suggestive of hyper- or hypothyroidism, lead poisoning, anemia, or other chronic illness clearly need to be documented, and further workup should be pursued. The formal neurologic examination often includes testing of cranial nerves, gross and fine motor coordination, eye movements, finger sequencing, rapid alternating movements, impersistence, synkinesia, and motor overflow, testing for choreiform movements, and tandem gait tasks. The exam is often used to look for signs of previous central nervous system insult or of a progressive neurologic condition, abnormalities of muscle tone, and a difference in strength, tone, or deep tendon reflex response between the two sides of the body. The existence of nystagmus, ataxia, tremor, decreased visual field, or fundal abnormalities should be determined and further investigation pursued when found. This evaluation should be followed by a careful neurodevelopmental exam covering the following areas: motor coordination, visuoperceptual skills, language skills, and cognitive functioning. Although these tests are certainly not intended to be comprehensive or even moderately in-depth evaluations of these functions, they are invaluable as quick screening methods for relatively gross deficiencies in these neuropsychological functions. When deficits are noted, follow-up with more careful and extensive neuropsychological, speech and language, motor, and academic evaluations may be necessary to more fully document their nature and extent.

Routine physical examinations of children with ADHD are frequently normal and of little help in diagnosing the condition or suggesting its management. However, the physician certainly needs to rule out the rare possibility of visual or hearing deficits that may give rise to ADHD-like symptoms. Also, on physical inspection, children with ADHD may have a greater number of minor physical anomalies in outward appearance (eg, an unusual palmer crease, two whirls of hair on the head, increased epicanthal fold, or hypertelorism). However, studies conflict on whether such findings occur more often in ADHD, but certainly they are nonspecific to it, being found in other psychiatric and developmental disorders. Examining for these minor congenital anomalies may only be beneficial when the physician suspects maternal alcohol abuse during pregnancy, to determine the presence of fetal alcohol syndrome. The existence of small palpebral fissures and midfacial hypoplasia with growth deficiency supports this diagnosis. Finally, given the considerably greater distress children with ADHD present to their caregivers, their risk of being physically abused would seem to be higher than normal. Greater attention by physicians to physical or other signs of abuse during the examination is therefore required.

The routine examination for growth in height and weight is also often normal, although one study reported a younger bone age in children with minimal brain dysfunction, including hyperactivity. Nevertheless, when a physician contemplates a trial on a stimulant drug, accurate baseline data on physical growth, heart rate, and blood pressure are necessary against which to compare findings from subsequent exams during the drug trial or during long-term maintenance on these medications.

Similarly, the routine neurologic examination is frequently normal in children with ADHD. These children may display a greater prevalence of soft neurologic signs suggestive of immature neuromaturational development, but again these are nonspecific for ADHD. Findings of choreiform movements, delayed development of laterality, fine or gross motor incoordination, dysdiadochokinesis, or other soft signs may suggest that the child requires more thorough testing by occupational or physical therapists and may be in need of some assistance in school with fine motor tasks or adaptive physical education. Children with ADHD may also have a somewhat higher number of abnormal findings on brief mental status examinations or screening tests of higher cortical functions, especially those

related to frontal lobe functions (eg, sequential hand movement tests, spontaneous verbal fluency tests, and go–no-go tests of impulse control). When these are found, more thorough neuropsychological testing may further delineate the nature of these deficits and provide useful information to educators for making curriculum adjustments for these children. In some cases, findings on brief mental status exams may have more to do with a coexisting learning disability in a particular case than with the child's ADHD. When problems with visual–spatial–constructional skills or simple language abilities are noted, they are most likely signs of a comorbid learning disorder. It is often the case that these brief mental status examinations are normal. More sensitive, and lengthier, neuropsychological tests may often reveal deficits not detected during a brief neurologic screening or mental status exam. Even so, the routine use of extensive neuropsychological tests to assess children with ADHD is likely to have a low yield. These tests should be conducted only when there is a question of coexisting learning or processing deficits that requires further clarification. Laboratory studies, such as blood work, urinalysis, chromosome studies, electroencephalograms, averaged evoked responses, magnetic resonance imaging (MRI), single photon emission computerized tomography (SPECT), or computed axial tomograms (CT scans), should not be used routinely in the evaluation of children with ADHD. Only when the medical and developmental history or physical exam suggests the presence of a genetic syndrome or of a treatable medical problem, such as a seizure disorder, would these laboratory procedures be recommended, and yet such cases are quite rare. When children with ADHD are placed on the stimulant drug pemoline (Cylert®), routine liver function studies need to be done at baseline and again periodically during the use of this drug because of an apparently greater risk of hepatic complications from this medication. This is not the case for the more popular stimulants, such as Ritalin®, Concerta®, Metadate® CD, or Focalin® (all are methylphenidate delivery systems), Dexedrine® (dextroamphetamine), and Adderall® or Adderall® XR (mixed amphetamine salts). Blood assays of levels of stimulant medication have so far proved unhelpful in determining appropriate dosage and, therefore, are not recommended as part of routine clinical titration and longterm management of these medications. The use of tricyclic antidepressants for treating children with ADHD, especially those with anxiety or depressive symptoms, requires that a baseline routine electrocardiogram be done and then repeated several weeks after drug treatment has begun because of the greater potential for arrhythmias and cardiotoxicity of these drugs. Whether blood levels of the tricyclics are useful in titrating them for maximum clinical response is debatable, as there is little standardized information to serve as a guide in the matter. With the recent availability of atomoxetine (Strattera®), a selective noradrenergic reuptake inhibitor, and evidence for its near-equal efficacy to methylphenidate in managing ADHD, the use of tricyclic antidepressants for management of ADHD is rightfully declining.

Conclusion

The assessment of children with ADHD is a complex and serious endeavor requiring adequate time (approximately 2 to 3 hours, exclusive of psychological testing), knowledge of the relevant scientific literature, familiarity with differential diagnoses, skillful clinical judgment, and sufficient resources to obtain multiple types of information from multiple sources (parents, child, teacher) using a variety of assessment methods. Telephone contact with a child's teacher should be made to follow up on his or her responses to the child behavior rating scales and to obtain greater detail about the behavioral problems the child exhibits in the classroom. Additional assessment methods may be necessary to screen for any of the comorbid problems often found in conjunction with ADHD in children.

Suggested Readings

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Practitioner and Patient Resources

Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD)
http://www.chadd.org
CHADD's primary objectives are to provide a support network for parents and caregivers; to provide a forum for continuing education; to be a community resource and disseminate accurate, evidence-based information about ADHD to parents, educators, adults, professionals, and the media; to promote ongoing research; and to be an advocate on behalf of the ADHD community.

Attention Deficit Disorder Association (ADDA)
http://www.add.org
ADDA provides information, resources, and networking opportunities to help adults with ADHD lead better lives. The association provides hope, empowerment, and connections worldwide by bringing together science and the human experience for both adults with ADHD and the professionals who serve them.

Council for Exceptional Children (CEC)
http://www.cec.sped.org/
The CEC is the largest international professional organization dedicated to improving educational outcomes for individuals with exceptionalities, students with disabilities, and the gifted. CEC advocates for appropriate governmental policies, sets professional standards, provides continual professional development, advocates for newly and historically underserved individuals with exceptionalities, and helps professionals obtain conditions and resources necessary for effective professional practice.

American Academy of Child & Adolescent Psychiatry (AACAP)
http://www.aacap.org
The AACAP Web site assists parents and families in understanding developmental, behavioral, emotional, and mental disorders affecting children and adolescents.

American Academy of Pediatrics (AAP)
http://www.aap.org
The AAP is committed to the attainment of optimal physical, mental, and social health and well-being for all infants, children, adolescents, and young adults. This site provides general information related to child health, more specific guidelines concerning a pediatric issue, the AAP's many programs and activities, policy statements and practice guidelines, publications, and other child health resources.

Learning Disabilities Association of America (LDA)
http://www.ldanatl.org
The LDA works to educate individuals with learning disabilities and their parents about the nature of the disability and inform them of their rights, encourage research in neurophysiologic and psychological aspects of learning disabilities, create a climate of public awareness, improve regular and special education through collaboration with the U.S. Department of Education and the state departments of education in each state, develop and disseminate an annual legislative agenda, disseminate information widely, provide advocacy information and training, establish career opportunities, and promote education and training on learning disabilities for special education and regular education teachers.

National Institute of Mental Health
http://www.nimh.nih.gov
This Web site provides information to the public, researchers, and clinicians on a range of mental disorders affecting adults and children, including depression, bipolar disorder, schizophrenia, anxiety disorders, eating disorders, suicide that occurs in the context of mental disorders, autism-spectrum disorders, ADHD, and other behavioral conditions that can adversely affect a child's healthy development. Clinicians will find a variety of consensus conference reports and patient education materials. There are also links to other federal government Web sites and resources such as the landmark Surgeon General's Report on Mental Health.

National Dissemination Center for Children with Disabilities
http://www.nichcy.org
This site has information about specific disabilities, early intervention services for infants and toddlers, special education and related services for children in school, resources and connections in every state, individualized education programs, parent materials, disability organizations, professional associations, education rights and what the law requires, transition to adult life, and much, much more.

Chapter 37

Comorbidity and Symptom Mimicry in Attention Deficit-Hyperactivity Disorder: Implications for Assessment and Treatment

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A comprehensive approach to the assessment of children with symptoms of inattention, impulsivity, and overactivity is crucial as various physical and psychological conditions can mimic or co-occur with attention-deficit hyperactivity disorder (ADHD) symptomatology. These factors must be appropriately considered to avoid misdiagnosis and to ensure proper treatment of the full range of problems displayed by the child. This chapter focuses on the issues of mimicry and comorbidity as they relate to diagnosis and treatment planning for children suspected of having ADHD.

ADHD is a chronic, heterogeneous, neurodevelopmental disorder of unknown etiology. It occurs in approximately 3 to 5% of the general population and represents one of the more common reasons children and adolescents are referred to pediatricians, family physicians, pediatric neurologists, child psychiatrists, and child psychologists.

Symptom patterns associated with ADHD are often easily identifiable, owing to the external focus and highly impairing nature of the disorder. However, assessment of ADHD diagnostic characteristics alone may not be sufficient for accurate identification of a child's presenting problems and treatment needs. Children with ADHD symptoms also often display a wide range of co-occurring features and comorbid disorders that may have substantial implications for diagnosis, long-term outcome, and treatment response.

The Issue of Symptom Mimicry

Problems of activity level, impulsivity, and inattention can be caused by various conditions other than ADHD. Although the topography of the behaviors displayed by the child may be similar, the underlying causal factors may differ. These include various psychological disorders, physical illnesses or conditions, and contextual influences.

Both child anxiety and depressive disorders can result in problems in concentration and symptoms of inattention, as well as increased levels of activity in some instances. Less frequently, childhood bipolar disorder, characterized by rapidly shifting moods, reflected in dysphoria, irritability, and manic symptoms, can mimic ADHD symptoms. Indeed, clinical studies have

suggested that hyperactivity is often among the earliest manifestations of pediatric bipolar disorder, thus increasing the risk of misdiagnosis. Likewise, children with histories of physical or sexual abuse or those who have been exposed to parental violence may display posttraumatic stress symptoms, which may be reflected in clinically significant problems of inattention. The behavioral disorganization that can occur in such cases may also result in increased levels of activity that, without adequate assessment, can be confused with ADHD symptoms. Furthermore, with the preschool child, it can sometimes be difficult to distinguish between ADHD and the noncompliant (and seemingly inattentive) behaviors associated with early oppositional defiant disorder. Children of this age may also demonstrate variations in attention and activity level due to their difficulty adapting to the requirements of new, more. structured environments (such as school or day care). Elevated expectations for behavioral control and maintenance of attention, combined with a greater number and diversity of stimuli associated with classroom settings, can pose a challenge to some children. This is particularly the case if the home environment or parental expectations differ meaningfully from that of the school or day care setting. Distinguishing between ADHD, mental retardation, and certain pervasive developmental disorders also can pose a challenge because of the problems of inattention and disorganization of behavior that may be seen in each of these conditions. Appropriate diagnosis in such instances is best accomplished by considering the total clinical picture and contextual influences rather than simply those behaviors commonly seen as core symptoms of ADHD.

Comprehensive assessment of physical conditions and consideration of the child's history is also necessary to appropriately diagnose ADHD and rule out alternative explanations for ADHD-like behavior. Sensory deficits, such as visual or auditory impairments, can result in problems of inattention and behavioral disorganization that can be confused with ADHD symptoms. Medication side effects from drugs, such as phenobarbital and phenytoin, can contribute to problems of inattention and activity level. In addition, although the findings are less clear, there is some clinical evidence that certain asthma medications, such as theophylline, can result in inattention and increased activity. Significant problems of inattention, mimicking the symptoms of inattentive-type ADHD, can also occur in the child with absence seizures or an auditory processing disorder. Likewise, children with resistance to thyroid hormone frequently display a full complement of ADHD symptomatology. One also might include developmental and genetic disorders (eg, fragile X syndrome) and endocrine and autoimmune disorders such as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) among those conditions that can mimic features of ADHD. Finally, children with sleep deprivation may also show signs of inattention during daytime hours.

Although these conditions are not likely to perfectly mimic the developmental history or constellation of symptoms of ADHD, children with these disorders are often referred for evaluation of ADHD. Given that psychological and physical factors, such as the ones cited here, can result in problems of inattention or activity level that can mirror ADHD symptoms, it is clear that such factors must be ruled out before rendering a diagnosis of ADHD. In attempting to make a differential diagnosis, it is important to evaluate possible causal factors, contextual influences, and neuroanatomic and physiologic data, as well as the pattern and severity of symptoms developmentally and across settings.

The Issue of Comorbidity

In the past two decades, there has been increasing focus on defining and evaluating the concept of comorbidity in psychiatric research and practice. Although there have been various definitions offered in the literature, the term is generally used in medicine to refer to the presence of two or more unrelated disorders displayed by the same individual. From a medical epidemiologic perspective, comorbidity has been defined as any distinct disease entity that has existed or may occur during the clinical course of another disease entity. Unlike disorders in the medical arena, where the etiology and pathologic processes of a specific disease entity are often reasonably understood, it has been argued that the use of the term "comorbidity" may not be appropriate with psychiatric disorders, the underlying causal factors of which are often less well understood. Unless the etiology of comorbid conditions is known, it is not possible to determine whether the conditions are, in fact, unrelated.

It is argued that despite attempts to develop reasonably objective classification systems, such as the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders-IV* (DSM-IV), health professionals cannot be certain that individuals meeting diagnostic criteria for more than one disorder actually have unrelated disorders. What appear to be separate disorders may instead be the result of overlapping diagnostic criteria from categorical distinctions between what are thought to be different syndromes but that are really variations of the same underlying condition. Those who criticize the use of the term "comorbidity" in the diagnoses of child and adult psychopathologies have often suggested the use of other terms, such as "diagnostic co-occurrence" or "covariation," to refer to diagnostic overlap at the descriptive rather than pathologic/etiologic level.

Although it should be used with caution in reference to psychopathology, the term "comorbidity" is used for

purposes of the present discussion for several reasons: (1) the term has come to be widely used in the psychopathology literature to refer to instances where individuals with one disorder also meet criteria for another disorder; (2) comorbidity studies of child psychopathology, specifically studies of ADHD, provide data suggesting that evidence of comorbidity is found even when one controls for overlap in diagnostic criteria; (3) recent research findings dealing with issues of family risk provide data that suggest that comorbidities related to ADHD are likely related to factors other than inadequacies of classification; and (4) there are ample data to indicate that children and adults with ADHD with comorbid entities have clinical, demographic, biologic/genetic, and family environmental characteristics that can result in distinctly different clinical course and treatment outcomes than those with ADHD alone.

The following findings regarding comorbidity are relevant to clinical practice:

- Approximately 25% of children with ADHD display a diagnosable learning disability of some sort. Many more show significant school-related difficulties, such as lowered levels of achievement, grade repetitions, school failure, and behavioral problems, that interfere with classroom learning.
- Perhaps as many as 50% of clinically referred children with ADHD show evidence of oppositional defiant disorder.
- Approximately 30 to 50% of children with ADHD go on to display more serious forms of antisocial behavior, consistent with a clinical diagnosis of conduct disorder.
- Between 25 and 30% of clinically referred children with ADHD show evidence of some type of anxiety disorder. This is especially true for younger children and those with ADHD whose problems are primarily reflected in inattention rather than hyperactive/impulsive behavior.
- Of clinically referred children with ADHD, between 10 to 30% are likely to show evidence of some sort of mood disorder (usually major depressive or dysthymic disorder). Although depressive disorders can result from various factors, there is speculation that some child depressive disorders may develop as a result of the social, academic, and other impairment resulting from ADHD.
- Findings regarding comorbidity with child/adolescent bipolar disorder are less clear, although it has been suggested that the degree of overlap between ADHD and bipolar disorder is on the order of 11 to 22%. Those with comorbid ADHD and bipolar disorder show substantially higher rates of early substance abuse problems.

Likewise, children with ADHD have been shown to display comorbid Tourette's syndrome or other tic disorders. Here, the number of children with ADHD who develop Tourette's syndrome is thought to be on the order of 7%. Clinical studies have suggested that 40 to 50% of those diagnosed with Tourette's show comorbid ADHD, with the development of ADHD typically preceding the onset of Tourette's symptoms. Several other clinical characteristics also are correlates of ADHD. Included here are speech and language disorders, as well as delayed motor coordination, frequent somatic complaints, health problems such as upper respiratory infections and allergies, sleep difficulties, and increased risk for accidents of various types. Indeed, it has been suggested that almost 50% of children with ADHD can be considered accident-prone. As many as 15% of children with ADHD experience multiple serious injuries, and as many as 20% experience accidental poisoning.

Patterns of correlates and comorbid conditions also differ as a function of ADHD course and characteristics. Children with inattentive-type ADHD are more likely to display internalizing symptomatology, learning disorders, and speech/language problems compared with those with hyperactive/impulsive or combined subtypes. Furthermore, children with early onset ADHD tend to display more comorbid aggressive symptoms, whereas those with later onset ADHD are more likely to have comorbid anxiety or depressive conditions. Comorbid conditions may differ across the lifespan as well, with certain disorders such as substance use disorder emerging more during adolescence and early adulthood.

Although many questions remain to be answered, it is clear that the issue of comorbidity is an important one for understanding, assessing, and treating children with ADHD. Indeed, as indicated above, there is evidence that many children with ADHD also display a wide array of comorbid conditions and other clinically relevant characteristics. Many children show more than one comorbid disorder, with the presence of comorbid disorders increasing during the adolescent years. These comorbid features have important implications for assessment and long-term outcome. Comorbid disorders may complicate the clinical presentation of ADHD symptoms. For instance, children with comorbid anxiety and ADHD tend to be less impulsive than those with ADHD alone. Children who display comorbid features often show more serious levels of impairment, are more likely to have longstanding problems (including substance use disorders), often have a poorer prognosis, and tend to show a greater use of healthcare services than do those without comorbidity.

Implications for Assessment and Diagnosis

Diagnosing ADHD and confirming the presence of comorbid conditions may require a comprehensive and detailed psychological or psychiatric evaluation. However, it is possible for primary-care physicians to appropriately

assess for the presence of ADHD and screen for other psychiatric conditions that a child may display. Screening data can be obtained either via interview or through the use of various, relatively brief, parent- child-, and teacher-report measures. Here, clinical practice guidelines for the evaluation of children with Attention Deficit/ Hyperactivity Disorder, such as those provided by the American Academy of Pediatrics, can serve as a useful framework for multimodal assessment.

Clinical Interview

A wealth of information can be obtained through an interview with the child and his or her parents or caretakers. Here, questions related to the child's functioning across domains such as school (eg, standardized test results, current grades, and teacher reports of inattentiveness, overactive behavior, and overall school performance), home (eg, attention/activity level, adjustment to routines, family interADHD actions), and social settings (eg, social adeptness, withdrawal, aggressive behavior) can provide valuable diagnostic information. A useful approach for obtaining information regarding the presence of both ADHD and other comorbid conditions can be patterned after any of several structured interview formats that have been developed for diagnosing child psychopathology (eg, Diagnostic Interview Schedule for Children, Anxiety Disorders Interview Schedule for Children, IV). These offer clinicians the opportunity to screen for psychiatric problems specifically based on DSM-IV diagnostic criteria as well as gather relevant developmental, psychosocial, and physical history.

Checklists

Other useful screening methods involve the use of parent report and teacher-report checklists that can provide information regarding symptoms of ADHD and conditions that often co-occur with or mimic ADHD symptoms. Examples of commonly used checklists of this type include the revised Conners' Parent Rating Scale (CPRS-R:L), the Conners' Teacher Rating Scale (CTRS-R:L), Behavior Assessment System for Children (BASC and the Child Behavior Checklist (CBCL). The CPRS-R:L is an 80-item parent-report measure that provides information regarding child behavior that is reflective not only of ADHD symptomatology (hyperactivity, impulsivity, and inattentiveness) but also of cognitive problems (which may suggest lowered intelligence or school-related difficulties, such as learning disabilities), anxiety, emotional lability, oppositional behavior. Of special note is the fact that the Conners' rating scales provide measures that are specifically reflective of DSM IV Hyperactive-Impulsive and Inattentive symptoms. The BASC is an objective parent-report measure that provides scales assessing hyperactivity and attention problems as well as measures of aggression, conduct problems, anxiety, depression, atypical behavior, withdrawal, and adaptive behavior. The CBCL (113 items) is an additional parent report measure that provides information regarding possible comorbidities. Among the CBCL scales are those reflective of attention problems, social problems, somatic complaints, anxiety/depression, withdrawal, thought problems, and oppositional/aggressive and conduct-disordered behavior. Teacher-report versions of each of these measures are also available. Given that child behavior often varies across situations, obtaining data from multiple informants in different settings can provide a more accurate picture of a child's clinical symptoms and associated levels of impairment than can be obtained from parent ratings alone. Child/adolescent versions of the Conners, BASC, and CBCL are available as well. These may be particularly useful in those cases where the child is suspected of having a comorbid anxiety or depressive disorder as children are thought to be more accurate reporters, than parents and teachers, regarding the presence and severity of internalizing problems.

Although interview data and measures such as these, used alone, are not always sufficient to make a definitive diagnosis of ADHD and certain comorbid conditions, they are frequently useful in providing the clinician with data that can be of value in diagnostic and treatment decision making. In other instances, this type of screening information can be of value in deciding whether a referral to other professionals may be necessary.

There are some cases where screening data are ambiguous, where time constraints or other factors (eg, a parent who is a less-than-adequate informant) do not permit clear conclusions to be drawn regarding the presence or absence of ADHD and comorbid features. In these sorts of situations, it may be useful to refer the child for full psychological evaluation so that a more comprehensive approach to assessment can be undertaken. The psychological evaluation of a child with ADHD may vary in complexity, depending on the case, and typically includes using multiple sources of information. The assessment will usually consist of a review of available records (eg, educational, medical) to capture information about prior functioning and interventions and accommodations previously used, as well as the onset and course of presenting problems. A developmentally oriented parent interview is also generally conducted. This interview is usually designed to obtain information about family medical and psychiatric history, pregnancy and birth complications, alcohol, tobacco or drug use during pregnancyearly illnesses or injuries, the age at which developmental milestones were met, early child temperament the nature of family and peer relationships, the child's academic functioning, the range of problems displayed (eg, problems of activity and inattention, other disruptive

behavior problems, symptoms reflective of anxiety or mood-related difficulties), variability of problematic behavior across settings, and factors that might contribute to these difficulties. It is important for the clinician to obtain interview data that may shed light on the extent to which the child displays symptoms of ADHD and assess for clinical characteristics that may signify the presence of comorbid conditions. The parent interview is usually supplemented by an age-appropriate interview with the child.

Interview findings may be supplemented by psychological testing to further rule out the presence of features that may mimic ADHD symptoms and further assess for comorbid features. Testing can also help to answer questions posed by parents or the referral source and to address other clinically relevant issues raised during the course of the evaluation. Here, testing can include individually administered measures of intelligence, academic achievement, and processing measures (of value in assessing children suspected of having intellectual deficits or learning disabilities), as well as a range of personality assessment measures.

Included here are parent-report measures, such as those discussed earlier, that assess for ADHD symptoms as well as possible comorbid conditions. These measures are usually supplemented by assessment data obtained from teachers and others familiar with the child, as well as by direct observation of the child's behavior. Commonly, the child may be administered computerized measures of attention and impulsivity to supplement parent and teacher ratings. In general, the focus of assessment is on obtaining data from multiple methods and multiple sources that address the diagnostic requirements of ADHD and consider the full range of possible comorbid features and conditions that can mimic ADHD symptoms. A comprehensive ADHD evaluation will also assess the extent to which the child displays evidence of impairment in areas such as school/academic, family and social functioning. Material in the Pelham et al. article, listed in the suggested readings, reviews available evidence-based measures of impairment. It should be emphasized that an assessment of impairment is an essential aspect of a comprehensive evaluation, as treatment should not be limited simply to symptom reduction but should also target impairments in family, school, and social functioning that are likely to be associated with negative long-term outcomes.

Again, the extensiveness of the evaluation will vary, depending on the complexity of the case. The assessment of a child who demonstrates symptoms only of ADHD may be relatively straightforward (and, indeed, may be dealt with directly by the primary-care physician), whereas the evaluation of a child with multiple presenting problems may, of necessity, be much more detailed in nature. In these more complicated cases, where the results of a comprehensive assessment highlights the presence of relevant comorbid features, assessment data can be very useful in planning efficient and effective approaches to intervention.

Implications for Treatment

Given the assumption that proper assessment should lead to optimal treatment, it follows that treatment planning for children with ADHD should address the full range of problems highlighted by the assessment findings. Here, assessment includes both the identification of comorbid conditions as well as a detailed examination of relationships among these conditions and relevant associated factors.

For children with ADHD and other comorbid conditions, simply treating symptoms of ADHD is not enough. Appropriate case management involves addressing the full range of clinical problems displayed. For example, in instances where a child not only shows characteristics of ADHD but also meets diagnostic criteria for oppositional defiant disorder and learning disability, treatment should focus on problems associated with each of these three areas. This might involve pharmacologic treatment for dealing with the child's hyperactive/impulsive and inattentive behaviors, parent-oriented behavior management approaches to assist parents in modifying oppositional behavior, and employing special education interventions and classroom accommodations to assist the child academically. Likewise, in the case of a child who has ADHD and major depressive disorder, it will be important to treat both ADHD symptoms and depressive features. Current clinical practice guidelines suggest that, if depressive features are especially severe, it may be necessary for this to be the initial focus of treatment. In cases where the depression is less severe, a trial on stimulants may be an appropriate first step. If depressive symptoms remain after a course of stimulant drug treatment, cognitive-behavioral therapy, interpersonal psychotherapy, and antidepressants may then be used in treating the child's depressive symptoms. Similarly, in the case of the child with ADHD and comorbid Tourette's syndrome, it will be necessary to develop a treatment approach that addresses both classes of symptoms. In such cases, proper treatment can sometimes represent a clinical challenge, as stimulant drugs, often found useful in treating ADHD, can sometimes exacerbate Tourette's symptoms (especially at higher doses). Although the use of stimulants with children displaying Tourette's syndrome or other tic disorders was once seen as something to be avoided, stimulants are no longer thought to be strictly contraindicated in treating ADHD symptoms in children with tic disorders. In such cases, if tics become more pronounced with initial stimulant drug treatment an alternative stimulant may be tried. If stimulants are found to be useful in controlling ADHD symptoms but tics continue or worsen, the use of an alpha agonist such as clonidine or guanfacine is often used in tic management. In some cases,

alpha agonists are considered first in treating children with comorbid ADHD and Tourette's syndrome if tics are severe.

The nature of the relationship between ADHD and comorbid conditions is also important to consider when developing treatment goals. Some comorbid conditions, although not resulting directly from ADHD, may be related to the natural consequences of ADHD-related problem behavior. For instance, in some cases of comorbid depression, depressive features can result from increases in negative responses from peers and adults who witness or experience a child's ADHD-related behavior or behavior resulting from comorbid conditions. In such instances, it is possible that the amelioration of ADHD symptoms may lead to more positive social interactions, and, in turn, support improvements in depressive symptoms without targeting depression directly. Alternative treatments of depression (see above) may be required when the child's depression results from other factors. As can be seen, effective treatments for children with ADHD and associated comorbidities are likely to be multimodal and multidisciplinary in nature with evidence-based psychosocial treatments often being particularly useful in treating comorbid conditions and addressing areas of impairment and necessarily more extensive and complex than treatments for children with "uncomplicated" ADHD.

In all cases, successful treatment of ADHD requires an understanding that the disorder is chronic and, thus, not curable. As such, effective interventions address ADHD symptoms in conjunction with any comorbid disorders that are present and focus on the long-term management of the disorder. It is important to note, however, that the specific symptoms of ADHD may change as a function of developmental factors and situational contexts. Furthermore, symptoms associated with certain comorbid conditions may be more transient in nature and more responsive to certain treatments than others. Consistent assessment and monitoring of a child's presenting problems is a necessary aspect of any successful treatment.

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Practitioner and Patient Resources

Children and Adults with Attention-Deficit Disorders (CHADD)
499 N.W. 70th Ave., Suite 101
Plantation, FL 33317
Phone: (800) 233-4050
http://www.chadd.org
Founded in 1987 by a group of concerned parents, CHADD works to improve the lives of people with attention-deficit hyperactivity disorder through education, advocacy, and support. Working closely with leaders in the field of ADHD research, diagnosis, and treatment, CHADD offers its members, and the public, information they can trust.

National Resource Center on ADHD
8181 Professional Place, Suite 150
Landover, MD 20785
800-233-4050
http://www.help4adhd.org
A joint venture of the Centers for Disease Control and C.H.A.D.D., the National Resource Center on ADHD is a clearinghouse to disseminate science-based information on ADHD. Information is available online, as well as from a comprehensive library of books, journals and reports housed in the home office. The center also provides numerous fact sheets on all aspect of ADHD. Overall, this center is an excellent information source for both parents of children with ADHD and professionals working in this area.

Chapter 38

Attention-Deficit/ Hyperactivity Disorder Psychosocial Intervention: Parent Training and Social Skills Training

Thomas A. Blondis, MD

Kerry Brown, PhD

Attention-deficit/hyperactivity disorder (ADHD) (combined type, predominantly inattentive type, and predominantly hyperactivity-impulsivity type) are neurodevelopmental and neurobehavioral disorders that impair executive function, self-regulation, and in some cases inhibition. These impaired neural processes may lead to childhood academic underachievement, rule-breaking behavior, adaptive behavior delays, and a failure in communicative output. At least one major behavioral dysfunction must be present in order to be this disorder.

ADHD is a chronic disease that presents during childhood and requires child and parent teaching, psychopharmacologic titration, organizational training, output intervention, educational modifications, and parental and educational behavioral modification during childhood. Compliance with those who participate in management is essential to successful performance and an ADHD person's ultimate successful independent living. Comorbidities constitute a significant aspect of the morbidity. Learning disabilities, oppositional defiant disorder, and overanxious disorder of childhood are the most frequent co-occurring conditions.

The National Institute of Mental Health (NIMH) Multimodal Treatment Study (MTA) is a long-term study of ADHD that began in 1997. The study design randomized ADHD patients into one of four groups of intervention: (1) community treated, (2) comprehensive psychosocial treatment (CPT), (3) rigorously controlled medication regimen (RCMR), and (4) a combination of CPT and RCMR. Data from the first 14 months of the MTA study showed that medication alone was enough to alleviate the core behavioral symptoms of ADHD. However, if one looked at the dysfunction produced by the core behaviors, then CPT and RCMR was the superior intervention. Medication lost some of its efficacy for decreasing core symptoms after 24 month data were analyzed. According to presentations since this, psychosocial interventions have proved to be very important in overall function and parent-child interactions.

The CPT arm of this study consisted of 35 sessions of group and individual parent training (PT); an intensive, child-focused 8-week summer treatment program that stressed social interaction and communication; 12 weeks of a half-time paraprofessional aide in the school classroom; and school-based teacher consultation, all delivered in a

coordinated and comprehensive manner. The cost of this approach is not practical. However, the cost of PT, social skills training, and educational intervention is not nearly as expensive.

Parenting the ADHD child is a major burden, requiring significant effort and time. During childhood, the competent parent of an ADHD child participates in home management, school management and system, and outside programs that can improve parent management and child success. This task is monumental for families in which both parents work or in which one or both of the parents also have ADHD. If the parent also has ADHD, adult treatment may be required to achieve competent parenting. Every effort should be made to find a PT for the family.

PT

PT is an effective treatment for the reduction of parent-child conflict, child defiance, and disruptive behavior that may result in conduct disorder. Clinical research shows variability across studies because of different populations and measures. Reviews have tended to be optimistic but not definitive about the efficacy of PT. PT has produced changes in child behavior, and in various ways, it has improved parent and family functioning. PT has improved parent self-esteem and decreased parent stress.

Four different behavioral approaches for the management of ADHD have undergone empirical investigation: (1) clinical behavioral therapy; (2) direct contingency management, (3) cognitive behavioral intervention, and (4) intensive, packaged behavioral treatment.

PT Sessions

Most PT programs consist of eight to 10 sessions. Table 38-1 depicts the general issues covered during each session. The goal of PT is to interrupt disrupted parenting, which can lead to child defiance and social aggression, family stressors, and further an ADHD temperament.

During the initial session, the clinician must be brief and clarify what pertains to the general population of ADHD. If comorbidity is discussed, parents may infer that their child is doomed to a life filled with failure. The parents should learn that the outcome is determined by a large number of factors, of which ADHD is one of many features. The session is improved if the parents have an opportunity to ask questions and voice their emotional reactions to the lecture format. The clinician discusses Web sites and texts that can help the parent to further their knowledge. In some cases, a videotape is available to help parents deal with guilt, anger, and sadness.

During the second session, parents learn about factors that can contribute to the ADHD child's ongoing difficulties. These include child characteristics, parent characteristics and stresses impinging upon the family, and parenting styles. Some parenting styles may include harsh criticism, and sometimes the style is inconsistent. In this session, the parents learn about general behavioral management. Different types of positive reinforcement, ignoring, and punishment strategies are discussed. These are outlined in the section "Behavioral Modification" of this chapter.

TABLE 38-1. Parent Training Sessions

Session	1—Orientation and ADHD general information
Session	2—Parent-child relations
Session	3—Improving attending skills
Session	4—Extending attending skills and improving child conditions
Session	5—Establishing a home token/point/or allowance system
Session	6—Response cost method of punishment
Session	7—Using time-out
Session	8—Behavior in public places
Session	9—School issues and fading
Session	10—Booster session

ADHD = attention-deficit/hyperactivity disorder.

Adapted from Anastopoulos step parent training program.

The third session focuses on parent-child interactions. Many parents try to avoid interacting with their ADHD child due to the child's resistance. In this session, the leader stresses the need to attend positively to the individual of all ages. The child often becomes negative if the parents adopt at directive, corrective, intimidating, and unhelpful parenting style. Parents are asked to create a special time, which encourages quality time with the child during which they remain nondirective and do not correct their child. They are encouraged to catch their child doing a good job and showing concern.

During the fourth session, parents are taught how to use positive attending strategies. Parents are taught how to increase independent child play while they engage in home activities. They learn that they need to define request situations that lead to better compliance. Parents need to recognize compliance when it does occur. The clinician points out the need to pay positive attention to children when they are compliant.

The fifth session teaches parents to set up a home token, allowance, or point system to reward their children for good performance and good behavior. In the Anastopoulos system, parents generate a list of daily, weekly, and long-range privileges that are interesting and motivating to their child. They also make a list of regular chores to do; household rules that parents would like them to follow. When they return home they can formulate a contract with their child, which allows for child's input. Parents should reward their children a percentage of a maximum sum of points, tokens, or allowance that is setup. In the case of points or

tokens, a menu of motivating privileges, toys, rental games, movies should be formulated by the parents. Awards occur on a weekly basis, and bonuses can be awarded for good grades and quality homework. Some parents will say that they have used reward systems before and it does not work. This is faulty thinking, and it may lead to a weak attempt to try the reward system again. A good clinician should use cognitive therapy to dispel the parents' misconception.

The sixth session reviews and evaluates the parents their attempt to create the token system. There are inevitably problems that arose, and the session helps parents to clarify what went wrong or resolve any confusion. After this discussion, the parents learn that they can deduct points, tokens, or allowance for noncompliance. So not only does the child fail to earn points but also loses points for noncompliance. If the child expended minimal effort to earn the points the week before, then the response cost often increases that overall level of compliance with parental expectations.

The seventh session again reviews the home token system with the parents. The clinician begins discussing "time-out." This is used for serious types of noncompliance or aggressive behavior. The parents learn the mechanics of carrying out a time-out. Parents learn that (1) the child must serve a minimum amount of time (generally minutes per year of age is used to set the minimum time), (2) the parents do not explain why the child is receiving a time-out, (3) the parents only go back to the time-out area when the child violates the time and must redo the time-out in a menacing way. Once the time-out has been completed, the parent reissues the command or request that led to the time-out.

In the eighth session, attention is directed to behaviors outside of the home. Settings that tend to be difficult for the parent include grocery stores, other large stores, department stores, malls, restaurants, theaters, and churches. Parents must review their expectations before going out to these stores with their children. They must specify the consequences of breaking the behavior that they have outlined.

The ninth session deals with school issues. In this session, the parents learn about their child's rights. The "Other Health Impaired" classification covers ADHD children under The Individuals with Disabilities Education Act. Parents learn that classroom modifications are guarantied by the Rehabilitation Act, Section 504. They learn about Specific Learning Disability intervention, and what special education provisions are available for learning disabled children. Parents are strongly encouraged to work with school personnel in as collaborative and cooperative manner as possible. During the ninth session, parents also learn about the daily report card system, in which home-based consequences are setup based upon written daily feedback from the teacher. On the basis of the teacher daily report card, points, tokens, or money can either be rewarded or lost depending upon performance. Teachers may use the card to let parents know about a new long assignment and the due date.

During this session, parents also discuss problems they have had dealing with the teachers and with the school. If they have tried to work with the school in a co-operative manner and if the school has been resistant to all their efforts, they are advised of their right to mediation and due process if necessary. The final part of this session deals with termination issues. This may include agreeing to a booster session date or adding a medication session.

Behavioral Modification

Behavioral modification is a methodology used to change behaviors targeted by the neurodevelopmental pediatrician, psychologist or social worker, and the parents. The premise holds that if a targeted behavior (TB) draws parental or teacher attention and rewards, the person will perform the TB more often. It is wise to begin a program by writing a contextual contract with the child. Routine is a key element to success (eg, children in the family spend a half hour after dinner doing designated home chores).

PT is essential to achieving effective behavioral therapy, and it becomes more difficult when the parent has adult ADHD. It is essential that parents attend all meetings and do the homework required to be competent in behavioral management and to maintain parent interventions. Thus, a major factor limiting the success of PT is poor group attendance, which is more of a problem among disadvantaged, socially isolated, single-parent families, or when one or both parents have psychopathologies (ADHD, depression, and anxiety). The studies that have been completed regarding this issue indicate that two keys to parenting an ADHD child are reordering the family environment to make possible the external behavioral therapy through gradual internalization of targeted goals and altering neurobiological characteristics with medication. Recent studies also demonstrate that this may require more than many families are able to provide.

Parents who participate in management and meet compliance requirements learn to identify and discuss the consequences of obvious errors through the use of videotaped models. Parents suggest alternative strategies they find more suitable and explain why they prefer the strategy over one that has been suggested. The proposed solution is modeled by group leaders, and parents practice skills through both role play and homework exercises. This particular program has been outlined by Cunningham (1993, 2006). It is similar to other PT programs, but the process relies less on instruction and more on collaborative problem solving. The uniqueness of each participating family must be respected so that all parents play an active role.

TABLE 38-2. Components of Behavioral Modification

Component	Usage	Elements
Positive feedback	To be used whenever a positive target behavior occurs.	A positive statement Specific statement indicating what was done appropriately. Statement is made immediately after the behavior. Statement is true.
Ignore-attend-praise	Used when one or more groups are engaging in inappropriate behavior (useful when "attention getting" behavior is exhibited).	Ignoring the child behaving inappropriately. Attending to child behaving appropriately. Praising child behaving appropriately. Praising misbehaving child when appropriate behavior is resumed.
Teaching interaction	Used to correct child who is behaving inappropriately and child who has not learned part of a skill. It is used to have the child practice an appropriate alternative or practice the part of the skill that was missing.	Interrupt inappropriate action or make a positive statement related to the situation. Ask the child for an alternative way of behaving. If child is unable, verbalize or model alternative behavior or missing step of skill. Have the child practice the appropriate behavior or skill. Give the child positive feedback for improvement. Give the child homework to practice appropriate behavior or skill.
Direct prompt	Procedure used for highly disruptive behavior when the ignore-attend-praise has not worked.	Isolate the child from group or playing area. Use a calm voice and direct eye contact. State the expected behavior. Watch for appropriate behavior. Praise the behavior when identified.
Sit-and-watch procedure	Technique used for highly disruptive behavior used when children have become aggressive or distructive.	Remove child from the group for 2 to 5 minutes (time-out). Totally ignore child. Admit child back to the group only if he behaves quietly.

Techniques of Behavioral Modification

Principal behavioral techniques use is outlined in Table 38-2, along with the components of each technique. These include (1) positive feedback, (2) ignore-attend-praise, (3) teaching interaction, (4) direct prompt, and (5) sit-and-watch procedure. These are taught during all behavioral therapy training. Table 38-2 is inserted as a reference point for the following text.

Positive feedback should be used frequently, whenever the TB occurs. At the moment TB occurs, the parent makes a positive statement. This should be a specific statement indicating that the specific behavior was done appropriately. No behavior that was done close to TB or was merely an attempt receives a positive statement. When it does achieve the level of TB, the parent would say, "Rich, you did a good job tonight, the fact that you completed all of your homework without any help was excellent."

Ignore-attend-praise is a technique used when someone in a group is engaged in negative behavior, which usually is "attention-getting" behavior. The use of this method includes several steps. The parent ignores the child behaving inappropriately, praises the child behaving appropriately (if that child is nearby), praises the misbehaving child when appropriate behavior resumes. For example, Sean starts talking to Brandon. Brandon stops talking to Sean because he has homework to do and not a lot of time to do it. The parent can praise Sean for stopping and resuming what he needed to do.

If the ignore-attend-praise technique fails, the parent should use direct prompting. The parent should not be negative in his or her response. The child will interpret a negative tone as "nagging." The parent should make direct eye contact and say in a cool but firm voice, "You know what you have to do Steve." When Steve gets up to take care of his responsibility, the parent thanks him.

The parent is teaching interaction when he/she intervenes to correct a child who missed a step in a problem or is really misbehaving. The parent interrupts the offensive behavior by stopping the child's behaving, indicating an alternative way of behaving, and then having the child practice the alternative. The parent makes positive statements at the time of the misbehavior. For example, if a child interrupts the parent's conversation, the parent can say, "son, I understand you have something to say-hold that thought." Later, the parent can commend him for delaying and tell him that he wants him to practice holding his thoughts until the other person finishes their thought.

Incidental teaching refers to techniques that the parent can be taught during involvement in the parent group. Emphasis is always on ignore-attend-praise, teaching interaction, and direct prompting. The parent should be expected to describe the techniques, which involves memorization of the technique's component. The parent is taught decision making by determining which strategy fits the situation. Parents role play the techniques with a partner who plays the child. It is important for the parent to have the child practice self-monitoring and self-evaluation. To start this practice is by writing a contextual contract with the child that includes the TB and tokens earned. This approach puts parents in a better position to obtain the correct response when the opportunity for directed self-monitoring and self-evaluation arises.

PT should also teach parents how to structure the home in order to improve ease of work and avoidance of conflicts. Initially, the parent must be involved during the meetings to supervise the play during role playing. Through this mechanism, the parent needs to see that as time goes on they need to withdraw supervision.

PT also focuses on the social life of the ADHD child. If the child has a difficult time making a good friend, then the parent should seek to find a child that might have similar interests. At school, sometimes the teacher can help the parent pick out a child who would be a good match. Parents need to foster their child's social life at home and finding a child who bonds well with their ADHD child is very important. They should focus on social groups in which their child feels comfortable.

In short, parents need to become a case manager for their ADHD child. They need to understand the neurobiological aspect of the disorder that makes it a chronic disorder and not a problem that can be completely fixed. They will need to offer support to the child throughout childhood and through adolescence. Renewing contextual contracts through early elementary and middle childhood should be pursued if this was helpful initially. This needs to be transformed to expectations during adolescence. Physicians need to remind parents that behavioral treatment can be tedious (especially for working parents), but that positive outcome is dependent upon the investment they make into management.

Social Skills Training

Clearly, many children with ADHD have deficits in social skills, and these are among the more difficult of their problems to treat. Scientific investigations have shown that rejection by peers remains stable across time even when children with ADHD make behavioral improvements. Peers then form negative attitudes and continue to reject the child who has ADHD on the basis of his or her initial "bad" or "spacey" reputation (Pfiffner et al., 1997; Pelham et al., 1998).

The child with ADHD, combined type tends to be rejected by peers, whereas the child with ADHD, predominantly inattentive tends to be ignored by most peers. The rejection of the child with ADHD, combined type occurs when the child attempts to socialize but becomes disruptive and sometimes aggressive. The child with ADHD, predominantly inattentive type is not aggressive and many times is too passive and withdrawn when peers neglect him or her. Sometimes these children are bullied, tricked, and teased by several of their peers. Generally, these children have slower cognitive tempo and suffer from delays in skills that many cause them to be inhibited when engaging in activities that require confidence and speed. Less research has been done regarding social skill failures of children with ADHD, predominantly inattentive type and also with girls who have ADHD.

Medication has been shown to improve social skill interventions by decreasing disruptive and aggressive outbursts, and in some cases, improving the child's social standing. However, medication does not have a normalizing effect on social behavior, and some children with ADHD actually show social withdrawal while receiving stimulants. Medication also does not indirectly improve social skills if the parents' child has substantial social deficits. In some cases, medication improves the output of children with inattentive-type ADHD and this greatly relieves school anxiety. Children with substantial social skill deficits often have generalized anxiety and struggle throughout childhood.

Research of direct social skills training with children who have ADHD has been modest. Generalization of social skills has been a major problem. However, investigation of newer broad-based social skills training has been encouraging. In order to improve the child's social skills, Pfiffner has developed a broad-based social skills training program for the ADHD patient that targets teaching the children those social skills that they have not developed. It is built upon the understanding of verbal and nonverbal social cues. It promotes generalization by incorporating parents, teachers, and other caretakers.

In a study that produced large effects, children assigned to the parent-generalization group received concurrent sessions with parents, wherein the parent and clinician discussed the importance of social skills and social status. The parents' role was to help their child improve peer relations. Both the social skills training group without parent-generalization group involvement and the parent-generalization group demonstrated improvement on parent reports of social interaction and home behavior problems. The parent-generalization group showed some generalization in the school setting, which was maintained the following school year with new teachers.

The program encompasses the modules listed in Table 38-3. Teaching includes didactic instruction, symbolic

TABLE 38-3. Modules of Social Skills Treatment

Module	Components of Module
Good sportsmanship	Following Directions Participating and staying in game Following game rules Sharing and encouraging teammates Being polite to players from the opposing team
Accepting consequences	Accepting negative consequences without loss of control Ability to reflect upon cause of consequence Resolution to avoid cause of consequence in the future
Assertiveness	Distinguishing among passive, aggressive, and assertive responses Using assertive communication
Ignoring mild provocation	Inhibiting verbal reactions Inhibiting nonverbal interactions
Problem solving	Identifying and solving a problem Use of a five-step approach to problem solving
Recognizing and dealing	Identifying feelings in others with feelings Dealing with anger

Adapted from Pfiffner et al. (2000).

role playing, behavioral rehearsal, and modeling. A response/cost-based point system is implemented to address behavioral concerns during the group. Children's points are exchanged for child-selected activities when the formal session is concluded. Parents review the teaching that their children received throughout these modules.

Parents can be taught to support their child's social development by planning and organizing their child's social life outside of school. For example, to develop friendship skills, parents might identify children who are good "play dates" matches for the child and obtain suggestions from teachers. Initially, the parents are advised to be involved during the "play dates" to supervise the play, with the idea that as success occurs they can withdraw this supervision. A proactive stance on the part of the parent in helping the child plan the "play date" activities is important for facilitating the success of the get-together.

Comorbidities

PT and social skills training may not be appropriate in cases in which the child has a significant generalized anxiety disorder, dysthymia, comorbid bipolar disorder, or conduct disorder. In these cases, counseling, medication therapy, and therapeutic school may be the first step toward habilitation. Obviously, the parent can still benefit from PT, and if it is possible, the parent should receive this training. In some cases, the PT takes place in conjunction with social skills training, and in this case, it may be better for the parent to wait for the ADHD child to overcome their associated disability before entering into PT coupled with social skills training. The parent still can attend Children and Adult with Attention Deficit Hyperactivity Disorder (CHADD) local chapter parent sessions and also informational sessions given by community psychiatrists, psychologists, developmental pediatricians, pediatric neurologists, and social worker.

Although the cognitive-behavioral approaches have worked for some disorders (eg, generalized anxiety disorder), the most rigorous of studies that include PT and teacher training fail to support their efficacy for children with ADHD. This methodology teaches verbal self-instruction, problem-solving strategies, cognitive modeling, self-monitoring, self-evaluation, and self-reinforcement but does so outside the realm of social development. Investigations point to two reasons why this may be the case: (1) children with ADHD (on medication) have problems applying more complex tasks that demand a more active working memory to their everyday life and (2) these children perform poorly under conditions of inconsistent (partial reinforcement). Investigations of the use of cognitive-behavioral approaches have to date not looked at its whether or not it might be more beneficial for ADHD adults.

Lack of PT and Social Skill Programs

Obviously, the pediatric neurologist and the pediatric neurodevelopmental disability professional do not have time to be the clinician for a PT program or social skills program. If they have the professionals working with them as a part of their practice, this could be developed. However, if they want to refer for these services, they will very often not find such services in their community or neighboring communities.

Charles E. Cunningham has proposed and instituted the "COPE" model to hopefully create more PT and social skills training programs. This is a large-group, community-based, family-centered PT model. His model is a 10-session workshop for parents of 4 to 12-year-old ADHD patients. The sessions are almost identical to the sessions that we have reviewed in this chapter. However, the structure of large-group sessions is different. Such large groups would increase the availability of PT for parents of ADHD children. Conducting his COPE groups in accessible community locations, scheduling groups at convenient times, and offering a children's social skills activity group would increase utilization by family and parents with ADHD children with more severe problems, cultural minority families, and disadvantaged families. This is a major public health need in our society for such a prevalent chronic disease as ADHD.

Conclusions

The MTA and other studies have now concluded that a comprehensive psychosocial intervention is needed for ADHD patients and their families. The model used by the MTA group is too expensive and would not be covered by insurance companies. Most families would have a difficult time paying for this out-of-pocket. However, PT is an effective treatment for the reduction of parent-child conflicts, child defiance, related disruptive behavior, and the functional development of the ADHD child.

PT definitely adds benefit to medication treatment and can be great resource especially for families or low socioeconomic status and families of children who have ADHD and are at-risk or have comorbidities. It can also be a resource to help parent's foster adaptive and social growth to ADHD children. ADHD adults who do not succeed generally become Antisocial Personality Disordered people. PT and social skills training coupled with counseling psychology and medication has the greatest chance of helping ADHD children to avoid such a negative outcome. The road to parenting successfully an ADHD child is an effortful job. Two parent families that participate will in most cases make parenting less arduous. Parent burnout and parental discord make habilitation ever more problematic. Physicians need to recognize this and help families to secure these services.

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Resources

Agencies:
CHADD
<http://www.chadd.org>
ADDA
<http://www.adda.org>
The ADD Warehouse
1-800-ADD-WARE

Chapter 39

Treatment of Attention Deficit Hyperactivity Disorder: Individual Child and Family-Based Therapies

James H. Johnson, PhD

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Steven K. Reader, PhD

This chapter focuses on treatment approaches for attention-deficit hyperactivity disorder (ADHD) that are primarily psychosocial in nature and that involve working with the individual child and the family. Emphasis is on evidence-based interventions and on their place in the overall clinical management of the child with ADHD.

Approaches to the treatment of ADHD vary depending on a variety of factors. These include the professional background and training of the clinician, with medically trained clinicians being more likely to select pharmacologic approaches to intervention and nonmedically trained clinicians tending to employ psychosocial treatments at the individual or family level. Treatments for ADHD can also range from those that are relatively straightforward and involve a single approach to intervention to those that are maximally complex and require intervention at multiple levels. Providing appropriate classroom accommodations, along with parent education regarding the management of ADHD, may be sufficient to manage a first-grader with predominately inattentive type ADHD of mild to moderate severity. A much more complex approach to management may be required in dealing with a 12-year-old with severe combined-type ADHD who also has multiple comorbidities. In such cases, treatment may require multimodal interventions at the individual, family, school, and perhaps community levels. Cases such as these often require a multidisciplinary approach to both assessment and intervention and may involve several professionals working as part of a multidisciplinary team that may include physicians, psychologists, school personnel, and others (eg, speech pathologists, audiologists).

In the clinical management of ADHD, the approach to and complexity of treatment should be dependent on the ways in which core symptoms of ADHD and associated features are manifested in a given child and the degree to which the child displays impairment in important areas such as family, school, and social functioning. Children with ADHD vary markedly, and treatment approaches need to be matched with an individual's needs. In selecting treatment approaches it is also important, where possible, to focus on interventions supported by research findings. Only a limited number of approaches for the treatment of

ADHD can be considered evidence-based. Currently, interventions that enjoy the strongest empiric support include the use of stimulant medications, behaviorally oriented parent training programs, classroom-based interventions, and ADHD summer treatment programs. Stimulant medications are generally considered to be most effective in managing the *core symptoms* of ADHD, whereas psychosocial treatments are usually deemed most valuable in dealing with the psychological and behavioral problems that children with ADHD often display. To date, approaches such as biofeedback, dietary restrictions, allergy treatments, and play therapy have received little support from controlled studies assessing the treatment of children with ADHD.

Assessment for Treatment Planning

Assessment is an essential prerequisite for effective treatment. Obviously, it is essential for the ADHD evaluation to involve a careful assessment of the presence and severity of core symptoms of hyperactivity/impulsivity and inattention, the age of symptom onset, symptom duration, pervasiveness, and the degree of impairment in social, academic, and family functioning that results from these symptoms. Although it is necessary for the assessment to provide information regarding the degree to which the child meets diagnostic criteria outlined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), a comprehensive assessment involves more than this; it should rule out conditions that mimic symptoms of ADHD and should provide information regarding possible comorbid conditions that need to be considered in treatment planning.

A number of conditions mimic symptoms of ADHD (Chapter 37, "Comorbidity and Symptom Mimicry in Attention Deficit-Hyperactivity Disorder: Implications for Assessment and Treatment" considers mimicry and comorbidity in greater detail). Included here are conditions such as anxiety and mood disorders, seizure disorders, auditory processing disorders, specific sensory deficits (eg, visual and auditory impairments), medication side effects, posttraumatic stress disorder (often resulting from physical or sexual abuse), bipolar disorder, and conditions such as resistance to thyroid hormone that can result in both increased activity and attention problems. Clearly, it is necessary to rule out these conditions to avoid misdiagnosis and inappropriate treatments.

It is important that approaches to assessment also be broad enough to highlight other conditions that may coexist with ADHD. Here, it can be noted that approximately one-half to two-thirds of clinical cases display some sort of comorbidity. Among the most common comorbid conditions are learning disabilities, oppositional defiant and conduct disorders, and anxiety and depressive disorders, with a smaller but significant number of children also displaying comorbid tic disorders. A small number of children may also display evidence of bipolar disorder, which not only can mimic ADHD symptoms but also can occur as a comorbid condition.

For children displaying comorbid conditions, simply treating core symptoms of ADHD is likely not enough. Appropriate case management requires addressing the full range of presenting clinical problems. For example, in instances where a child not only shows features of ADHD but also meets diagnostic criteria for oppositional defiant disorder and learning disability, treatment should focus on problems associated with each of these areas. This might involve pharmacologic treatment for managing the child's core ADHD symptoms, parent-oriented behavior management approaches to modify oppositional behavior, and specially designed educational approaches to assist the child academically. Likewise, in the case of a child with ADHD and comorbid depression, it will be necessary to treat the child's depression as well as the symptoms of ADHD. With children displaying other patterns of comorbidity, other approaches to treatment may be required.

A comprehensive approach to assessment should also provide a strong foundation for treatment planning and the monitoring treatment outcome. Especially important in this regard is the use of evidence-based measures that assess areas of impairment. Measures of impairment are important because they provide information regarding how the child's symptoms affect his/her real-world functioning in important areas, such as in the home, at school, and with peers. And, research suggests that children who have comorbid conditions in addition to ADHD are likely to show greater levels of impairment across these key domains. It is essential that treatments of children with ADHD target impairments in these areas, as impairments in family, school, and social functioning are highly related to negative long-term outcomes (See Pelham, Fabiano & Massetti, 2005). Note that indices of impairment, like symptoms, should also be assessed over time to document treatment progress.

Role of Pharmacologic Approaches to Treatment

Although this chapter focuses largely on psychosocial approaches to the treatment of children with ADHD, it is important to comment, at least briefly, on the usefulness of drug treatments (see Chapter 41, "Current Pharmacotherapy for ADHD"), as they are often used in

combination with psychosocial treatments. Suffice it to say that numerous well-controlled studies indicate stimulant medication involving different formulations of methylphenidate and amphetamine, in both short- and long-acting forms, is highly effective in treating children and adolescents with ADHD. Indeed, the American Academy of Pediatrics has suggested that at least 80% of children will respond to one of the stimulants. The use of stimulant medication has clearly been shown to be an empirically supported treatment approach for managing the "core symptoms" of ADHD. Indeed, it is likely the most effective treatment available for this purpose. In addition to stimulants, a new ADHD medication, atomoxetine (Strattera®), has recently received approval from the United States Food and Drug Administration. This drug, a non-stimulant norepinephrine reuptake inhibitor, is currently enjoying widespread use as a result of its purported effectiveness, reduced side-effect profile, and the fact that unlike stimulants it is not a controlled substance. Regarding the use of medication, it can be noted that findings from the Multimodal Treatment Study of Children with ADHD suggest that although pharmacologic approaches have been found to be effective in the management of core ADHD symptoms, psychosocial treatments are useful in dealing with comorbid conditions and other problems that may result from or otherwise accompany core symptoms. The following sections briefly describe the nature of the child and family-based psychosocial treatments likely to be effective in managing symptoms of ADHD and treating the broad range of difficulties often experienced by children with ADHD and their families.

Individual Approaches to Intervention

School-Based Interventions

As children with ADHD typically display symptoms and impairments across settings, it is often necessary for the child's treatment plan to involve school-based interventions. This planning may include the development of a 504 plan that outlines classroom accommodations designed to minimize the impact of ADHD symptoms in the school setting. The focus of the 504 plan is often on providing the child with a learning environment that encourages appropriate behavior, helps the child focus and concentrate, and fosters academic achievement. An example of such accommodations might include seating the child in the front of the classroom, near the teacher and away from doors, windows, and other children who might be distracting. Working with the child to break large tasks down into smaller units, providing advance notice about transitioning from one classroom activity to another, and providing more time for the child to complete tasks are examples of other, often useful classroom accommodations.

Children with ADHD also often benefit from a classroom that has a favorable teacher–student ratio (that better enables the teacher to redirect the child if he or she gets off task and to reward on-task behavior), is relatively structured, and has clearly defined classroom rules. It is helpful if instructions provided to the child are simple and succinct and teachers make certain that the child understands instructions and repeats them, if necessary, to ensure understanding. The use of day planners to ensure that the child has correctly written down assignments and allowing parents to indicate that assignments have been completed can also help minimize the impact of attention problems. Likewise, it is often helpful for teachers to adhere to a routine where they alternate low-energy activities with higher energy physical reprieves throughout the day. Because children with ADHD often find it easier to maintain attention when learning materials are highly stimulating, it is helpful for lesson plans to combine hands-on projects, films, and small group work with traditional instructional approaches whenever possible.

Classroom accommodations like those just described are often combined with behaviorally oriented interventions carried out within the classroom. Teachers may reward the child for staying in his or her seat, for staying on task, and for behaving appropriately while ignoring or using other methods such as time-out procedures in response to disruptive child behavior. Programs where children receive points or tokens for appropriate behavior (that can be exchanged for back-up reinforcers) and negative consequences (eg, the removal of tokens or points) for inappropriate behaviors are also frequently used. Last, daily report cards that outline specific targeted behaviors (eg, staying seated, staying on task, and raising a hand before talking) are frequently used as an effective teacher-to-parent feedback device.

It is important to note that while these types of classroom accommodations can be useful in dealing with the child's core symptoms in the classroom, children who have comorbid learning disabilities may require special educational assistance as well.

Summer Treatment Programs

In addition to the beneficial individualized classroom accommodations provided throughout the academic year, children with ADHD have also been shown to profit from participation in summer treatment programs designed to deal with a range of difficulties they often display. These intensive treatment programs, carried out in settings that involve both academic and recreational activities, typically combine a range of treatment components that have been shown to be effective in working with this clinical population. As such, they often include behavioral parent training, a token or point system involving positive reinforcement, the use of effective commands, time-out

procedures, a daily report card, social skills training, and training in effective problem-solving. Research suggests that children who participate in this type of intensive treatment milieu typically make gains in a wide range of areas where they have previously demonstrated impairment. For example, such treatment programs appear to improve children's peer relationships, their interactions with adults, their academic performance, and their level of self-esteem.

Cognitive Behavior Therapy

Cognitive behavior therapy (CBT), as applied to children with ADHD, has traditionally involved helping these children improve their adaptive skills and become better problem-solvers. Through modeling and role-playing, therapists can help children learn to (1) better monitor their own behavior, (2) consider, implement, and evaluate the outcomes of various possible solutions to problem situations, and (3) provide themselves with contingent reinforcement for their behavior. The premise behind these intervention goals is that children with ADHD lack sufficient self-regulatory skills as a result of their impulsivity and hyperactivity. Although intuitively appealing, research on the effectiveness of CBT approaches in improving *core features* of ADHD has not convincingly demonstrated clinical efficacy in modifying behavioral or academic functioning. The major problems appear related to children's difficulty in generalizing the skills to different situations, particularly in the absence of prompting from others.

Although of limited effectiveness in modifying the core symptoms, cognitive behavioral approaches seem more useful in treating comorbid conditions that often occur with ADHD, including both externalizing (oppositional defiant disorder, conduct disorder) and internalizing (anxiety, depression) disorders. CBT can help children with externalizing disorders develop anger management strategies and become better problem-solvers through learning to generate more adaptive self-statements, taking other people's perspectives, generating alternative solutions in anger-provoking situations, and evaluating consequences of behavior. When used within the context of treatment for internalizing conditions, cognitive behavior strategies help children modify maladaptive or distorted thoughts, beliefs, or images that are contributing to anxiety or depressive symptoms. Behavioral strategies for anxiety can also include relaxation training and in-vivo exposure, whereas interventions for depression can also include increasing pleasant activities.

Social Skills Training

Children with ADHD often experience peer interaction problems as a result of their difficulty in attending and responding appropriately to social cues and their difficulties in behavioral regulation. Research has further shown that aggressive behavior, often displayed by children with ADHD, is a strong risk factor for peer rejection. Social skills training has, therefore, been implemented as a treatment option to encourage more effective and positive interactions between ADHD children and their peers. Specifically, social skills groups often involve modeling appropriate social interactions and using contingency management approaches to increase children's self-awareness and self-monitoring, improve social problem-solving skills, teach anger management strategies, and shape adaptive conversational skills. An important part of social skills training for ADHD children with comorbid aggressive behaviors is to help these children modify their maladaptive tendency to attribute hostile intent to peers during ambiguous social interactions. Some have indicated that social skills training tends to work better in a group format because of the difficulty children with ADHD have with self-observation and the opportunity in groups for feedback, modeling, and contingent reinforcement.

Unfortunately, studies evaluating clinic-based social skills training programs with children displaying ADHD suggest only limited efficacy. More recent research suggests small, short-term improvements in social behavior for young children with conduct problems who receive group social skills training at school. The heterogeneity within the ADHD population (presence of comorbid disorders, varying levels of baseline social skills deficits) and the difficulty in tailoring interventions accordingly have been cited as reasons for the lack of effects. Generalizability of treatment effects to home and school has also been limited, likely in part due to the limited involvement of caregivers in many of the social skills groups evaluated and the difficulty children have in applying skills in different settings. More recent research suggests small, short-term improvements in social behavior for young children with conduct problems who receive group social skills training at school. Involving caregivers in training and peers as tutors, or involving children in student-mediated conflict resolution programs, may improve treatment effects. However, more research will be necessary before firm conclusions can be drawn.

Family-Based Interventions

Parent Training Programs

Behavioral parent training is a prime example of a family-based treatment that has been shown to be highly effective in managing many of the disruptive behaviors displayed by children with ADHD as well as those with co-occurring conditions such as oppositional defiant or conduct disorder. Within this type of program, parents learn to create a structured, predictable environment in which they reward positive behaviors and apply negative contingencies in response to problem behaviors. Reinforcements can include praise, positive attention, or tangible rewards; and

depending on the severity of the child's inappropriate behavior, punishments can take the form of loss of previously earned rewards, time-out, or other contingencies such as ignoring. Careful monitoring and the application of consistent contingencies by the parent are crucial to the success of parent training programs.

One popular parent training regimen is based on the principles outlined in Gerald Patterson's book on coercion theory (1982) and is further illustrated in his book *Living with Children*, written specifically for use with parents and teachers. This program is applicable for children and adolescents between the ages of 6 and 16 and employs multiple treatment sessions, with the content of sessions patterned after material included in *Living with Children*. This treatment guides parents in identifying specific problem behaviors that serve as targets for treatment, monitoring and rewarding positive behaviors, and ignoring or using negative consequences to deal with problem behaviors. Numerous studies have documented the effectiveness of this social learning approach in fostering positive interactions between parents and children and in decreasing child/adolescent conduct problems. Indeed, this treatment approach has been documented sufficiently to warrant its designation as an evidence-based child treatment.

Another empirically supported treatment for dealing with childhood behavior problems is Videotape Modeling Parent Training developed by Carolyn Webster-Stratton at the University of Washington. This treatment approach also teaches parents practical behavior management skills but does so through the use of videotaped lessons. This form of treatment is usually administered by a therapist in a group situation, with ample opportunities to discuss the presented material at the conclusion of the lesson.

An additional evidence-based parent-training program that is worth mentioning in greater detail is parent–child interaction therapy (PCIT). PCIT is designed to improve dysfunctional exchanges between parents and their preschool-aged children and reduce the behavior problems often seen in young children with ADHD and comorbid oppositional defiant disorder. PCIT incorporates two phases of treatment. The first phase sets the stage for effective discipline by enhancing a positive relationship between parent and child, thus encouraging a nurturing and positive environment within which therapy will take place. During the first stage of PCIT, child-directed interaction (CDI), parents must consistently avoid commands, questions, and criticisms as they play and interact with their children. Once parents have mastered the skills that strengthen the attachment relationship, treatment progresses to the second phase, parent-directed interaction (PDI), during which parents learn to give clear, direct commands in various play situations. Parents also practice setting limits through the use of contingencies. A parent gives praise if the child complies with an instruction but uses time-out when the child disobeys. During both phases of therapy, parents wear a "bug-in-the-ear" device through which therapists observing behind a one-way mirror can provide coaching on how to use the newly acquired interaction skills. There is no predetermined number of sessions the parent–child dyad must attend; completion is criterion-based and depends upon mastery of skills and a significant decrease in noncompliant and problematic behavior. PCIT is an evidence-based intervention that has been demonstrated to be highly effective in dealing with the oppositional-defiant and conduct disordered behaviors. Although PCIT was initially developed as an approach for treating young children with conduct problems, it has now been demonstrated to be of value in working with abusing parents and their children, developmentally delayed children with disruptive behavior disorders, and has also been adapted for use with children displaying anxiety related difficulties.

More recently, research appears to suggest that, apart from its usefulness in treating oppositional defiant/conduct disordered behavior, PCIT has the potential to directly impact ADHD symptoms, leading to reductions in hyperactive behavior, more flexible temperament, and *potentially* a decreased need for stimulant medication Additional research, is currently underway at the University of Florida to further determine the usefulness of PCIT in reducing core symptoms of ADHD in very young children diagnosed with ADHD who are not being treated pharmacologically. A question of some importance is whether a psychosocial treatment such as PCIT can, when used with very young children, decrease the need for pharmacological treatment in managing ADHD symptoms.

Family System Interventions

Most family-based approaches to treating ADHD have focused on reducing problem behaviors displayed by the ADHD child rather than on systematic attempts to intervene at the broader family systems level. Although reducing core symptoms of ADHD and symptoms of common co-occurring conditions through the use of medication or other treatments is clearly desirable, it is clear that parents (and siblings) of children with ADHD can also be affected by having a child with ADHD in the family. Indeed, family stress resulting from this disorder can contribute to a range of difficulties for family members and family functioning.

The potential impact of ADHD on the family is highlighted by the fact that children with this disorder often display behaviors parents and other family members find highly disruptive. This stress results not only from dealing with the child's inattention, impulsivity, and hyperactivity, but also from the burden placed on parents as a result of the child's problem behaviors. For instance, parents must often deal with repeated phone calls from teachers resulting from their

child's misbehavior or their academic problems. They often have to "explain" their child's behavior to other parents. They are often restricted socially because of their inability to find someone to care for their child. They often must miss work to attend clinic appointments. Many worry incessantly (with some justification) about the possibility of accidental injury to their child as a result of his or her behavior. Dealing with problem behaviors displayed by a child with ADHD can also leave too little time to meet the needs of siblings and often results in parental conflict regarding how to discipline the ADHD child. These represent only a few of the many stressors experienced by parents of children with ADHD.

That these types of stressors can have an impact on the family is supported by studies suggesting that ADHD-related behaviors can result in negative parent–child interactions that may in turn contribute to the development of conduct disordered behavior. ADHD-related stress can also contribute to the development of problems in parents as well. For example, parents of children with ADHD have been shown to display elevated levels of alcohol consumption, increased levels of marital discord, increased role restriction, higher levels of social isolation, increased problems of psychological adjustment and experience other stress-related outcomes. Such findings suggest there is a significant family burden associated with having a child with ADHD and that this can have a significant impact on family mental health and functioning. As research has consistently demonstrated the negative effects of stress on attention, it seems likely that increased levels of stress may also decrease the parents' sensitivity to the nuances of their child's behavior. This may make it more difficult for parents to attend to the range of details required to effectively implement complex child behavior management programs that are designed to reduce the very behaviors that contribute to parental stress.

Although more research is needed to clarify the full range of outcomes associated with ADHD, existing findings suggest attention needs to be given to assessing family stress levels in this clinical population. Where indicated, parents and other family members should also be helped to find ways to cope with ADHD-related stress so as to reduce potential negative outcomes. Although there are presently no empirically supported treatments specifically designed to reduce stress in families of children with ADHD, it would seem that attempts to intervene with families experiencing high levels of ADHD-related stress might involve several elements.

One essential element is likely to involve family education to help parents and siblings better understand the nature of ADHD. Often the level of family stress can be greatly minimized once all family members understand the nature of the disorder and that the child's ADHD is not the result of inadequate parenting or something that parents or siblings are responsible for and must feel guilty about. Learning that excessive activity often declines in adolescence, learning about the types of situations that may exacerbate or decrease symptom severity, and recognizing that there are classroom interventions that can help with their child's inattention and discovering that many children with ADHD grow up to be successful adults can also decrease parent stress levels.

A second essential element involves parents receiving increased levels of social support as they attempt to deal with their child's ADHD symptoms and associated stressors. Here, support might come from working with parents in ADHD therapy groups or through parent involvement with groups such as Children and Adults with Attention-Deficit Disorders (CHADD), which has chapters in many larger communities. Social support has been repeatedly shown to serve as an important stress buffer and may be especially helpful when the support comes from individuals who are aware of how stressful parenting an ADHD child can be.

Training parents in ways to effectively manage difficult child behavior can also minimize the stress of dealing with the ADHD child. Such training is likely to not only reduce the stressfulness of the child's behavior as behavior change occurs, but also to increase the parent's sense of control, their sense of parenting competence, and their satisfaction with parenting. In some instances, individualized approaches to parent stress management that involve other methods such as relaxation training and cognitive behavioral interventions may also be helpful.

Although not applied specifically to families of children with ADHD, it is noteworthy that a family-based intervention approach that included the elements discussed here has been successfully used to reduce parent anxiety, depression, and family stress and increase feelings of parental competence, satisfaction, and attachment while decreasing problem behavior in families of preschool children with difficult temperament, which is often seen as a precursor to ADHD. It seems likely that similar approaches may prove useful with parents of children with ADHD, especially if combined with other individualized approaches to stress management.

It must be emphasized that treatments for ADHD should not focus solely on the child. Given the seemingly ubiquitous nature of ADHD-related stress in families of children with ADHD, it would seem important to routinely assess stress levels in these families and assist parents and other family members in coping with this stress. The problem of ADHD is not just the child's—it belongs to the entire family! And, in different ways, all may need help in coping with it.

Suggested Readings

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Practitioner and Patient Resources

Children and Adults with Attention-Deficit Disorders (CHADD)
499 N.W. 70th Ave., Suite 101
Plantation, FL 33317
Phone: (800) 233-4050
http://www.chadd.org
Founded in 1987 by a group of concerned parents, CHADD works to improve the lives of people with ADHD through education, advocacy, and support. Working closely with leaders in the field of ADHD research, diagnosis, and treatment, CHADD offers its members, and the public, information they can trust.

National Resource Center on ADHD
National Resource
8181 Professional Place, Suite 150
Landover, MD 20785
800-233-4050
http://www.help4adhd.org
A joint venture of the Centers for Disease Control and C.H.A.D.D., the National Resource Center on ADHD is a clearinghouse to disseminate science-based information on ADHD. Information is available online, as well as from a comprehensive library of books, journals and reports housed in the home office. The center also provides numerous fact sheets on all aspect of ADHD. Overall, this center is an excellent information source for both parents of children with ADHD and professionals working in this area.

Chapter 40

The Role of the Pediatric Neurologist in the Management of Attention-Deficit Hyperactivity Disorder

Esther Cardo, DCH, MRCP

This chapter presents an overview of the clinical assessment and diagnosis of attention-deficit hyperactivity disorder (ADHD) in children from the pediatric neurologists' perspective. Our purpose is to provide a better understanding of medical and neurological diseases, which may mimic or be associated with ADHD symptomatology and an appreciation of the importance of a rigorous physical evaluation and its integration in the clinical management of ADHD.

Those of us who practice on the front lines of pediatric neurology, developmental pediatrics, or general pediatrics are well aware that ADHD is the most common pediatric neurodevelopmental disorder of childhood, which has a polygenic and multifactorial origin.

According to the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV), an individual with ADHD has symptoms related either to inattention or to hyperactive-impulsive behavior. ADHD is classified by the DSM-IV criteria in terms of three different subtypes: a primarily inattentive subtype, a primarily hyperactive-impulsive subtype, and a combined subtype, combining more or less equal elements of inattentiveness, hyperactivity, and impulsivity.

Various epidemiologic surveys using a variety of different sampling techniques estimate the incidence of ADHD to be between 5 to 12% of the childhood population. The diagnosis of this particularly common disorder has been increasing overtime and is seemingly diagnosed more in the female population, in younger children, in preschoolers, and, of course, in adulthood.

Hypotheses on the etiology of ADHD span various domains, such as behavioral genetics, molecular genetics, acquired biological factors, neuroanatomy, neurochemistry, neuropsychology, and psychosocial environment. There are various theories to explain various aspects of ADHD, but none of them explain the full spectrum of symptoms of the disorder. ADHD represents a public health concern with significant effects on children's functioning across multiples areas. Referrals to health care professionals for children suspected of having the disorder is increasing in Europe and continue at a high rate in the United States.

The medical management of ADHD combines the expertise from a medical perspective of pediatric neurology, psychiatry, and developmental pediatrics, but of course also requires the input of educators, psychologists, and occupational therapists among others.

The challenge for a pediatric neurologist is to look at the differential diagnosis because ADHD is a syndrome with only symptoms, and there are many neurologic conditions with the same symptoms.

Medical History and the Structured Interview

Most aspects of an adequate medical interview are identical to taking any medical history. However, to gather information which will aid us in making a differential diagnosis from other medical, neurologic, or metabolic conditions, one needs to review the child's genetic background, prenatal and perinatal events, and developmental and medical history, as well as the child's current health, nutritional status, and gross sensory-motor development with greater emphasis.

General evaluation should clarify presenting complaints, make a systematic evaluation of psychopathologic symptoms, and describe how problems developed. The developmental history is important and should include previous professional reports.

A detailed pregnancy and birth history is important to record possible causes that could interfere with the fetal well-being: not only tobacco and alcohol intake but also fetal growth, toxemia, bleeding or severe infections in pregnancy, maternal diabetes or epilepsy, other maternal illnesses or traumas, poor nutritional state of the mother, use of medications. These inquiries should be made mainly about the second and third trimesters of pregnancy when the process of neurogenesis and synaptogenesis is taking place and there is a greater vulnerability of damaging the brain. Documentation of fetal growth, toxemia, bleeding or severe infections in pregnancy, maternal diabetes or epilepsy, other maternal illnesses or traumas, poor nutritional state of the mother, use of medication, as well as nicotine, alcohol or drugs, gestational age, birth complications, birth weight, and neonatal complications should be examined. The nutritional aspects during pregnancy are also important. The growth and differentiation of the central nervous system are closely related to the presence of iodine and thyroid hormones. It has been hypothesized that neurobehavioral disabilities of childhood, such as ADHD or learning disorders, can be attributed to fetal thyroidal endocrine disruption in utero. However, other authors failed to show these associations. So far, it is clear that there is a high prevalence of ADHD in children with generalized resistance to thyroid hormones. This might suggest a common ADHD pathogenesis mechanism consisting either of reduced sensitivity of the nuclear receptors to thyroid hormone (generalized resistance to thyroid hormones) or reduced availability of intracellular T3 for nuclear receptor binding.

Gestational age, birth complications, birth weight, and neonatal complications should be reported. Marked differences are seen in neurologic and health status, intellectual functioning, school performance, and behavior between children born prematurely and those born at term. Assessment in the follow up to school entry of preterm babies shows learning disabilities, difficulties in visual-motor integration and perception, selective motor coordination disorders, behavior problems, ADHD, and reduced educational achievement. The same is true with low Apgar scores (mainly below 7), which have also been associated with higher incidence of ADHD among other neurobehavioral problems and a lower score in motor performance. In rare cases, ADHD may arise from metabolic disease, such as phenylketonuria that will be detectable in the neonatal metabolic screening program. Children with early and continuously treated phenylketonuria have prefrontal dysfunction and show problems in inhibiting responses.

A detailed early developmental history should be obtained (milestones for psychomotor, development, language, attachment, sleep and feeding problems, growth, and early temperament). Some of these children are very difficult to feed and satisfactory breast-feeding is not reported. Short duration of breast-feeding has been reported as a possible environmental risk factor of ADHD symptoms, but whether it is a cause or a consequence of the feeding difficulty seen in some newborns babies with ADHD needs further investigation. It is also important to record the temperament of the newborn baby (alert, irritable, too sleepy, requirement of attention, etc). They often have difficulties in achieving normal sleep patterns, they wake up very often at night, and they may be very irritable. These issues are likely to interfere with correct and healthy mother and child bonding, with further worsening of these patterns. It is very important to support and train parents at this point, which is likely to improve maternal confidence and the child's pattern of behavior.

In the medical history, it is important to record other more serious diseases that may affect the brain function, such as Reye's syndrome, a hypoxic-anoxic event, such as near drowning or severe smoke inhalation, significant head trauma, or a central nervous system infection or cerebrovascular disease. Any minor assault to the brain could also lead to ADHD. It is well known that a perfectly normal child who suffered from meningitis or encephalitis that has an apparently full recovery may later develop ADHD.

ADHD has also been associated with significant lead or other metal or toxic poisonings, which will require treatment in their own right. It is also necessary to determine whether the child's conduct or learning problems are related to undetected seizures, such as in petit mal or temporal lobe seizures, or are secondary to the medication being used to treat the disorder. Petit mal absence or temporal lobe epilepsy could easily be misdiagnosed as ADHD. Parents have difficulties in understanding the difference between true absences caused by petit mal from attention deficit, even if you describe to them the difference between absences that is a true interruption of consciousness versus attention deficit. In these cases, it is important to do an electroencephalogram (EEG) to make a diagnosis.

More than 50% of children referred to neurology for possible absence seizures have ADHD. Furthermore, as many as 30% of epileptic children may have ADHD as a comorbid condition, and some antiepileptic drugs (AEDs) may exacerbate the symptoms of ADHD. Understanding the interrelationships among comorbidities, epilepsy, and their treatments is essential to optimal management of pediatric patients. Treatment should be individualized with consideration for specific comorbidities and concomitant medications. Key treatment goals are to achieve seizure control and optimal physical and cognitive functions using the simplest possible AED regimen. Newer AEDs, such as lamotrigine, topiramate, gabapentin, oxcarbazepine, and tiagabine, may benefit children with epilepsy and some comorbid disorders.

Physical Evaluation

Height, weight, and head circumference should always be recorded. A general examination is always needed, including assessment of physical health and any evidence of breakdown of care and any stigmata of congenital disorder (eg, fetal alcohol syndrome, Williams syndrome, and neurofibromatosis [NF]).

Vision (Snellen chart) and hearing (clinical screen and audiogram if indicated) should be checked.

Children with ADHD are more likely to have medical conditions related to immaturity, such as otitis media or "glue ear," enuresis, encopresis, thyroid dysfunction, or iron deficiency. ADHD is not seen as arising from these other conditions but as being comorbid with them. Many publications have related low serum ferritin as an association or causative role for ADHD, but many others have failed to confirm this relationship.

Ocular problems, such as accommodative dysfunction and convergence insufficiency (CI) or amblyopia, are common pediatric vision problems that were associated in the past with an increase in ADHD symptoms. The results from some studies suggest that school-aged children with symptomatic accommodative dysfunction or CI have a higher frequency of behaviors related to school performance and attention. Again, whether this is a comorbid problem or a consequence of vision-specific symptoms that affect children when doing schoolwork needs further study. However, the physician certainly needs to rule out the possibility of visual or hearing deficits that may give rise to ADHD-like symptoms.

Other common somatic complaints associated with ADHD are headache, eczema, and allergies. Although most cases of enuresis and encopresis are not an effect of underlying physiologic disorders, all cases of these elimination problems should be evaluated by a physician before beginning nutritional and behavioral interventions. Children with significant allergies or asthma require frequent medical consultation and management of these conditions, often by specialists who appreciate the behavioral side effects of medications commonly used to treat them. Theophylline, for example, is increasingly recognized as affecting children's attention span and may exacerbate a preexisting case of ADHD.

The examination should look particularly for any evidence of neurodevelopmental immaturity in gross and fine motor functions and for motor and vocal tics. Some children may have a personal or family history of tic disorders or Tourette syndrome, which would dictate caution in prescribing stimulants in view of their greater likelihood of bringing out such movement disorders or increasing the occurrence of those that already exist.

It is important to do a complete neurologic examination and look at the phenotype because sometimes it could lead to some specific syndrome; and look specifically to the skin for possible neurocutaneous findings, as both skin and nervous system derive from ectoderm. Frequent neurologic diseases that could be misdiagnosed as ADHD are neurofibromatosis, Fragile X syndrome, fetal alcohol syndrome or Williams syndrome, among others.

NF type 1 (NF1) is a neurocutaneous disorder with a prevalence of approximately one in 3,500 people. Academic difficulties and school failure are the most common reported complications of NF1 in childhood and are present in 40 to 60% of the cases. NF1 is also associated with high incidence of brain tumors, hydrocephalus, and optic glioma among others. It is easily detectable by the presence of café au lait spots. Recent advances in the recognition and characterization of the cognitive phenotype in NF1 patients have provided a better understanding of the neuropsychologic deficits that account for the impairments in cognitive performance and social interaction. Additionally, recent advances in the understanding of molecular and cellular mechanisms underlying the cognitive deficits in NF1 and developments in neuroimaging and molecular genetic techniques are starting to yield a global and integrative picture of the molecular, cellular, and brain system processes affected by this condition. There are also recent preclinical studies that point toward potential pharmacologic interventions for NF1 patients. Children with ADHD may have a greater number of minor physical anomalies or "soft dimorphic features," such as unusual palmer crease, low-set ear, increased epicanthal fold, or hypertelorism. However, studies conflict on whether such findings occur more often in ADHD, but certainly, they are nonspecific to it, being found in other psychiatric and developmental disorders. Examining for these minor congenital anomalies may only be beneficial when the physician suspects maternal alcohol abuse during pregnancy, to determine the presence of fetal alcohol syndrome. The existence of small palpebral fissures and midfacial hypoplasia

with growth deficiency supports this diagnosis. In some cases, these dysmorphic features lead to specific diagnosis, such as Fragile X syndrome. As many as 54 to 59% of boys with Fragile X syndrome meet diagnostic behavioral criteria for either ADHD-inattentive type only, ADHD-hyperactive type only, or ADHD-combined type based on parent or teacher report. Other rare dimorphic syndromes also present an ADHD behavior phenotype, such as the Williams-Beuren syndrome (WBS), a multisystem condition with characteristic cardiovascular, cognitive, and behavioral features.

It is also important to test the cranial nerves, gross and fine motor coordination, eye movements, and whether there are "soft neurologic signs." Subtle neurologic signs include difficulty with sequencing (finger sequencing, rapid alternating movements), impersistence, synkinesia and motor overflow, testing for choreiform movements and tandem gait tasks, motor overflow, and clumsiness. Clumsiness refers to the performance of fine and/or gross motor tasks in an immature, slow, irregular, or inconsistent fashion. Skills are imprecise rather than grossly impaired. Soft neurologic signs are present in many children with learning and behavioral disorders. These children may display a greater prevalence of soft neurologic signs suggestive of immature neuromaturational development, but again these are nonspecific for ADHD.

The exam is often used to look for signs of previous central nervous system insult or of a progressive neurologic condition, abnormalities of muscle tone, and a difference in strength, tone, or deep tendon reflex response between the two sides of the body. The existence of nystagmus, ataxia, tremor, decreased visual field, or fundal abnormalities should be determined and further investigation pursued when found.

This evaluation should be followed by a careful neurodevelopmental exam covering the following areas: motor coordination, visuoperceptual skills, language skills, and cognitive functioning. Although these tests are certainly not intended to be comprehensive or even moderately in-depth evaluations of these functions, they are invaluable as quick screening methods for relatively gross deficiencies in these neuropsychologic functions. When deficits are noted, follow-up with more careful and extensive neuropsychologic, speech and language, motor, and academic evaluations may be necessary to more fully document their nature and extent.

More sensitive and lengthier neuropsychologic tests may often reveal deficits not detected during a brief neurologic screening or mental status exam. Even so, the routine use of extensive neuropsychologic tests to assess children with ADHD is likely to have a low yield. These tests should be conducted only when there is a question of coexisting learning or processing deficits that requires further clarification. Laboratory studies, such as blood work, urinalysis, chromosome studies, electroencephalograms, averaged evoked responses, magnetic resonance imaging, or computed axial tomograms (computed tomography scans), should not be used routinely in the evaluation of children with ADHD. Only when the medical and developmental history or physical exam suggests the presence of a genetic syndrome or of a treatable medical problem, such as a seizure disorder, would these laboratory procedures be recommended, and yet such cases are quite rare.

Investigations should not be routine but guided by history and physical examination. If there is a history suggestive of seizures, an EEG should be carried out. If there is a developmental delay, then chromosome analysis and a DNA assessment of the Fragile X gene should be done (further gene assessments may be recommended in the near future, but at present, the clinical significance of variant alleles is not clear). Audiograms are needed when a clinical evaluation has not ruled out significant hearing loss. Brain scanning and neuropsychologic tests are not necessary unless there is particular reason to suspect a structural brain lesion. Functional imagining remains at present a research technique.

Conclusion

In conclusion, the role and challenge of the pediatric neurologist in this condition is to think of other syndromes which should be excluded and properly treated.

Summary Points

- A health history and a physical/neurologic/developmental assessment are necessary to identify or rule out problems in the biomedical realm of the ADHD differential diagnosis.
- Deficits in sensory areas may result in classroom difficulties and produce restless or inattentive behaviors. Children with neuromaturational delays or neurologic "soft signs" are at risk for learning and behavioral disorders.
- On the basis of history and physical examination, further workup may be indicated in areas, such as genetic or chromosomal, neurologic, or biomedical conditions.

Physical Examination

- Growth parameters: height, weight, and head circumference require measurement and comparison to standardized graphs.
- Vital signs: blood pressure, pulse
- Screening of vision and hearing
- Findings suggestive of hyperthyroidism or hypothyroidism, lead poisoning, anemia, or other chronic illness

clearly need to be documented and further workup should be pursued.

- Overall physical appearance
  - Dysmorphism
  - Minor physical anomalies may signal genetic abnormalities (low-set ears, large or undescended testicles, high-arched palate, etc)
  - Signs and symptoms of abuse

Neurologic examination

- Examination of the skin for signs of neurocutaneous disease (café au lait spot in neurofibromatosis or abnormalities (eg, motor or vocal tics, asymmetry or abnormality of reflexes or motor tone, tremors)
- Soft neurologic signs
  - Subtle neurologic signs including difficulty with sequencing, dysrhythmia, mirroring, motor overflow, and clumsiness. Clumsiness refers to the performance of fine and/or gross motor tasks in an immature, slow, irregular, or inconsistent fashion. Skills are imprecise rather than grossly impaired. Soft neurologic signs are present in many children with learning and behavioral disorders.
- Assessment of developmental status
  - Observation of child's activity level in examination room, ability to converse appropriately, ability to follow directions, and cooperativeness
- History of delays or questionable areas:
  - Auditory perception
  - Expressive language
  - Visual and sequential processing
  - Memory
  - Fine and gross motor function
- Cognitive screening tools

The provider may find the following helpful. Responses are age dependent.

- Ask the child to tell about a recent event—birthday, sports event. (Note whether language is fluent, coherent, and organized.)
- Ask parent if child has difficulty taking telephone messages or retaining classroom instructions, if age appropriate. (Short-term memory)
- Observe the child using a pencil to copy symbols and words. (Visual perceptual motor)
- Ask the child to perform a three-step command. (Sequencing)
- Ask the child to repeat four words, remember them, and repeat them again when asked in 5 minutes or 10 minutes. (Memory, attention)
- Ask the child to repeat three, then four digits forward; then repeat three, then four digits backward. (Concentration)

Suggested Readings

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Practitioner and Patient Resources

ADHD EINAQ

<http://www.einaq.org/>: European Interdisciplinary Network for ADHD Quality assurance (EINAQ)

E-mail: info@einaq.org

EINAQ is comprised of an independent working group of ADHD experts from universities, hospitals, and private practices who have set a goal to assure quality of care for patients with ADHD.

The educational goal of EINAQ is to advance the awareness, acceptance, diagnosis, and treatment of patients with ADHD by sharing the full range of current evidence-based knowledge and experience on ADHD and associated problems.

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Chapter 41

Current Pharmacotherapy for Attention-Deficit Hyperactivity Disorder

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The term "attention-deficit hyperactivity disorder" (ADHD) describes a group of disorders that commonly cause behavioral disturbances and academic underachievement. Current pharmacotherapy is highly effective but should be used in the context of a comprehensive management plan that addresses associated conditions.

In isolation, inattention is highly problematic for children, caregivers, and teachers because one must *attend* to learn. In 50 to 70% of cases of ADHD, associated problems are present, such as oppositional defiant disorder, conduct disorder, anxiety, tics, depression, bipolar disorder, and learning disorders. In each child with ADHD, there is a unique mix of concerns that affect behavioral and school performance. Thus, the approach to each child must be individualized, taking care to evaluate his or her unique "portfolio" of strengths and weaknesses. Treatment for ADHD involves classroom accommodations, parent support, and medication. This chapter succinctly reviews first-line choice of medication.

Despite the fact that medication can have immediate and profound beneficial effects on attention, behavior, and school performance, many families and teachers are considerably resistant to the diagnosis of ADHD. Many are fearful and angry about the "ADHD label" and about the proposal to prescribe stimulant medication. Use of the "R" word (Ritalin®) has a way of triggering strong reactions among family members, despite the drug's excellent track record with safety and effectiveness. It seems as if the resistance to diagnosis and treatment is highest among parents who themselves meet diagnostic criteria for ADHD. A typical scenario involves a father with undiagnosed ADHD who fails to attend a clinic visit and provides his spouse with the following instructions: "They can put him on any medication as long as it's not Ritalin!" These attitudes are powerful barriers to management of ADHD and take considerable time to overcome. Practitioners may find it useful to describe ADHD as a disorder of impulses whereby the frontal lobes—the "brake pads of the brain"—are "too thin to prevent impulsive behaviors." Medications like methylphenidate are designed to "stimulate the frontal lobes" and provide the brain with the means to be more functional and to "put the brakes on problem behaviors and improve attention." When ADHD is described in terms of brain anatomy and chemistry, parents and caregivers may be somewhat less resistant to a therapeutic trial. It is also important to underscore the point that treatment can be stopped at any time without harm to the child. This "trial" of medicine is potentially life-changing and low risk. Many parents report a positive transformation in behavior within days of starting therapy. As such, few conditions in medicine are as rewarding to diagnose and treat as ADHD.

Many in the community strongly believe that ADHD is a "made-up diagnosis," a misperception often reinforced by the media. Some licensed health professionals have publicly stated that "ADHD is the worst medical fraud of the 20th century." Despite the fact that National Institutes of Health (NIH) Consensus Conferences have declared ADHD a real neuropsychiatric entity, many uninformed people have not accepted the fact that ADHD represents a group of disorders that affect behavior, learning, and school performance. As the saying goes, "The fewer the facts, the stronger the opinion."

For some reason, concerns regarding overdiagnosis and OVERTREATMENT are not shared for migraine or epilepsy, despite the fact that epidemiologic studies show these conditions to be very prevalent. However, data on outpatient visits across the USA suggest a nearly 10-fold increase in numbers of visits for ADHD over the last 10 years (see Chapter 1, "Common Neurologic Complaints and Conditions"), while the number of visits for migraine and epilepsy have remained relatively stable.

ADHD is highly variable and each patient and family faces a unique set of challenges. In many ways it is as if each patient has his or her very own disorder. In addition, further complicating management is high variability in attitudes of caregivers, teachers, and schools toward the safety, tolerance, and effectiveness of medication. Although few people would question the existence of migraine or epilepsy and that pharmacotherapy can be very helpful, it seems as if many people deny the existence of ADHD and are, therefore, strongly opposed to the use of medication—even though it has been shown to improve behavior, learning, and school performance. This special characteristic of ADHD adds to the burden of management because of the time required to educate, coach, and promote adherence to therapies.

Though ADHD ranks among the most common conditions referred for specialty consultation, many neurologic practices have opted to not manage ADHD, even when psychiatric resources in the community are limited or overburdened. Though comorbid conditions and psychosocial issues often complicate management of children with headache or epilepsy, ADHD can place an even greater burden on caregivers and practitioners. There are probably many reasons why child neurologists have not uniformly welcomed "the ADHD business" (eg, caregiver education costs, school coordination costs and review of records, time to screen and cost of standardized tools, controlled drugs, case management costs, complicated comorbid issues, behavioral management). However, for practitioners who choose to be part of the solution for children with ADHD, there is no question that stimulants continue to be the most commonly used, most effective, best-studied agents for children with inattentiveness, impulsivity, and hyperactivity. Up to 70% of children will respond to optimally titrated doses of medications. Stimulants reduce aggressive outbursts, reduce defiance, improve social interactions, and improve school performance.

Although both methylphenidate and amphetamine increase the synaptic availability of the monoamines dopamine and norepinephrine, they do so by different mechanisms of action. Methylphenidate blocks the reuptake of dopamine and norepinephrine and binds to the dopamine transporter (DAT) with high affinity. Amphetamine however may be viewed as a "releasing agent" in its displacing of monoamines from intraneuronal stores in a Na^+-dependent process. The effectiveness of stimulants has been demonstrated repeatedly, most recently in a large National Institute of Mental Health study of 600 children treated over a 14-month period (The MTA Cooperative Group, 1999). Stimulants were as effective as stimulants combined with intensive behavior therapy, which was better than behavior therapy alone. Nonpharmacologic measures were valuable in managing comorbid conditions and drug doses were reduced when combined with behavior management. All three treatment arms fared better than routine community care (usually with the same stimulants). The possible reasons subjects had better outcomes than those in community care include closer follow-up, protocol-driven dose adjustments, and higher doses given more continuously during weekends and vacations.

On this basis, many practitioners recommend starting methylphenidate when ADHD impairs function at home and in school (ie, Connors' rating scales completed by parents and teachers are positive). When there is significant disagreement between parent and teacher reports, the child is referred to a comprehensive ADHD program for detailed psychological and psychosocial evaluations. In most cases, there is agreement in parent and teacher Connors' rating scales. The majority of new therapeutic choices for clinicians treating ADHD are novel once daily pharmaceutical dosage formulations that disperse the already well-established molecules methylphenidate or amphetamine in different patterns throughout the day. Recently established practice guidelines on the pharmacotherapy of ADHD have not identified an agent of first choice, but generally recommend starting with either a methylphenidate or amphetamine formulation. *dl*-threo-methylphenidate, the most widely prescribed medication for ADHD is available in numerous oral dosage forms including short-acting agents, intermediate-acting, and extended release (ER) or modified release agents. Recently, a transdermal patch (ie, Daytrana®) has become available. All of the newer once daily formulations (Table 41-1) have been proven effective on primary ADHD symptoms. One approach commonly used is to

TABLE 41-1. ADHD Pharmacotheraphy

Generic Name	Trade Name	Web Site	Dosage Forms	Initial Dose	Usual Doses	Putative Mechanism(s) of Action
Atomoxetine	Strattera®	http://www.strattera.com/index.jsp	Capsule: 10, 18, 25, 40, 60, 80, and 100mg	Children and adolescents up to 70kg body weight initiate at 0.5mg/kg. If greater than 70 kg initiate at 40 mg	Usual target daily dose is 80 mg to a maximum of 100 mg.	Selective reuptake inhibition of pre-synaptic norepinephrine transporter.
Bupropion*	Wellbutrin® Wellbutrin® SR Wellbutrin® XL	http://us.gsk.com/products/assets/us_wellbutrinXL.pdf	Tablet: 75 mg, 100 mg Slow-release (SR) tablet: 100 mg, 150 mg, and 200 mg SRER (XL) tablets: 150 mg and 300 mg	IR: For adults,100 mg PO BID. SR: For adults, initiate at 150mg once daily for several days until tolerability is established, then twice daily. XL: For adults, 150mg daily to establish tolerability with a target of 300mg/d	1.4–6 mg/kg/d (usual maximum 300 mg of IR tablets, 400 mg of SR tablet, and 450 mg/d of the XL formulation)	Dopaminergic effects; weak reuptake inhibitor
Clonidine*	Catapres®, Catapres-TTS® Generics	http://www.bidocs.com/renetnt:/Prescribing+Information/PIs/Catapres+Tabs/CatTab.pdf	Tablet: 0.1 mg, 0.2 mg, 0.3 mg Transdermal patch: 0.1 mg/d, 0.2 mg/d, 0.3 mg/d-change q5–7 days	0.05–0.1 mg PO qhs	Maximum of 0.9 mg/d in divided doses q8h, with the majority given at bedtime. If used for sleep, use maximum of 0.4mg PO qhs	Inhibits norepinephrine release
Desipramine*	Norpramin®, generics	http://products.sanofi-aventis.us/norpramin/norpramin.pdf	Tablet: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg	10–25 mg PO daily	1–5 mg/kg/d in divided doses (usual maximum 300 mg/d)	Inhibits reuptake of monoamines-primarily norepinephrine
Dextroamphetamine	Dexedrine® and generics	http://us.gsk.com/products/assets/us_dexedrine.pdf	Sustained-release capsule: 5 mg, 10 mg, 15 mg Elixir: 1 mg/mL Tablet: 5 mg, 10 mg	2.5–5 mg PO QAM; can adjust at weekly intervals.	0.1–0.5 mg/kg in divided doses all before 5 PM or QAM as a sustained-release product (usual maximum, 40 mg/d)	Increases synaptic availability of dopamine and norepinephrine
	Adderall® generics	http://www.adderallxr.com/assets/pdf/prescribing_information.pdf	Tablets: 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 30 mg	5–10 mg PO QAM; can adjust weekly.	5–30 mg QD or 5–15 mg BID	
Mixed amphetamine salts	Adderall XR®		Capsules: 5 mg 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg	10 mg QD	10–30 mg QD	
Guanfacine	Tenex® generics		Tablet: 1 mg, 2 mg	0.5 mg/day PO qhs	0.5mg PO BID to a maximum of 2 mg PO BID	Inhibit norepinephrine release
Imipramine	Tofranil® generics	http://pharmaceuticals.mallinckrodt.com/_attachments/PackageInserts/47-Tofranil.pdf	May increase by 5–10 mg intervals q weekly as needed Capsule: 75 mg, 100 mg, 125 mg, 150 mg Tablet: 10 mg, 25 mg, 50 mg	10–25 mg PO daily	1–5 mg/kg/d in divided doses (usual maximum 200 mg/d)	Blocks reuptake of neurotransmitters dopamine, norepinephrine, and serotonin (5-HT)

TABLE 41-1. ADHD Pharmacotheraphy (Continued)

Generic Name	Trade Name	Web Site	Dosage Forms	Initial Dose	Usual Doses	Putative Mechanism(s) of Action
dl-methylphenidate	Ritalin®, Methylin™, and generics	http://www.pharma.us.novartis.com/product/pi/pdf/ritalin.pdf	Tablets: 5 mg, 10 mg, 20 mg	2.5–5 mg PO with breakfast and lunch; can adjust at weekly intervals	0.3–2 mg/kg/d in divided doses all before 5 PM or QAM as a sustained-release product (usual maximum, 60 mg/d for *dl*-methylphenidate, 20 mg/d for dexmethylphenidate)	Elevates synaptic dopamine as well as norepinephrine in the brain by blocking monoamine reuptake.
dl-methylphenidate	Concerta®	http://www.concerta.net/html/concerta/patient_info.pdf?	OROS™ tablets: 18 mg, 27 mg, 36 mg, 54 mg	18 mg PO QAM; can adjust at weekly intervals		
	Metadate CD®	http://www.celltechgroup.com/Products/PI/Metadate_CD_R312E.pdf	Biphasic capsule: 10 mg, 20 mg, 30 mg	10 mg PO QAM; can adjust at weekly intervals		
	Ritalin-SR®, Methylin™ ER, Metadate ER®, and generics	http://www.pharma.us.novartis.com/product/pi/pdf/ritalin_ritalin-sr.pdf	Sustained-release tablet: 10 mg, 20 mg	10 mg PO QAM; can adjust at weekly intervals		
dl-methylphenidate	Ritalin® LA	http://www.pharma.us.novartis.com/product/pi/pdf/ritalin_la.pdf	ER capsule: 10 mg, 20 mg, 30 mg, 40 mg	10 mg PO QAM; can adjust at weekly intervals		
	Daytrana™	http://www.daytrana.com/PrescribingInformation.aspx	Transdermal patch: 10, 15, 20, and 30mg delivered over 9 hr wear time	10 mg patch applied to hip 2 hrs before desired effect.		
d-methylphenidate (dexmethylphenidate)	Focalin® Focalin® XR	http://www.pharma.us.novartis.com/product/pi/pdf/focalin.pdf	Tablet: 2.5 mg, 5 mg, 7.5 mg, 10 mg	2.5 mg PO with breakfast and lunch; can adjust at weekly intervals		
		http://www.focalinxr.com/info/tools/prescribing.jsp	ER capsules: 5 mg, 10 mg, 15 mg, and 20 mg			
Nortriptyline*	Pamelor® Generics	http://pharmaceuticals.mallinckrodt.com/_attachments/packageinserts/40-pamelor.pdf	Capsule: 10 mg, 25 mg, 50 mg, 75 mg Solution: 2 mg/mL	10–25 mg PO daily	10–75 mg/d or 0.4–4.5 mg/kg/d (usual maximum 150 mg/d)	Blocks reuptake of monoamines

Continued on next page

TABLE 41-1. ADHD Pharmacotheraphy (Continued)

Generic Name	Tmax (hrs)	Protein Binding (%)	Elimination	Half Life (hrs)
Atomoxetine	1–2	99	hepatic$^{\psi}$	5–6
Bupropion*	2 hrs with IR and ~6 hrs with SR formulation	84	hepatic	9–21
Clonidine* (oral)	2–3	20–40	Unchanged and as metabolites in the urine and feces	6–20
Desipramine*	4–6	70–90	hepatic	12–60
Dextroamphetamine	1–1.5	16	hepatic, pH dependent renal elimination	6–8 in children
Guanfacine*	1–4	70	unchanged and as metabolites in the urine	10–30
Imipramine*	1–2	85–95	hepatic, including metabolism to desipramine	6–28
Methylphenidate	1–2 for IR oral formulation	~28	metabolism by carboxylesterase-1, little CYP450 involvement	2–4
Mixed amphetamine salts (XR)	7 with XR and ~3 with IR	Not reported, dextroxamphetamine component reported at 16%	hepatic, pH dependent renal elimination	11–13
Modafinil	2–4	~60	hepatic	15

Generic Name	Precautions	Adverse Events	Drug Interactions
Bupropion*	Avoid in patients with eating disorders, seizure disorders and individuals on MAO inhibitors and the additional bupropion product utilized for smoking cessation and marketed under the proprietary name Zyban®	Agitation, insomnia, fever, headache, psychosis, confusion, restlessness, dizziness, seizures, nausea, dry mouth, constipation, weight loss, hallucinations	Although little published clinical data. exist, in vitro studies suggest the possibility for increases in the clearance of carbamazepine, phenytoin, and phenobarbital through CYP induction; may *decrease* the clearance of other therapeutic agents through inhibition of CYP2D6/2B6; may cause hypertensive crisis in patients on monoamine oxidase (MAO) inhibitors.
Clonidine*	Avoid in patients with cerebrovascular disease; do NOT abruptly discontinue therapy, taper over 1 week or more	Drowsiness, dizziness, dry mouth, constipation, orthostatic hypotension, mental depression	β-blockers may potentiate bradycardia and may increase the rebound hypertension of withdrawal; TCAs inhibit the hypotensive effects of clonidine
Desipramine*	Avoid in patients with cardiovascular disease, seizure disorders, hyperthyroidism, suicidal risk; do not discontinue abruptly	Dizziness, drowsiness, headache, weight gain, nausea, dry mouth constipation, postural hypotension, tachycardia, seizures, sudden death	May cause hypertensive crisis in patients on MAO inhibitors; antagonize the hypotensive effects of clonidine; potentiation of sympathomimetic agents
d-amphetamine/mixed amphetamine salts	Avoid in patients with cardiovascular disease, hypertension, hyperthyroidism, agitation, psychosis, seizures, substance abuse, or tics	tachycardia, nervousness, insomnia, anorexia, stomach ache, increased blood pressure, dry mouth	May cause hypertensive crisis in patients on MAO inhibitors; arrhythmias in patients receiving general anesthetics; oppose the effects of adrenergic blockers and antihypertensive agents; alkalization of urine prolongs $t_{1/2}$ of amphetamines, acidification shortens $t_{1/2}$ of amphetamines
Guanfacine*	Avoid in patient with severe cerebrovascular disease	Somnolence, dizziness, dry mouth, constipation, fatigue, nausea	TCAs, antihypertensive agents, and sympathomimetic agents may affect blood pressure
Imipramine*	Avoid in patients with cardiovascular disease, seizure disorders, hyperthyroidism, suicidal risk; do not discontinue abruptly	Dizziness, drowsiness, headache, weight gain, nausea, dry mouth constipation, postural hypotension, tachycardia, seizures, sudden death	May cause hypertensive crisis in patients on MAO inhibitors; blocks hypotensive effects of clonidine, potentiation of sympathomimetic agents

TABLE 41-1. ADHD Pharmacotheraphy (Continued)

Generic Name	Precautions	Adverse Events	Drug Interactions
Methylphenidate	avoid in patients with marked anxiety, tension, agitation, hypertension, psychosis, seizures, substance abuse, or tics	tachycardia, nervousness, insomnia, anorexia, stomach ache	Although package insert materials suggest it may increase blood concentrations of TCAs, warfarin, phenytoin, phenobarbital and primidone, but there is poor documentation of these interactions which find their basis in older and limited case reports, and recent in vitro studies indicate methylphenidate does not inhibit any of the major CYPs; avoid use within 14 days of MAO inhibitor use.
Modafinil*	Avoid in patients with mitral valve prolapse and left ventricular hypertrophy.	Insomnia, headache and nausea are among the most commonly reported side effects.	Modafinil has the ability to modestly induce CYP3A4, 1A2, and 2B6 suggesting medications metabolized through these systems including oral contraceptives (CYP3A4) may have efficacy reduced. Additionally, modafinil may inhibit the activity of CYP2C9.
Nortriptyline*	Avoid in patients with cardiovascular disease, seizure disorders, hyperthyroidism, do not discontinue abruptly	Dizziness, drowsiness, headache, weight gain, nausea, dry mouth constipation, postural hypotension, tachycardia, seizures, sudden death	May cause hypertensive crisis in patients on MAO inhibitors; antagonizes hypotensive effects of clonidine, potentiation of sympathomimetic agents.

ΨThe designation of "hepatic metabolism" within the present table generally refers in broad terms to oxidative metabolism (eg, CYP450)
*indicates drug is not currently FDA-approved for the treatment of ADHD

initiate a single 18 mg morning dose of OROS™ methylphenidate that approximates the time course of immediate-release (IR) drug taken every 4 hours, or thrice daily dosing (see Table 41-1). Maximal doses are in the range of 60 mg; children weighing less than 25 kg should rarely receive a single dose of methylphenidate > 20 mg. However, weight-based dosing has not ultimately been shown to be helpful and dosing remains largely empiric. There are no standard titration schedules but waiting a week for feedback from caregivers before changing the dosage is recommended. Finally, the use of therapeutic drug monitoring has not proven useful with methylphenidate or any of the psychostimulants and is an unwise use of resources. As in the MTA Trial, it is preferable to not discontinue stimulant medication during weekends or holidays unless the need for medication in the coming school year must be assessed.

There are no consistent data indicating better results with dextroamphetamine, or mixed salts of dextroamphetamine and levoamphetamine (Adderall®) but unlike methylphenidate, which is FDA-approved for use in children 6 years of age and older, amphetamines are approved for use in children as young as 3 years of age although there is ample evidence of use of other agents in this preschool aged population. Nevertheless, between 3 and 6 years of age, it is my own practice to use dextroamphetamine for children with ADHD.

Most adverse effects with methylphenidate or amphetamines can be viewed as a class effect. Typically, they are mild and easily improve with adjustments in dose and timing. Behavioral rebound, appetite suppression, and mood instability are much less common with ER formulations of psychostimulants than with IR compounds. With regard to drug interactions with methylphenidate and amphetamine formulations, much of the information found within the package insert materials or Physician's Desk Reference (PDR) is based upon isolated case reports rather than any formal *in vitro* or *in vivo* study. This is largely a consequence of "holdover" information contained in package literature in the past with recognition that methylphenidate and amphetamine have been in continuous clinical use for approximately 50 and 80 years, respectively. Some interactions such as those purported between methylphenidate and various anticonvulsants are highly questionable, while others, such as the influence of urinary pH on amphetamine excretion, appear well founded. Recent studies indicate neither drug affects or is influenced by the polymorphic efflux drug transporter P-glycoprotein. Atomoxetine (Strattera®) one of the newest medications to become available for ADHD treatment, joins the methylphenidate and amphetamine formulations as the only agents that presently have specific FDA approval for treating ADHD. Atomoxetine is the

only molecule introduced for ADHD in over a decade that represents an entirely novel drug entity rather than just a dosage form refinement of an existing medication. Atomoxetine is a norepinephrine reuptake inhibitor that is attractive to many clinicians because, unlike the psychostimulants, it is not a controlled substance with all the attendant regulatory issues, and valid concerns over drug diversion and abuse. Further, an attribute particularly welcomed by the parents or caregivers of ADHD children was its non-Schedule II status thereby avoiding the need for monthly written prescriptions and allowing for refills at the prescribers' discretion. Caregivers largely welcomed atomoxetine because it was effectively marketed as a non-stimulant with essentially no abuse potential. However, post-marketing experience suggest it may not be as effective as the psychostimulants for managing core ADHD symptoms, and clearly the onset of therapeutic effects is not as immediate as those generally seen with methylphenidate or amphetamine formulations. Additionally, atomoxetine does not have a substantially improved side-effect profile compared to traditional agents. In my practice, atomoxetine is first-line therapy for ADHD when caregivers strongly resist the use of traditional psychostimulants despite the best educational efforts. It should be recognized that the oral bioavailability and clearance of atomoxetine are highly influenced by cytochrome P450 (CYP) 2D6 (CYP2D6) activity. CYP2D6 poor metabolizers (5–10% of the general population) may have up to 10-fold higher plasma concentrations as extensive metabolizers receiving the same dose. Higher blood concentrations are associated with increased side-effects. Likewise, coadministration of medications that inhibit CYP2D6 activity (eg, paroxetine) can result in significantly elevated concentrations of atomoxetine.

Sleep difficulties are common in ADHD and can be aggravated by use of psychostimulants. Initial dosage, dose timing or dosage interval adjustments, as well as education or reinforcement to caregivers of the fundamentals of good sleep hygiene, are conservative initial measures which may alleviate this problem. Additionally, some long-acting psychostimulants (eg, mixed amphetamine salts) may produce greater sleep disturbances than others in individual patients. Should these measures be insufficient, the use of the α_2 agonist clonidine (Catapres®) is effective in most children with ADHD and insomnia and can also address some symptoms of ADHD and other behavioral disorders which often co-exist. The use of over-the-counter substances such as the neurohormone melatonin is formally being investigated but cannot be recommended for routine use presently. Finally, there are many anecdotal reports of patients who in fact have *improved* sleep with psychostimulant treatment.

Although not FDA approved for this indication, clonidine is first-line therapy in children with ADHD and tic disorders because the drug is effective in both; if clonidine does not adequately suppress severe tics, second generation antipsychotics in combination with psychostimulants can be effective for both tics and associated ADHD. There is extensive clinical experience and published data with clonidine use in children for this disorder. If clonidine suppresses tics but produces excessive sedation, guanfacine (Tenex®) has been an effective alternative medication from the same class (ie, α_2 agonist) because it is less sedating. There has been some controversy in the literature with regard to the combination of methylphenidate and clonidine after a series of 4 sudden deaths in patients reported to the FDA. However, closer examination of these individual cases found no firm connection with this particular medication combination and the deaths reported. Additionally, an enormous amount of patients receive this combination daily, and the only formal prospective studies available that assess the safety of this combination have found it to be safe. Routinely obtaining an electrocardiogram (ECG) before initiating clonidine, guanfacine, or tricyclic antidepressants (TCAs) is advised because of potentially life-threatening complications associated with using these drugs in children with cardiac arrythmias or conduction defects. When increasing doses of adrenergic drugs (clonidine and guanfacine) or TCAs to usual maximum-tolerated doses, ECGs are obtained.

In 2005, after a number of years of carrying a boxed warning, the FDA concluded that the overall risk of liver toxicity from pemoline (Cylert®) and generic pemoline products outweighed the benefits of this drug. In May 2005, Abbott Laboratories chose to stop sales and marketing of proprietary Cylert in the U.S. All generic companies also agreed to stop sales and marketing of this product, thus it is no longer a treatment option. The TCAs imipramine, desipramine, and nortryptiline are effective yet not preferred first-line therapies in ADHD. These drugs are most useful when psychostimulants or other non-stimulants (eg, atomoxetine, clonidine) fail to adequately control ADHD symptoms. When ADHD and migraine co-exist, or if ADHD and anxiety coexist, nortriptyline is the drug of choice. In patients with complex ADHD, unstable mood disorders, and substance abuse, bupropion is an effective non-TCA.

Modafinil (Provigil®) is a novel vigilance and wakefulness promoting agent whose exact mechanism of action is unknown. However, it does not appear to have direct or indirect dopaminergic or noradrenergic activity and is believed to act through the histaminergic system and, at lower doses, does not appear to activate areas of the brain associated with reward. Consequently, it is viewed as having lower abuse potential than methylphenidate or

amphetamine and is classified as a Schedule IV controlled substance. Modafinil is presently FDA approved for the treatment of narcolepsy, obstructive sleep apnea/hypopnea, and shift work sleep disorder in individuals 16 years of age and older. It has been evaluated for the short-term treatment of ADHD in both children and adults in several large double-blind, randomized, placebo-controlled studies that utilized a film-coated tablet and appeared to be effective in reducing ADHD symptoms using a number of standard rating scales. Insomnia and headache were the most commonly reported side effects in clinical trials. However, it should be noted that modafinil has not received FDA approval for the treatment of ADHD to date, and it is unclear if approval will be forthcoming. The drug is however, frequently prescribed "off-label" for ADHD and may represent an alternative choice for some patients.

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Practitioner and Patient Resources

See available Web sites for each drug in Table 41-1.

Chapter 42

Is My Child Ready for School?

Daune L. MacGregor, MD, FRCP(C)

To answer the question, frequently asked by parents of young children, "Is my child ready for school?" the pediatrician or family physician must assess a child's maturational and neurodevelopmental status, physical and emotional health, and overall well being. A review of these issues and knowledge of available screening tests enable physicians to make an appropriate recommendation.

Simply defined, school readiness means a child is prepared to participate successfully in formal schooling. School readiness implies there is capacity to learn, grow, and achieve in a school environment. Whether a child has the social or preacademic skills necessary for school readiness depends on many factors. The following areas are considered prerequisites for school readiness: good physical health, emotional maturity, social confidence, satisfactory language development, and general knowledge.

An appreciation of the elements necessary for school readiness requires an understanding of the crucial dimensions of child development, including self-regulation, the establishment of early relationships, knowledge acquisition, and the development of specific skills. These in turn are affected by individual neurobiology, relationships with caregivers, and physical or psychosocial exposures in the caregiving environment.

School readiness defined more broadly implies that schools are ready for children, children are ready for school, and parents and communities support a child's developmental progress. In a different context, school readiness can be considered a measure of performance of the success of various early childhood programs.

Research studies have demonstrated that both biologic and environmental factors influence intelligence and school success. Studies of adopted children have shown that biologic and adoptive parents' socioeconomic status and intelligence contribute to the child's status at early school age. Evidence also suggests that long-term educational, intellectual, and behavioral problems are associated with prenatal and passive exposure to tobacco smoke, with research demonstrating independent association of children's household exposure to tobacco smoke and early school failure.

The reduction in costs for home computers and educational software has resulted in more children having exposure in their preschool years to computers. Children with access to a computer when tested, have better performance on school readiness and cognitive development. Early television viewing has also been studied. Viewing child-audience (rather than general-audience) information programming between two and three years of age is predictive of high performance on tests of reading, math, receptive vocabulary and school readiness.

Other work has confirmed that all but the most severe perinatal complications have been alleviated or "washed out" by the time a child is 10 years old. Early intervention can improve short- and long-term outcomes for socially disadvantaged children and those with high biologic risks—low birth weight or chronic health conditions, such as sickle cell anemia, cystic fibrosis, diabetes, or iron deficiency.

Interpretation and strengthening of school readiness skills now requires a different focus or approach given the technologic nature of the information-based economy and society in which children grow and develop. There is an increasing emphasis on the learner having an active role in seeking and applying knowledge. Self-regulated learning requires children to achieve different skills in goal-setting, strategy use, and self-monitoring.

The physician plays a crucial role in the early identification of children who are not ready to begin the tasks of academic learning. The goal of child health supervision is to promote optimal growth and development using the tools of surveillance, anticipatory guidance, and advocacy.

Neuromaturational Factors

An understanding of the neurologic aspects of school readiness can be achieved by analyzing prereading and number skills and reviewing the contribution of the development of language, attention, and memory. Higher-level executive or organizational abilities must be adequately developed for school success.

In the prereading stages, three skills contribute to a child's ability to successfully learn to read. One skill involves the ability to analyze sound patterns into segments according to their phonemic structure. This implies that a child is able to analyze the stream of sound into its constituent patterns and rhythms. The second skill concerns print-level knowledge. This involves the ability to track print across a page and requires intact horizontal eye tracking. Another aspect of print-level knowledge is what the child knows about the letters, numbers, and the conventions of print. The third skill required for early reading involves the ability to associate sound patterns with visual symbols.

Children must have a well-developed understanding and use of number concepts, including performance of specific mathematical operations and mental calculations under time constraints. These skills evolve to solving applied arithmetic word problems and understanding quantitative concepts.

Other important skills to be acquired include increased speed of processing information and the ability to concentrate and pay attention. Attention and concentration require a variety of skills, including the ability to sustain attention over time, which is measured by vigilance tests, and the complementary ability to control interfering information.

A similar variety of skills are involved in memory: the ability to register incoming information and hold it in memory, learn new habits, store information in long-term memory, and recall it in the context of experiences or when and how a memorable event occurred. Remembering also involves the ability to impose an effective organization on what is heard such that efficient schemes are established and mental frameworks developed to guide the retrieval of information from long-term memory in an organized manner. Another important aspect of school readiness involves a child's oral language and speech capacities. Language abilities must be assessed by evaluating various component skills: listening, speaking, semantics (knowledge of words, including their meaning and relationship to other words), and syntax (the ability to sequence words and organize phrases to form grammatically appropriate sentences).

Developmental Factors

Practitioners will be able to judge school readiness, in part, by assessing a child's developmental strides in motor, language, emotional, and cognitive skills over time. Language development during infancy and the preschool years is considered the strongest correlate of academic achievement.

A recently published research study associated a history of otitis media and related hearing loss in infancy with lower scores on school readiness measures of mathematical skills. Direct measures of language development did not show a significant relationship when other factors, such as the child's gender, socioeconomic status, maternal education level, and responsive home or child-care environment, were considered. Difficulties with mathematics were associated with lower scores in auditory closure tasks.

The influence of school entrance age on reading and mathematics achievement has been examined at the first grade level. The results of this research show that younger children in the first grade of academic exposure make as much progress over the school year as do older first graders. Entrance age is not a good predictor of learning or academic risk.

A child who has been identified as having a developmental delay or disability will require special consideration in the transition from a preschool setting. Concern should be focused on the following factors:

- The child's readiness for a more structured or full-day program
- Behavioral issues. Is the child disruptive? Can the child pay attention and participate in group activities and instruction? Does the child engage in socially appropriate behavior?
- Safety in less closely supervised school settings
- The child's ability to locate and manage belongings
- The child's ability to use the toilet, eat, and dress as required in the school setting

Assessment of School Readiness: Screening Testing

The American Academy of Pediatrics' committees on School Health, Early Childhood Education, Adoption, and Dependent Care have provided a consensus statement, noting that there must be caution in the use of school readiness testing. The statement comments on the high degree of variability in normal development and emphasizes that school programs should be flexible and adaptable to each child's individual needs and characteristics.

The following principles are considered important:

- All children are entitled to education in an environment where the great variability in early child development is understood and supported.
- Readiness testing that relies on screening instruments and procedures should not be the sole basis for special education placement or services, nor should it be used to keep a child from access to formal education if the child is of legal age to attend school.
- If readiness screening suggests that a child has significant developmental delays or signs of emotional or behavioral problems, standardized tests that evaluate all relevant aspects of development need to be administered on a one-on-one basis by qualified professionals (experienced with children of preschool age) to determine whether special class placement or special services are needed.

Screening tests should not be used to make placement decisions. The requirement for a special education service must be based on careful analysis of data obtained from individually administered standardized developmental tests. Qualified professionals required for testing children for preschool and academic entry include child psychologists, speech and language pathologists, educators, and pediatricians.

The purpose of screening by physicians for school readiness is to ensure that individual children have skills for successful early school achievement and to develop a comprehensive plan with other professionals that will evaluate and monitor children who are at risk for school failure.

The pediatric assessment at a 5-year-old's health maintenance visit should focus on physical health and developmental and behavioral functioning by detailed medical history review and physical evaluation.

Table 42-1 reviews the screening tools available. Routine isolated use of brief school readiness testing by pediatricians or family physicians is of concern because the predictive validity and reliability of these tests are

TABLE 42-1. Screening Tools to Assess School Readiness

Test	Age Level	Administration	Comments
Denver Developmental Screening Test	Up to age 6 years	Pediatric clinicians	Valid for screening Tends to result in under-referral of children at risk
Bracken Basic Concept Scale – Revised	2½–7 years	Some special training required	Measures 6 areas of concepts and readiness
Minnesota Preschool Affect Rating Scale (MN-PARS)	3–6 years	Some special training required	Affect rating scale for self-regulatory behaviours
Pediatric Examination of Education Readiness (PEER)	4–6 years	Requires special training	Lengthy Not recommended for routine screening
Metropolitan Readiness Test (MRT)	Kindergarten	No special training	Evaluates skill acquisition Comprehensive measure of prereading skills
Brigance K and 1 Screen	Kindergarten and first grade	No special training	Quick screening
Early Screening Inventory (ESI)	4–6 years	No special training	Easily learned Tends to result in over-referral
Minneapolis Preschool Tool Screening Instrument (MPSI)	3½–5½ years	Some special training	Valid screening
Wechsler Preschool and Primary Scale of Intelligence – Revised (short form)	Up to 6 years	Requires special training	Indicates cognitive and perceptual difficulties
Wide Range Achievement Test (WRAT)	5 years to adult	Requires special training	Determines specific academic disabilities
Springle School Readiness Screening Test (SSRST)	5–6 years	Pediatric clinicians	Some correlation with reading achievement
Stanford-Binet, 4th Edition	5–6 years	Requires special training	Measure of global intelligence
Peabody Picture Vocabulary Test-Revised (PPVT-R)	2½–17 years	Some special training	Measure of receptive vocabulary
Beery Developmental Test of Visual-Motor Integration Revised	3–17 years	Requires special training	Measure of visual perception and motor coordination
Goodenough-Harris Draw-A-Man Test	5 years	Pediatric clinicians	Useful only for screening at the start of the kindergarten year
Preschool Readiness Experimental Screening Scale (PRESS)	5 years	Pediatric clinicians	10-point scale
Boehm Test of Basic Concepts – Third Edition Preschool	3–5 years	No special training	Concepts of size, direction, position in space, time, quality and classification
Test of Gross Motor Development, Second Edition (TEMD-2)	3–11 years	No special training	Tests locomotion and object control (catching)
Phelps Kindergarten Readiness Scale - II (PKRS-II)	5–6 years	Requires special training	Measures verbal, perceptual and auditory processing

not established. Interpreting psychological reports is reviewed in Chapter 43, "An Introduction to Pediatric Neuropsychological Evaluation."

Discussion and Recommendations

The pediatrician or family physician can assess school readiness using a thorough, careful medical history and physical examination. Evaluation should review developmental, family, medical, and social (environmental and socioeconomic) factors that place a child at risk for academic difficulty. In the office or clinic, screening testing can be used as an adjunct—with caution in interpretation.

Physicians should insure that they are aware of the web-based resource materials provided by local school boards to parents in their practice catchment area. It is also appropriate to have knowledge of school readiness issues for disadvantaged children and children in the developing world.

Appropriate levels of developmental services to be provided by pediatricians and family practitioners include routine developmental assessments and guidance and counseling for parents on common developmental issues. After identification, referral is required for intervention programs. Strategies assessed as effective by evidence-based methods that assist the practitioner in promoting development and literacy include "Reach Out and Read." This program involves modeling book sharing and giving books to children and parents to take home from an office visit.

The practitioner should also be aware of new Web-based interaction screening tools that identify children at risk for school failure by measuring school readiness and phonologic awareness. These programs are linked to evidence based interventions (including skill-specific lesson plans, teaching strategies, and behavior management techniques).

A child flagged by the screening tool is then assessed using curriculum-based checklists, with production of an individual learning profile. A database search using this profile as a guideline provides appropriate interventions. The child at school entry who has demonstrated adequate developmental progress in the preschool years and shows age-appropriate social skills should be expected to achieve academic success. If a practitioner suspects or identifies developmental delay or specific learning disabilities, then referral for comprehensive testing and program planning is required.

Suggested Readings

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Practitioner and Patient Resources

American Academy of Child and Adolescent Psychiatry
http://www.aacap.org/
"Facts for Families" gives parents information on a variety of topics.

American Academy of Pediatrics
http://www.aap.org/
A variety of patient and professional information is available.

Neuropsychology Central
E-mail: apa@psych.org
http://www.neuropsychologycentral.com
Neuropsychology Central was established by the American Psychiatric Association in 1995. The primary objectives of this Web site are to describe the importance of neuropsychology as a science of brain and behavior, to increase public knowledge of neuropsychology as a branch of practical medicine, to indicate the contribution which neuropsychology is making to the neurosciences, and to act as a resource for the professional and layperson.

Ready Web – a resource for parents and educators.
Early Childhood and Parenting (ECAP) Collaborative, College of Education
University of Illinois at Urbana-Champaign
http://www.readyweb.crc.uiuc.edu
http://www.successby6-fl.org

Success by 6 is identified with a community's activities undertaken to ensure that children under the age of 6 enter school prepared to be successful throughout the years that follow. The Web site contains many helpful resources, including a publication titled *Will these children be ready for school?* (Maria, 2000).

CHAPTER 43

AN INTRODUCTION TO PEDIATRIC NEUROPSYCHOLOGICAL EVALUATION

MARY C. KRAL, PHD

Though the practitioner will likely receive results from various psychological screenings to consider in evaluating a patient, this chapter focuses specifically on neuropsychological assessment, given its particular relevance to the topics surveyed in this textbook. A thorough overview of the theory and practice of pediatric neuropsychology is beyond the scope of this brief introduction. A number of seminal texts are available for the interested reader.

The field of neuropsychology, which has gained eminence within the past 50 years, seeks to address the integrity of brain processes as expressed in observable behaviors. Within a developmental context, pediatric neuropsychology has emerged as a field distinct from adult neuropsychology and is characterized by inquiry into such areas as development of the frontal systems, plasticity of brain function, cognitive sequelae of various pediatric conditions, and individual differences in the rate and pattern of development. Pediatric neuropsychology attempts to address not only the neurocognitive sequelae of brain injury, but also the neuroanatomic correlates of a broad spectrum of disorders, including psychopathology, developmental disabilities, and cognitive aspects of various pediatric conditions.

The Purpose of Pediatric Neuropsychological Evaluation

Initially, the field of neuropsychology emphasized the detection and localization of brain lesions, often using a single psychometric instrument. The strictly diagnostic function of neuropsychological evaluation has been eclipsed by recent advances in technology (eg, neuroimaging) that have increasingly assumed this role with greater accuracy. More recently, neuropsychological evaluation focuses largely on the behavioral or functional sequelae of central nervous system impairment. This shift in emphasis involves a description of "impaired" versus "spared" abilities, or functional strengths and weaknesses. Some have referred to this evolution as the "psychologizing" of neuropsychology, in that the qualitative aspects of an individual's performance have become an important aspect of neuropsychological evaluation, in addition to the profile of quantitative scores. For example, a "process approach" to neuropsychological assessment considers an individual's use of strategies, as well as their idiosyncratic patterns of errors, when problem-solving.

Currently, pediatric neuropsychological evaluation has a number of purposes, including fine diagnostic discriminations (eg, mild traumatic brain injury), diagnostic screening, and differential diagnosis (eg, subtypes of neurodevelopmental disorders, psychiatric versus organic etiology). Neuropsychological evaluation also provides a baseline of performance against which to

compare a child's recovery of function, developmental progress, or response to treatment intervention. Finally, neuropsychological assessment informs treatment, such that a child's profile of functional strengths and weakness guides specific targets for remediation. The future of neuropsychological assessment will include the validation of psychometric instruments with various brain imaging techniques. In addition, the field will be characterized by an increasing emphasis on cognitive rehabilitation. This shift from a diagnostic-oriented approach to a treatment-oriented approach will be concerned with relating a child's neuropsychological profile to enhancement of daily functioning.

Developmental Considerations

Pediatric neuropsychological assessment is a complex enterprise, and an accurate conceptualization of higher-order cognitive processes in children cannot simply be a generalization of adult-based models. The relationship of brain injury within the context of development is a complex interaction of multiple variables. For example, children may experience different sources of brain insult (eg, prenatal exposure to teratogens, birth trauma, and postnatal infections) compared with those of adults (eg, cerebral vascular accidents and dementing conditions). Moreover, the course of recovery of function is quite different for the developing brain, although a child and an adult may experience similar sources of central nervous system injury (eg, brain tumor, traumatic brain injury, seizure disorders). Children may perform differently at various developmental stages because they employ different cognitive strategies as they mature. Children who experience brain insult at an early age may not demonstrate the full range of deficits until certain cognitive functions that rely upon the impaired cortical regions reach maturity at a later age. The pediatric neuropsychologist also considers contextual variables, such as socioeconomic status, psychosocial variables (eg, family dynamics, trauma history, or stressors), and educational attainment, each of which has demonstrated sizable contributions to cognitive outcome following neurologic trauma. Finally, premorbid functioning is a crucial part of neuropsychological assessment, especially when establishing a decrement in functioning subsequent to brain insult.

Approaches to Pediatric Neuropsychological Evaluation

Because the goal of neuropsychological assessment is the evaluation of the behavioral expression of brain function, no single psychometric test can adequately assess the broad range of brain-behavior relationships. Therefore, comprehensive neuropsychological evaluation involves the collection of multiple sources of information obtained through clinical interviews with a child's caregivers and teachers, review of educational and medical records, administration of psychometric measures designed to assess various aspects of neurocognitive functioning, and careful observation of behaviors during the evaluation. Psychometric instruments yield samples of behavior from which the relative integrity of brain functions are inferred. Because the structures of the brain function in concert, these psychometric measures do not provide "pure" assessments of unitary cognitive functions. Therefore, a battery of psychometric instruments is selected by the pediatric neuropsychologist to obtain a confluence of data regarding specific domains of neuropsychological functioning.

Early on in the field of neuropsychology, "fixed" batteries of psychometric instruments were widely used that were more quantitative in emphasis. Advantages of this approach included objective, standardized procedures and empirically defined, scaled scores that could be compared across tests. The first fixed batteries for children were essentially downward extensions of adult batteries, such as the Halstead Neuropsychological Test Battery for Children (HNTB-C; Reitan and Davison, 1974) and the Luria-Nebraska Neuropsychological Battery—Children's Revision (LNNB-C; Golden, 1986). Because the aforementioned instruments were essentially adult measures that were renormed for use with children, these test batteries lacked tasks that were developmentally appropriate. More recently, the NEPSY (which derives its name from the NE in "neuro" and the PSY in "psychology;" Korkman, Kirk, and Kemp, 1998) provides a well-normed measure designed for children ages 3 through 12 that is based on Lurian theory (Luria, 1973). It is a battery of 27 subtests designed to assess the neuropsychological domains of attention/executive function, language, sensorimotor ability, visuospatial processing, and memory/learning.

In contrast to the fixed battery approach, the "flexible battery approach" has been characterized as more qualitative in emphasis. Although standardized test procedures and derived scores are obtained with the flexible battery approach, a battery of tests are selected from an array of instruments in an attempt to tailor the evaluation to the specific referral question and suspected neurocognitive deficits. This approach often begins with a core battery of tests that assess the broad domains of neurocognitive functioning. Performance on this battery subsequently informs the selection of additional measures for both a comprehensive and individualized neuropsychological assessment.

General Components of the Neuropsychological Evaluation

Regardless of the testing orientation used, a measure of general intelligence is often administered, as intellectual functioning provides a reference for performance in other cognitive domains. Intellectual functioning also provides

useful information for making predictions about a child's performance academically. Thus, measures of academic achievement also are administered. Although measures of intellectual functioning and academic achievement provide important information about a child's cognitive status, reliance upon these measures exclusively is problematic for a number of reasons. First, the summary score yielded by measures of general intellectual functioning, often called an "intelligence quotient" (IQ), fails to capture the full range of a child's cognitive abilities. Though this summary or composite score is statistically reliable, much information is lost about performance in specific cognitive domains. More recent versions of intelligence tests address this concern by providing various index scores, each of which assess different cognitive abilities, in addition to an overall composite score. Second, the summary score provided by traditional measures of general intelligence often underestimate the cognitive abilities of children with language-based learning disabilities, as many of the tasks on these measures require verbal mediation. Measures of "nonverbal intelligence" that minimize the demands placed on language have emerged as an alternative to more traditional measures.

In addition to measures of general intellectual functioning and academic achievement, specific domains of neurocognitive functioning are assessed in a pediatric neuropsychological evaluation. These specific domains of neurocognitive functioning may include language, motor functions, perceptual ability (visual, auditory, and tactile), visuospatial/visuomotor functioning, memory/learning, attention, and executive functions (eg, planning/organization, cognitive flexibility, and inhibition). Several examples of psychometric instruments that assess these various neuropsychological domains appear in Table 43-1.

TABLE 43-1. Examples of Psychometric Instruments Used to Assess the Various Neuropsychological Domains

Functional Domain	Assessment Instrument
Intellectual functioning	Differential Ability Scales (DAS; Elliott, 1990) Kaufman Assessment Battery for Children—2nd Edition (KABC-II; Kaufman & Kaufman, 2004) Stanford-Binet Intelligence Scales, 5th edition (SB5; Roid, 2003) Wechsler Intelligence Scale for Children—4th Edition (WISC-IV; Wechsler, 2003)
Academic achievement	Wechsler Individual Achievement Test—2nd Edition (WIAT-II; Wechsler, 2003) Wide Range Achievement Test—3rd revision (WRAT3; Wilkinson, 1993) Woodcock-Johnson III—Tests of Achievement (WJ-III; Woodcock, McGrew & Mather, 2001)
Language	Boston Diagnostic Aphasia Examination—3rd Edition (Goodglass, Kaplan & Barresi, 2000) Clinical Evaluation of Language Fundamentals—4th Edition (CELF-4; Semel, Wiig & Secord, 2003) Comprehensive Test of Phonological Processing (CTOPP; Wagner & Torgesen, 1999) Oral and Written Language Scales (OWLS; Carrow-Woolfolk, 1995) Peabody Picture Vocabulary Test—3rd Edition (PPVT-III; Dunn & Dunn, 1997)
Motor functions	Grip Strength Test and Finger Tapping Test of the HNTB-C (Reitan & Davison, 1974) Grooved Pegboard Test (Klove, 1963) Purdue Pegboard Test (Tiffin & Asher, 1948)
Perceptual ability (visual, auditory, tactile)	Seashore Rhythm Test and Speech Sounds Perception Test of the HNTB-C (Reitan & Davison, 1974) Reitan-Klove Sensory Perceptual Examination (Reitan, 1984) Tactual Performance Test of the HNTB-C (Reitan & Davison, 1974)
Visuospatial functions	Beery-Buktenica Developmental Test of Visual-Motor Integration—5th Edition (DTVMI; Beery, Buktenica & Beery, 2004) Rey Complex Figure Test (RCFT; Meyers & Meyers, 1995)
Memory/learning	California Verbal Learning Test—Children's Version (CVLT-C; Delis, Kramer, Kaplan & Ober, 1994) Children's Memory Scale (CMS; Cohen, 1997) Test of Memory and Learning (TOMAL; Reynolds & Bigler, 1994) Wide Range Assessment of Memory and Learning—2nd Edition (WRAML-2; Sheslow & Adams, 2003)
Attention and executive functions	Delis-Kaplan Executive Functions System (D-KEFS; Delis, Kaplan & Kramer, 2001) Conners' Continuous Performance Test—2nd Edition (CPT-II; Conners, 2000) Tests of Variables of Attention (TOVA; Greenberg, 1996) Tests of Everyday Attention for Children (TEA-Ch; Manly, Robertson, Anderson & Nimmo-Smith, 1999) Wisconsin Card Sorting Test (WCST; Berg, 1948)

As previously stated, pediatric neuropsychological evaluation is increasingly used to address the daily implications of a child's unique profile of cognitive strengths and weaknesses. Thus, a comprehensive neuropsychological evaluation also includes assessment of social/emotional and behavioral functioning. Assessment of behavioral functioning contextualizes neuropsychological functioning. Both parent and teacher ratings of behavior are commonly administered, and in this regard, both broad-band behavior rating scales and narrow-band behavior rating scales are available. Broad-band behavior rating scales assess internalizing behavior problems (eg, symptoms of depression and anxiety, somatic complaints, social withdrawal) and externalizing behavior problems (eg, aggressive and rule-breaking behaviors). Narrow-band behavior rating scales are selected for the purpose of assessing specific symptoms, such as inattention, hyperactivity, or depression. Measures of adaptive behavioral functioning assess practical, everyday skills needed to effectively and independently take care of oneself and the skills necessary to interact with other people. Finally, self-report measures are designed to assess a child's perception of his or her social and emotional adjustment. See Table 43-2 for a list of measures commonly administered for the assessment of social/emotional, behavioral, and adaptive functioning among children.

Psychometric Issues

Again, neuropsychological assessment involves gathering samples of behavior in order to infer the relative integrity of brain function. The psychometric properties of an instrument offer an objective indication that the observed sample of behavior is representative of the child's general behavior. In this regard, the pediatric neuropsychologist selects psychometric instruments that are well standardized. Standardization refers to uniformity of content, administration, and scoring. For example, uniform administration of a psychometric instrument includes adherence to detailed administration procedures that include clearly delineated rules regarding presentation of test materials, time limits, specific oral directions, teaching/demonstration during sample items, queries permitted, and methods of handling questions. Standardization reduces measurement error. Also, the pediatric neuropsychologist seeks to select psychometric instruments that are well normed. Normatization of a psychometric instrument involves the selection of a large, representative sample of individuals for whom the measure is designed. Adequate norms permit comparisons of an individual's performance to the representative group, or standardization sample, so that objective statements can be made about a child's level of performance. In addition, adequate norm-referenced scores permit the comparison of a child's performance on one test to their performance on another test. When choosing a psychometric instrument, the pediatric neuropsychologist also considers whether the characteristics of the normatization sample are comparable to the demographic characteristics of the child.

A sound psychometric instrument also must be reliable and valid. Reliability means that the results a test yields are repeatable and consistent. For example, a child will obtain comparable scores on two different administrations of a test, barring compromise of central nervous system functioning, if the measure is highly reliable. A psychometric instrument is reliable if it is free from measurement error and yields an individual's "true score." Some degree of measurement error is inevitably involved in neuropsychological assessment. Therefore, scores are usually presented along with "confidence intervals." The confidence interval indicates the range within which a child's "true score" is likely to fall, with a given degree of certainty (eg, 90%). Validity means that the psychometric instrument measures the construct (ie, specific neuropsychological ability) that it purports to assess. A valid psychometric instrument

TABLE 43-2. Examples of Behavior Rating Scales and Self-report Measures for Use with Children

Behavioral Domain	Assessment Instrument
Broad-band rating scales	Achenbach Child Behavior Checklist (CBCL; Achenbach, 2001) Achenbach Teacher Report Form (TRF; Achenbach, 2001) Behavior Assessment System for Children (BASC; Reynolds & Kamphaus, 1992)
Narrow-band rating scales	Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy & Kenworthy, 2000) Conners' Rating Scales—Revised (Conners, 1997)
Adaptive behavior rating scales	Adaptive Behavior Assessment System—2nd Edition (ABAS II; Harrison & Oakland, 2003) Vineland Adaptive Behavior Scales: Interview Edition (VABS; Sparrow, Ballas & Ciccetti, 1984)
Child self-report measures	Beck Youth Inventories (Beck, Beck & Jolly, 2001) Behavior Assessment System for Children—Self-Report of Personality (BASC-SRP; Reynolds & Kamphaus, 1992) Piers-Harris Children's Self-Concept Scale—2nd Edition (Piers & Herzberg, 2002) Revised Children's Manifest Anxiety Scale (RCMAS; Reynolds & Richmond, 1998)

permits the pediatric neuropsychologist to draw inferences about a child's performance (eg, make statements about a child's ability to sustain auditory attention on a measure of sustained auditory attention). Statistical procedures, such as confirmatory factor analysis, provide evidence for the validity of specific test instruments. Validity evidence is particularly important when adult measures are renormed for use with child populations.

Pediatric neuropsychological evaluation involves quantifying behavioral samples by transforming raw test scores into norm-referenced scores. Raw scores have little meaning and cannot be used to compare a child's performance to typically developing age-mates. In contrast, norm-referenced scores permit comparison of a child's performance to the performance of children in the normatization sample. The collective performance of children in the normatization sample forms a distribution of scores that is typically bell-shaped. This normal distribution has a range of scores and the majority of scores fall in the center of the distribution. In a normal distribution, one-half of the scores fall below the average, or mean, and one-half of the scores fall above the mean (Figure 43-1). The statistical properties of this normal distribution permit transformation of raw scores into norm-referenced scores, such as percentile ranks, standard scores, and T-scores.

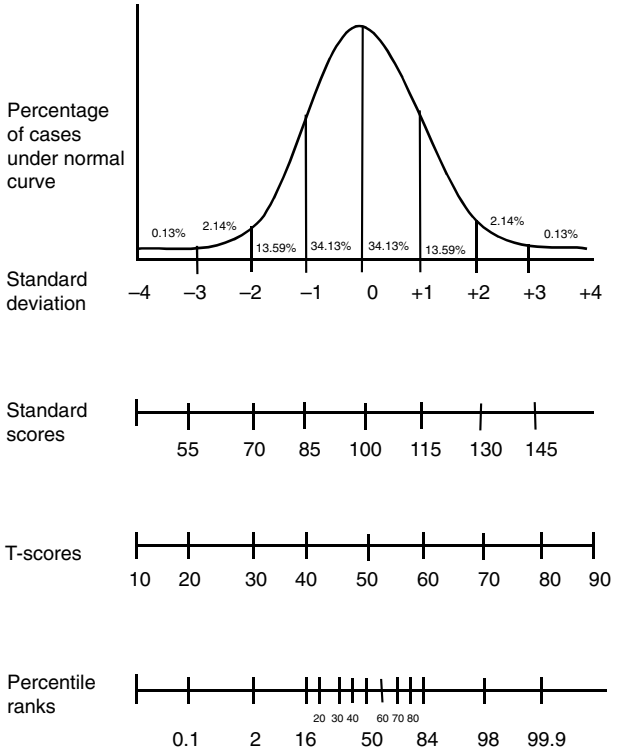

FIGURE 43-1. Normal distribution and norm-referenced scores.

Percentile ranks indicate the relative position of a child's performance when compared with the standardization sample. Percentile ranks provide results that are easily understood. However, percentile ranks may be confused with percentage correct. For example, a score at the 50th percentile does not mean the child obtained 50% of the items correct; rather, the child performed as well or better than 50% of children in the standardization sample. In this case, the child's performance also could be described as falling in the "average range." In addition, percentile ranks may be problematic in as much as they overemphasize differences in scores in the middle of the distribution and underestimate differences in scores at the extremes of the distribution.

Standard scores and T-scores are norm-referenced transformations that express raw scores in terms of standard deviation units from the mean. The standard deviation refers to the amount of variability in the distribution of scores around the mean. When the average standard score is 100 with a standard deviation of 15, approximately 68% of children in the standardization population obtained scores within one standard deviation above and below the mean (ie, 85 to 115). Standard scores also may be presented as "scaled scores" with a mean of 10 and a standard deviation of 3. T-scores also are a commonly used metric. T-scores have a mean of 50 and a standard deviation of 10. Figure 43-1 graphically displays a normal distribution curve and the relative position of various norm referenced scores within the distribution.

Communicating Results in Interpretive Reports

Results of a pediatric neuropsychological evaluation are typically presented in the form of a written report. Reports often are divided into sections that present detailed information about (1) the referral question or presenting problem, (2) developmental, medical, and psychiatric/psychosocial histories, (3) educational history, (4) evaluation procedures, including a list of psychometric instruments administered, (5) general observations of behavior during the evaluation, (6) test results and interpretation, (7) summary, including diagnostic impressions, and (8) recommendations. In addition to a presentation of test scores, a report also may detail qualitative aspects of a child's performance during test administration. The use of particular strategies for remembering a list of unrelated words, perseverative errors, slow cognitive tempo, and distractibility are examples of behaviors that may further explain a child's quantified performance (ie, test score). Many of the recently developed child neuropsychological instruments provide a means of quantifying behavioral observations and making comparisons to the normatization sample.

Although test results and qualitative observations of behavior often are presented within separate neuropsychological domains, these various functions make interactive contributions to a child's daily functioning. Thus, the summary section of the report integrates the findings and presents a profile of a child's neurocognitive strengths and weaknesses. This profile may be symptomatic of a specific developmental disability (eg, dyslexia or attention-deficit hyperactivity disorder) or characteristic of a certain pediatric condition (eg, seizure disorder or traumatic brain injury). The child's neurocognitive profile also may assist with differential diagnosis and inform etiology by localizing affected brain regions. Finally, the child's profile of strengths and weaknesses guides the selection of recommended interventions, including specific therapies (eg, speech/language therapy or occupational therapy) and pharmacologic, educational, and behavioral interventions. Repeated (serial) evaluation may be recommended to monitor developmental progress, gauge the effectiveness of a specific intervention, or assess the impact of a chronic illness on cognitive development.

The results of a pediatric neuropsychological evaluation also are communicated to the child's caregivers during an interpretive session. In contrast to the detail presented in the written report, the pediatric neuropsychologist usually summarizes the findings during the interpretive session. In this regard, a child's performance may be described qualitatively by using descriptive statements such as "average," "high average," or "mildly impaired." The use of descriptive statements may be used to educate the caregivers about child development. Also, the real-world implications of the child's neurocognitive and behavioral strengths and weaknesses tend to be the focus of the interpretive session. The pediatric neuropsychologist engages the child's parents in a dialogue to ensure understanding of the test results and encourage their partnership in effecting change on behalf of the child.

Suggested Readings

Baron IS. Neuropsychological evaluation of the child. New York: Oxford University Press; 2004.

Sattler JM. Assessment of children: cognitive applications. 4th edition. San Diego (CA): Author; 2001.

Yeates KO, Ris MD, Taylor HG. Pediatric neuropsychology: research, theory, and practice. New York: Guilford Press; 2000.

Practitioner and Patient Resources

American Academy of Child and Adolescent Psychiatry (AACAP)
http://www.aacap.org/
The AACAP, a 501(c)(3) non-profit organization, was established in 1953. It is a membership-based organization, composed of more than 6,500 child and adolescent psychiatrists and other interested physicians. Its members actively research, evaluate, diagnose, and treat psychiatric disorders and pride themselves on giving direction to and responding quickly to new developments in addressing the health care needs of children and their families.

American Society for Adolescent Psychiatry (ASAP)
http://www.adolpsych.org/
The ASAP has served the psychiatric profession since 1967. Focusing on teen, adolescence, and young adult issues, ASAP acts both as a professional network for its members and a specialized community dedicated to education development and advocacy of adolescents and the adolescent psychiatric field.

The Federation of Families for Children's Mental Health (FFCMH)
http://www.ffcmh.org/
The national family-run organization dedicated exclusively to helping children with mental health needs and their families achieve a better quality of life. FFCMH provides leadership to develop and sustain a nationwide network of family-run organizations, focuses the passion and cultural diversity of our membership to be a potent force for changing how systems respond to children with mental health needs and their families, and helps policy-makers, agencies, and providers become more effective in delivering services and supports that foster healthy emotional development for all children.

American Psychological Association (APA)
http://www.apa.org/
The American Psychological Association (APA) is a scientific and professional organization that represents psychology in the United States. Comprised of over 150,000 members, APA is the largest association of psychologists worldwide. The mission of APA is the advancement of psychology as a science and profession for the promotion of health, education, and human welfare via sound research and high standards of ethics, conduct, education, and achievement. Division 40, Clinical Neuropsychology, is a scientific and professional division within APA that is specifically devoted to the scientific study of brain-behavior relationships and the clinical application of this knowledge to the understanding and remediation of problem behaviors.

National Dissemination Center for Children with Disabilities (NICHCY)
http://www.nichcy.org/
The National Dissemination Center for Children with Disabilities (NICHCY) is an information center for parents and professionals concerning developmental disabilities. This website includes a wealth of information particularly regarding appropriate educational interventions for children and adolescents with developmental disabilities. Printable fact sheets on specific disabilities and a list of state resources are available in both English and Spanish on this website.

CHAPTER 44

SPEECH AND LANGUAGE DEVELOPMENT AND DISORDERS

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Speech and language disorders are the most common developmentally disabling condition of childhood. Physicians and other health care providers are the first line of defense concerning identification of these problems. Early recognition and intervention are necessary to provide children with the best possible outcome.

All humans communicate. The most effective and efficient communicators use a symbolic system for information delivery: language. Language represents objects or actions in symbolic form. Language communicates ideas, intentions, and emotions—all forms of expression. The listener must extract both explicit and implied meaning from what is said; this constitutes receptive understanding.

Speech and language disorders are the most prevalent developmentally disabling disorders affecting children. Early identification and management of these disorders is paramount to minimize or eliminate the social and educational problems that arise. Most children naturally acquire normal language understanding and expression, although concerns about speech and language skills are voiced by 30% of all parents when questioned by their child's physician during routine well-child check-ups. Current prevalence estimates of speech and language delay in preschool children range from 7 to 10%, with a significantly higher proportion of boys being affected. Pure disorders of receptive and expressive language alone are found in 3 to 6% of children in this age group. Almost any disruption in brain function can affect language acquisition; therefore disorders of language development often accompany a variety of other conditions. Likewise other developmental differences may result from language dysfunction.

The term *speech/language delay* implies that the child will catch up in their language abilities, and for some children, classified as "late talkers," the delay is not permanent. However, one long-term study revealed that 42.5% of young children whose early language delays showed improvement were later found to have reading or cognitive deficits. Preschoolers with language disorders are at higher risk for language-based learning disorders, social, and behavioral problems.

Neurobiologic Basis of Speech and Language

The general location of basic language centers was determined in the nineteenth century by Paul Broca and Carl Wernicke, which then led to the theory of cerebral dominance. For virtually all right-handed people and two-thirds of left-handed people, speech and language are processed in the left cerebral hemisphere. Lesions bordering the sylvian fissure of the dominant hemisphere usually cause disturbances in speech and language. A functional anatomic loop connects the eyes and ears to the visual and auditory system, an intrahemispheral section through white matter connects the temporal with the frontal lobes, and the frontal lobes connect to the mouth and hand. Meaning is provided to sounds and shapes through intrahemispheral and transcallosal pathways to the rest of the brain from the sylvian region.

Recent advances in functional neuroimaging studies have suggested specific cortical areas associated with individual

language skills. Positron emission tomography scans have shown increased metabolic activity across the left and right temporal and frontal cortex areas of the brain during speech and nonspeech acoustic processing. Functional magnetic resonance imaging studies show differences between the sexes, with activation in the left inferior frontal gyrus for males and activation in both right and left inferior frontal areas for females during phonologic tasks. Word analysis and articulation has been mapped to Broca's area of the inferior frontal gyrus, whereas skilled word form discrimination involves the occipitotemporal region.

A substantial heritable component exists in speech and language disorders, but the underlying genetic basis is complex and involves different risk factors. Close examination of families with persistent signs of disordered language skills have suggested a genetic basis; however, exclusive of recognized genetic disorders with strong, specific language differences (eg, velocardiofacial syndrome, Williams syndrome, or fragile X syndrome), no genetic markers for "developmental language disorder" have been clearly identified. Recent genome scanning techniques have identified chromosomes 2, 13, 16, and 19 as having potential candidate genes involved with more common forms of language impairment. Molecular genetic techniques are being initiated to investigate speech and language disorders. A clear understanding of the relationship between the genetic basis of speech (genotype) and various language phenotypes has not yet been developed. The "multi-factor/multi-effect" model is the framework for understanding the genesis of language disorders. That is, a complex variety of biological factors, psychological factors, and social factors act together to promote (or disturb) the process of language acquisition and usage.

Overview of Speech and Language Development

Speech produces complex acoustic signals that communicate meaning and is the result of interactions between the respiratory, laryngeal, and oral structures. This acoustic signal varies with regard to vocal pitch, intonation, and voice quality. The symbols need to conform to the language code so that they can be decoded as meaningful communication. A speech disorder reflects problems with creating the appropriate sounds representing the language symbols (the words), and, therefore, communication is impaired. These problems include speech fluency disorders (*stuttering*), voice disorders, and articulation disorders. Speech disorders may or may not also include weaknesses in expressive language.

Language involves both expressive and receptive components. Expressive language involves the communication of ideas, intentions, and emotions. Receptive language involves understanding what is said by someone else. Receptive language includes auditory comprehension (listening), literate decoding (reading), and mastery of visual signing.

Language involves a number of dimensions. *Phonology* involves phonemes and morphemes. Phonemes are individual sound units that are put together in a particular order to produce morphemes. *Morphemes* are the smallest meaningful units of a word that are combined to create a word. *Syntax*, or grammar, is the order or combination of words in phrases and sentences. The *lexicon*, or vocabulary, is the collection of all meaningful words in a language. *Semantics* are the meanings that correspond to lexical items and sentences. *Prosody* is the vocal intonation that can modify the literal meaning of what is said. *Discourse* is the linking of sentences so that a narrative is constituted. *Pragmatics* refers to the meanings of language in various contexts and can be thought of as the social use of language or the ability to "read" emotional expression. A language disorder may include inability in any of these areas, but will usually only be suspected if the individual demonstrates impaired daily functioning. For example, a child can be said to have a language disorder if he or she has a poor vocabulary, has difficulty generating meaningful messages, or has poor understanding of the use of language in different social contexts. Typical language milestones are listed in Table 44-1.

0 to 12 Months: Precursors to Speech and Language

In the first year of life, the infant's inherent biologic disposition interfaces with variable environmental conditions. Children show varying levels of desire for contact with the environment and the individuals in the immediate environment respond at different degrees of intensity. Very early in life, infants are capable of distinguishing between different classes of speech sounds. Although the child may seem more dependent on environmental reinforcement early on, the second 6 months of life shows clear self-driven imitation of other's speech sounds by the infant's imitative effects, with a rich interplay between the infant and the older individuals in his or her life.

Vocal development occurs in at least four stages: (1) phonation stage (0 to 2 months; quasivowels, glottals), (2) primitive articulation stage (2 to 4 months; cooing), (3) expansion stage (4 to 6 months; full vowels, raspberries, marginal babbling), and (4) canonical stage (6 to 10 months; well-formed syllables, reduplicated sequences). The phonetic characteristics of canonical babbling include well-formed syllables with rapid transitions between consonant and vowel elements and is an immediate precursor of meaningful speech. Vegetative sounds (coughing, sneezing, burping) and fixed vocal signals (crying, laughing, moaning, etc) are different from the *protophones*, or crucial sounds that are specific precursors to speech. Protophones

TABLE 44-1. Speech and Language Milestones

	0 to 12 months	12 to 24 months	24 to 42 months	3½ to 7 years	7 to 12 years
Receptive language	Listens selectively to words, understands 'no'; recognizes own name	Understands up to 50+ words; follows 1-step commands with (12 to14 months) and without (16+ months) a gesture	Knows primary colors, aware of past and future; follows 2-step commands	Follows 3 step commands; understands same vs different; understands "if," "when," "why" questions and common daily living words	Understands all declarative and interrogative sentences; understands abstract language (idioms, proverbs)
Expressive language	0 to 4 months: smiles reciprocally, coos 4 to 9 months, Babbling by 6 to 8 months, gestures by 9 months; first words by 12 months	Points to body parts; points to pictures; moves from single words to 2-word sentences; 25% intelligibility	Uses 3 word sentences; uses adjectives and adverbs, begins to ask questions, uses pronouns and plurals, uses negative, tells full name, age, sex; 50–75% intelligible	Uses complete sentences; Tells a story sequentially; uses past tense, defines in terms of use, asks definitions, uses mature sentence structure and form; by 4 yrs 100% intelligible	Uses mature discourse sentence length; can make infinite number of phrase/sentence combinations from a finite set of rules.

and speech are unique to humans, while vegetative sounds and fixed vocal signals are present in many species.

12 to 24 Months: Early Language

Language development after 1 year of age is often perceived as a general "wellness" indicator of a young child's developmental attainment. Typically, the period between 12 and 18 months of life show the child using language expressively to communicate increasing awareness of concepts and the association with linguistic "labels." The toddler conveys desires, "More!"; specific objects, "Cookie!"; and emotions, "No!" Increasing awareness and mastering of phonology, syntax, semantics, and pragmatics are demonstrated. There is a significant disparity between the receptive word knowledge and expressive use; 50 words may be understood before 10 words are said. Children understand much more than they say and the words understood are not necessarily used.

24 to 42 Months: Word Explosion

As the child's lexicon (vocabulary) increases, reliance on the prosody and facial expression of speakers diminishes. By 2 years of age, most children rely on their understanding of word meanings to develop a full appreciation of the discourse. This is the beginning of "literal" language interpretation, which continues through the late elementary school years for most girls and boys irrespective of cognitive ability. Between 2 and 3 years of age, most children show a dramatic increase in vocabulary (few dozen to 300 to 1,000 words) and expressive complexity. The child increasingly is able to understand and use more complex language forms, such as conditionals ("if...then"), connectors ("but," "however") and prepositions ("on", "under," "beside"). The ability to infer develops and is frequently demonstrated as the child supplies missing information when the speaker delivers an incomplete message. Pragmatically, the child's increasing ability to infer intent and meaning allows him or her to participate in settings away from home.

3½ to 7 Years: Mastering Fluency

In the preschool through the early elementary years, the receptive vocabulary multiplies to 1,000 to 8,000+ words. There is progressive understanding of more complex locational, relational, and temporal word associations. This increasing mastery of connected discourse allows the child to more accurately maintain a conversational topic, completely carry out instructions, and convey new information to an audience. The child improves his pragmatic flexibility as he adjusts speech and language to varying audiences, whereas a younger child often "rambles" with little plot or causal relationships. By 7 years of age, the child's narrative abilities include discourse with a beginning, a middle, and an end.

7 to 12 Years: Communicative Competence

The school years initiate the time of conveying information and mastering information. The school years also are the period where the child learns two skills highly dependent on language: reading and writing. Phonemic awareness must be intact, for fluent reading and written expression is highly dependent on semantic (word knowledge) range and syntactic (grammar) mastery. Although children enter school with varying levels of receptive and expressive abilities, it is expected that by middle school most students will attain adult linguistic levels. Although early adolescents do not fully resemble adults, pragmatically they are expected to demonstrate those skills necessary for larger group settings: taking turns, adapting to novel discourse rules, and cognitive flexibility in conveying ideas (ie, "code switching").

Disorders of Speech Development

Articulation Disorders

An articulation disorder (dysarticulated sounds) is a disorder of the quality of speech characterized by the substitution, omission, distortion, and addition of phonemes. Articulation errors may occasionally occur in typically developing children; however, by age 7 years a child should be able to produce all sounds and sound combinations. A rough rule of thumb is the "2/4, 3/4, 4/4 rule"; to strangers, at 2 years a child should be 50% ("2/4") intelligible, at 3 years 75% ("3/4") intelligible, and at 4 years 100% ("4/4") intelligible. Articulation disorders are the most prevalent type of language problem. Estimates of articulation disorders in preschoolers range from 10% to 15%, and 6% of school-age children. Over 50% of children with articulation disorders have delays in expressive language, and 10–40% have delays in receptive language.

Speech Apraxia/Dyspraxia

Dyspraxia is difficulty with complex movement and motor planning that is not secondary to paralysis, weakness, incoordination, sensory loss, or comprehension impairments. The deficits are presumed to be in the cortical motor association areas and cause disturbances in articulation, phonation, respiration, and resonance, resulting in dysfluent and unintelligible speech. Voluntary oral control during speech is impaired but other oral skills (chewing, swallowing, spitting) are preserved. Verbal dyspraxia is often comorbid with "neurologic soft signs," and associated expressive language delays are often observed.

Voice Disorders and Disorders of Nasal Resonance

Although differences in pitch, loudness, resonance, and quality may occur in isolation, they are often combined with receptive or expressive delays. Abnormalities in resonance lead to voice quality that may sound hypo- or hypernasal. Hypernasal speech is often secondary to velopharyngeal incompetence and may be related to a submucous cleft, palatal incompetence, overt cleft palate, or neurologic dysfunction. Alternatively, hyponasal speech quality may often reflect air impeded by the adenoids. Finally, poor pitch regulation (modulation of tone or volume) may be seen in children with sensory regulation differences (autism, pervasive developmental disorder, Asperger's syndrome), nonverbal learning disorders, and some genetic syndromes (eg, fragile X syndrome).

Fluency Disorders

Dysfluent speech (pauses, hesitations, interjections, prolongations, and interruptions) typically begins in very early childhood (2½ to 4 years), when the child's mastery of larger expressive units is expected, and is known as normal dysfluency of childhood. Continued or progressive dysfluency is more likely stuttering, which arises in the preschool years in 85% of affected children. Boys are affected more often than girls in a 4:1 ratio. Persistent dysfluencies are more likely to occur in repetitions of syllables ("fi-fi-fi-fi-fireman") and sounds ("g-g-g-g-o"), involve prolongations of sounds ("WWWWhy?") or silent 'blocks', in which no sound comes out and associated visible motor movements (such as grimaces or blinking) are seen.

Dysarthria

Dysarthria is a motor speech disorder that involves problems of articulation, respiration, phonation, or prosody as a result of paralysis, muscle weakness, or poor coordination. Motor function may be excessively slow or rapid, with poor timing and decreased range or strength. Dysarthric speech is characterized by weakness in specific speech sound production and is frequently associated with cerebral palsy. Dysarthric speech also may encompass problems in coordinated breath control and head posture.

Disorders of Language Development

Disordered language development may include understanding (receptive disorder), expressing one's thoughts (expressive disorder), or more commonly a mixed receptive/expressive language disorder (Table 44-2). Disordered development may be seen in all language areas: semantics, syntax, morphology, reading, written expression, and pragmatics. The most commonly used labels are developmental language disorder or specific language impairment. These designations imply a clinically significant discrepancy between the clinical cognitive level and formally assessed language skills. Some language specialists also use these two terms for children with formal language score ≥ 2 standard deviations below the mean value for age (ie, standard score ≤ 70), even if the overall cognitive level is not more than 20 points greater than the language score. An overview of the most common developmental language disorders is outlined in Table 44-3.

TABLE 44-2.

Receptive Language	Understanding what is said by someone else; includes auditory comprehension (listening), literate decoding (reading) and mastery of visual signing
Expressive Language	the communication of ideas, intentions and emotions (verbally or nonverbally)
Speech	complex acoustic signals that communicate meaning, and are the result of interactions between the respiratory, laryngeal, and oral structures

TABLE 44-3. Subtypes of Developmental Language Disorders

	Receptive			Expressive				
	Phonology	Syntax	Sematics	Phonology	Syntax	Semantics	Pragmatics	Fluency
Verbal auditory agnosia	↓↓	↓↓	↓↓	↓↓	↓↓	↓	↓	↓↓
Phonologic-syntactic deficit	↓	↓	↓	↓	↓	↓	↓	↓
Semantic-pragmatic deficit	NI	NI	↓↓	NI	NI	↓↓	↓↓	NI or ↓
Lexical-syntactic deficit	NI	↓	↓↓	NI	NI or ↓	↓↓	↓	NI or ↓
Verbal dyspraxia	NI	NI	NI	↓↓	↓↓	↓	NI	↓↓
Phonological production deficit (articulation)	NI	NI	NI	↓	↓	NI or ↓	NI	NI or ↓

Adapted from Current Management in Child Neurology, 1st edition, AU

Receptive Language Disorder

Accurate understanding of what is heard is dependent on abilities separate from innate language knowledge. Precise hearing is essential. The child must have an adequate attention span to register what is said, and memory functions (immediate recall, working memory, short- and long-term memory) must be intact for full meaning to develop.

As linguistic competence ensues, the young child relies more on linguistic knowledge and less on nonlinguistic strategies for comprehension (interpreting communicative gestures and nonword vocalizations, using supportive situational cues, etc). Previously discussed milestones of "typical" receptive language development allow comparison with the following abnormalities often seen in varying combinations: failure to grasp double word meaning, misapplication of emphasis with resulting misinterpretation, weak understanding of complex grammatical structures (eg, double negatives), rare use of clarification questions ("What do you mean?"), overuse of clarification questions ("Tell me again"), or inappropriate responses.

A caveat is that mild receptive disorders may not be discovered in the presence of more severe expressive delays. Adults may assume receptive skills are intact because the child has overcompensated by relying on contextual cues and routines and the adults have modified tasks by giving a series of one-step comments rather than multistep instructions.

Auditory Processing Disorders

The term *auditory processing disorder* (APD) has been recommended to replace the term *central auditory processing disorder* to emphasize the interactions of disorders at both peripheral and central sites. APD is a deficit in the processing of information despite normal auditory thresholds and can be characterized as a receptive language disorder. Characteristically, difficulties are found with comprehension of incoming verbal messages in competing speech or noise backgrounds. APD is not a single disease entity, but rather is a description of functional deficits. It is auditory specific, but is associated with a range of attention, language, and learning deficits, and is best diagnosed with a comprehensive assessment involving audiologists, speech/language pathologists, psychologists, and physicians.

Expressive Language Disorders

Expressive disorders reflect a broad range of delays, from developmentally inappropriate short expressive units (small mean length of utterances), word-finding weakness with phonologic substitutions ("mat" for "map"), semantic switches ("hat" for "scarf"), and inability to master grammatical morphemes (eg, plural "-s", past tense "-ed"). Over time, a child is expected to increase the accuracy and complexity of his or her expressive output. Signs of expressive delays may include the following: using many words to explain a word in lieu of the specific term ("circumlocutions"), use of nonspecific words ("like" or "stuff"), excessive use of "starters" ("you know"), and place holders ("um" or "uh"), difficulty generating a correctly ordered narrative, or using gestures excessively rather than words to convey meaning, more than is developmentally appropriate (eg, the "A-OK" sign with hands).

Mixed Receptive–Expressive Language Disorders

Unless formal language testing using standardized instruments supports the presence solely of an isolated articulation disorder or specific receptive or expressive weakness, a child with a past history of "language delays" should be presumed to have had some combination of language understanding and expression weaknesses. A variety of receptive–expressive subgroups have been labeled including: *verbal auditory agnosia*, an impairment in interpreting the phonology of aural information and resultant limited comprehension of spoken language; *phonologic–syntactic deficit*, extreme difficulty producing language with variable levels of comprehension; *semantic-pragmatic deficit*,

expressively fluent with sophisticated use of words but poor comprehension and shallow use of conversational speech; and *lexical–syntactic deficit*, word-finding weakness and higher order expressive skills weakness.

Pragmatic Disorders

Children with weak pragmatic skills show variable ability to apply the rules governing appropriate use of language for social communication. Generally speaking, the individual has difficulty saying the right thing at the right time with appropriate voice modulation and reciprocal body language and is unable to appropriately regulate social interactions using language. Specific behavior examples might include improper distance from the conversation partner; excessive voice pitch; problems initiating, maintaining, and terminating a conversation; modifying a topic for the audience; and including others in a conversation. Pragmatic weakness may occur in isolation from other disorders of language development but as with other areas may occur independently of cognitive level. Specific developmental disorders often accompany pragmatic weakness, including autism spectrum disorders (autism, Asperger's syndrome) and some nonverbal learning disorders.

Language-Based Reading Disorders

The term most commonly used to describe a reading disorder is *dyslexia*, yet dyslexia is a very specific form of reading disorder: the words are visually perceived but not understood. It is neurobiologic in origin and is characterized by difficulties with accurate and fluent word recognition and by poor spelling and decoding abilities. All weaknesses affecting normal language development can also affect reading or decoding, including poor phonologic awareness, semantic deficiency, syntactic problems, and weak metalinguistics.

Poor *phonologic awareness* impairs ability to associate the individual sounds with visual symbols (letters, words). Difficulties in this area can lead to weakness in decoding written words as well as encoding words during spelling. Weak *semantic abilities* result in the child having a restricted range of word meanings. This deficit affects reading comprehension in later school years, when the vocabulary exponentially increases with additional technical and specialized terms. Children with *syntactic weakness* may have difficulty with reading as the complexity of sentence structure increases. Inverted clauses, ambiguous references, and other "literary" modifications lead to labored reading rate and poor comprehension. Poor *metalinguistics* (ie, understanding how language works) often accompanies "*higher order*" *language weakness* and leads to poor comprehension as reading material transitions from more literal passages to more abstract, conceptual topics.

Written Expression Disorders

Efficient and effective written expression is a predominant and essential skill for academic attainment. Written expression comprises four basic skills: (1) fine motor (to hold and manipulate the writing instrument), (2) attention (focused attention to the task allowing effective task completion), (3) memory (visual memory to identify correct spelling, letter formation, alignment of the prose on the page), and (4) language (all the elements described in reading development). Writing is a very sophisticated skill with respect to language and children with specific language disorders are "at risk" for written expression weakness.

Emotional Responses to Disordered Language Development

Children who struggle to understand and be understood may become chronically frustrated: "...language may have a central role to play in the development of psychiatric disorders in that internalized language and verbally mediated rules play an important role in both self-control and achievement across domains." Vygotsky's earliest work emphasized language as a tool for thought. The child's earliest thoughts may represent internalized dialogues. If the child's language development does not progress normally, there can be interference in the way in which the child processes the social environment. Appropriate behavior and responses to the behavior of other's may ensue.

Language-based learning disabilities, such as disordered reading and written expression, also can be associated with emotional distress in young school-aged children and adolescents. Depressive disorders, separation anxiety and overanxious disorder are found more frequently in 9 to 15 year old students. Older adolescents (15–16 year olds) with reading difficulties (defined by single word reading accuracy at the 18th percentile or lower) have significantly more ADHD, affective disorders and anxiety disorders (specifically, social phobia and generalized anxiety disorders). Substance abuse increased as the reading disabled students became older.

Assessment and Diagnosis

Differential Diagnosis

When screening a child for speech and language impairments, etiologic factors as well as differential diagnosis must be considered. First, the hearing status of the child must be evaluated by formal audiometric evaluation. Even if a child passed a hearing screening at birth, formal behavioral

audiometrics should be completed on the child with a speech or language delay. This will evaluate for high-frequency or more severe hearing impairments resulting in a speech or language disorder. Cognitive status should be determined. A common reason for not meeting language milestones is mental retardation or global delay, and the first indicator of global impairment is a language delay. Landau-Kleffner syndrome must also be considered in the presence of normal socialization and nonverbal communication, seizures or abnormal electroencephalogram, and an acquired aphasia. Finally, a high index of suspicion for autism spectrum disorders must exist in a child with delayed onset of language and poor interactions. The earliest signs of an autism spectrum disorder are verbal and nonverbal language delay (lack of response to name, absence of joint attention, pointing or gesturing to regulate social interactions) with impaired socialization and delayed or absent parallel or interactive play skills.

Screening

Various screening tools exist to screen for language disorders in the pediatric setting, and the use of these will depend on the health care provider's level of interest and competency in screening techniques. It is extremely important to ascertain the reliability and validity of the screening tool before using that particular method. Screening tools include directly administered screens (eg, Early Language Milestones Scale, Clinical Linguistic Auditory Milestones Scale) and parent-completed questionnaires (eg, Receptive- Expressive Emergent Language Scale, language subscale of the Child Development Inventory). Informal techniques include observation of all oral language attempts (babbling, jargoning, true words) and nonverbal communication attempts (eg, facial expression, gesturing or pointing to indicate wants and to share enjoyment, presence of joint attention, body postures, and eye gaze).

If a language disorder is suspected or a child fails a language screen, a full evaluation should be completed by a certified speech and language therapist. Children with language regression should have an immediate neurologic evaluation as well as a formal speech/language evaluation, and the prospect of autism, Rett syndrome, and Landau-Kleffner syndrome considered.

Treatment

The goal of speech or language therapy is always to establish the skills necessary to effectively communicate with others, be that by verbal or nonverbal means. Speech or language therapy can help to prevent further delays as well as remediate problems of intelligibility, fluency, and language impairment. Most language specialists recognize that early language delays may herald later language irregularities. If a child had early language delays and subsequently has problems in reading, written expression, learning a foreign language, or age-appropriate social interactions, another formal language assessment should be considered.

Treatment of speech language disorders includes 3 components: causal, habilitative and supportive. Causal treatment is focused on repairing defects, correcting dysfunction, or eliminating factors that contribute to the language problem (e.g., cleft palate repair, hearing aids). Habilitative treatment is designed to directly improve the child's language skills (i.e., speech language therapy, counseling of parents to actively engage in the child's language development). Supportive treatment aims to boost language acquisition (e.g., training programs for speech-related skills, increasing social contacts).

Therapy and treatment goals will depend on the specific type of speech or language disorder that exists. For children ages 0–3, services can be obtained through the Individuals with Disabilities Education Act (IDEA), Part C. School-age children can receive services through the public schools. These services may include interventions for disordered reading and written expression skills if they co-exist. Psychosocial interventions also may be needed for older children and adolescents. It is essential to recognize that most children do not outgrow speech or language disorders. While no accurate statistics exist regarding persistence of specific language disorders through adulthood, they should be considered developmental disorders and thus may persist with differing presentations throughout the lifespan. Early identification and intervention are imperative in order to prevent further deterioration and allow improvement in communication abilities.

Suggested Readings

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Practitioner and Patient Resources

American Speech/Language and Hearing Association
http://www.asha.org
The ASHA Web site contains information for professionals and consumers regarding general information on speech/language disorders and state and local resources.

Apraxia/Dyspraxia
http://www.apraxia-kids.org
This Web site contains information on apraxia/dyspraxia for consumers.

KidSource Online
http://www.kidsource.com/NICHCY/speech.html
From the National Information Center for Children and Youth with Disabilities.

Chapter 45

Learning Disabilities

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Learning disabilities represent severe impairments in academic skill mastery that interfere with long-term occupational and psychosocial adjustment. Historically, much of the focus has been on diagnosing learning disabilities when the most important tasks are to prevent and remediate a child's academic difficulties. Children with learning disabilities show intractable learning difficulties that do not respond to quality instruction.

Learning disabilities are common neurobehavioral disorders that affect academic learning and other areas of adaptive functions in a large segment of our society. Estimates of the number of people with learning disabilities vary depending on how the condition is defined but range from 3 to 17% of the school-age population. Pediatric practitioners are commonly consulted by parents and others about learning disabilities and are asked to diagnose, refer, and provide advice. It is important for pediatric practitioners to have a good understanding of learning disabilities, in terms of not just how to manage the individual child, but also what it means to indicate that a person has learning disabilities. At the present time, major changes are being considered for how learning disabilities are defined by law, reflecting concerns ranging from the possible over identification of learning disabilities and lack of efficacy associated with diagnosis to the lack of a realistic concept of learning disabilities. We focus on current conceptualizations of learning disabilities as they derive from historical concepts of "unexpected underachievement." We suggest there are major weaknesses in how learning disabilities are typically diagnosed, reflecting the reification of concepts of learning disabilities despite an inadequate research base, which has led to ineffective practices. Children with learning disabilities cannot be reliably identified with a single assessment, reflecting the dimensional nature of these disorders and the arbitrary nature associated with setting cut points for any dimensional disorder. We suggest alternative ways to conceptualize learning disabilities that begin with the idea of prioritizing instruction as a prerequisite for diagnosis; the diagnosis of learning disability in the absence of clearly documenting the adequacy of the child's instruction program is inappropriate. We review current concepts of learning disabilities, seven research-based propositions that support these concepts and conclude with recommendations for assessment and intervention.

What Is a Learning Disability?

From a historical perspective, learning disabilities are synonymous with unexpected underachievement, representing a group of individuals for whom known causes of underachievement could be excluded, that is, sensory disorders, mental retardation, emotional disturbance, economic disadvantage, cultural and linguistic diversity (eg, English as a second language), and inadequate instruction. It has always been presumed that the causes of underachievement in the subgroup of people with learning disabilities represented constitutional factors mediated by the brain, implying that the student with learning disabilities required specialized instruction to achieve at age- and aptitude-appropriate levels, traditionally an intelligence quotient (IQ) score.

Although the learning disabilities rubric was formally developed as a term in the 1960s, the concept of unexpected underachievement has evolved in the medical and psychological literature since the mid-19th century as other entities were subsumed under learning

disabilities, such as dyslexia, word blindness, dysgraphia, and dyscal-culia. In 1962, the psychologist Samuel Kirk proposed the term *learning disabilities*, leading to formal recognition of the concept of this term as a marker for unexpected underachievement. Like his medically oriented colleagues (eg, Samuel Orton), Kirk equated learning disabilities with unanticipated learning difficulties in an otherwise capable child. He recognized that learning disabilities represented a heterogeneous group of academic and language disabilities. Of note was his concern that learning disabilities not be equated with reading disabilities, although reading was the most common form of learning disability, just as it is today.

The concept of learning disabilities has been widely accepted because it addressed a group of students with significant educational need. Until the category of learning disabilities became a legal entity, students whose failure to learn could not be explained by known causes had no access to special services or legal protection. Through advocacy by parents and professionals, learning disabilities became a recognized disability, first through the 1969 Learning Disabilities Act and then through the Education for All Handicapped Children Act of 1975 (Public Law 94-142). It is now part of the Individuals with Disabilities Education Act (IDEA), which provides for special education in 13 categories of disability. The learning disabilities category represents more than one-half (52%) of all children in public schools identified for special education and 6% of all students (about 6 million students), a significant increase since Public Law 94-142 was adopted (22% in 1978). The protections of IDEA are carried forth for adults through the Americans with Disabilities Act.

Despite this storied history, the concept of learning disabilities did not evolve from a strong scientific basis. Initial hypotheses about the nature of learning disabilities were directly influenced by advocacy efforts necessary to institutionalize the concept of learning disabilities and protect students with genuine learning issues. Concepts embodied in federal legislation since 1969 continue to dominate identification practices, not only in schools but also in medical settings, private clinics for learning disabilities, and even vocational settings for adults. Not only are components of the federal definition of learning disabilities not supported by research, definitions in standard medical and psychological classifications are not research-based. Yet changing practice seems as difficult as changing these classifications, reflecting the reification of certain notions about learning disabilities. Change is needed if for no other reason than the evidence that placing a child with learning disabilities in special education does not lead to improvement in academic skills nor do many standard practices have evidence of efficacy.

Definition and Classification of Learning Disabilities

Consider first the federal statutory definition of learning disabilities:

> Specific learning disability is defined as follows: (i) General. The term means a disorder in one or more of the basic psychological processes involved in understanding or in using language, spoken or written, that may manifest itself in an imperfect ability to listen, think, speak, read, write, spell, or to do mathematical calculations, including conditions such as perceptual disabilities, brain injury, minimal brain dysfunction, dyslexia, and developmental aphasia. (ii) Disorders not included. The term does not include learning problems that are primarily the result of visual, hearing, or motor disabilities, of mental retardation, of emotional disturbance, or of environmental, cultural, or economic disadvantage. (34 CFR 300.7(c)).

In 1977, recommendations for operationalizing the federal definition of learning disability were requested by states because of the vagueness of these guidelines, defining learning disability as follows:

> A severe discrepancy between achievement and intellectual ability in one or more of the areas: (1) oral expression, (2) listening comprehension, (3) written expression, (4) basic reading skill, (5) reading comprehension, (6) mathematics calculation, or (7) mathematic reasoning. The child may not be identified as having a specific learning disability if the discrepancy between ability and achievement is primarily the result of (1) a visual, hearing, or motor handicap, (2) mental retardation, (3) emotional disturbance, or (4) environmental, cultural, or economic disadvantage.

From this definition, the key historical components of the concept of learning disabilities are apparent, representing a heterogeneous group of disorders with an inclusionary marker of unexpected underachievement as a discrepancy between IQ and achievement and the exclu-sionary criteria that presumably lead to "expected" underachievement. Other parts of the regulations emphasize the need to ensure that the child's educational program provide adequate opportunity to learn. Implementation of this approach to identification is widespread in and out of schools, with significant variation in how the federal regulatory definition is implemented and interpreted. Consequently, there is substantial variability in who is served as learning disabled across schools, districts, and states.

The entrenchment of the federal regulatory definition is apparent in other classifications. The *International*

Classification of Diseases (ICD-10) and the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) define learning disorders in reading, math, and written language that are similar, simply changing academic domains. Consider the *ICD-10* definition of reading disability:

A. (1) a score on reading accuracy and/or comprehension that is at least 2 standard errors of prediction below the level expected on the basis of the child's chronologic age and general intelligence, with both reading skills and IQ assessed on an individually administered test standardized for the child's culture and educational system.
   (2) a history of serious reading difficulties, or test scores that met criterion A. (1) at an earlier age, plus a score on a spelling test that is at least 2 standard errors of prediction below the level expected on the basis of the child's chronological age and IQ.
B. The disturbance in criterion A significantly interferes with academic achievement or activities of daily living that require reading skills.
C. The disorder is not the direct result of a defect in visual or hearing acuity, or of a neurologic disorder.
D. School experiences are within the average expectable range (ie, there have been no extreme inadequacies in educational experiences).
E. *Most commonly used exclusion clause.* IQ is below 70 on an individually administered standardized test.

The less elaborate definition of reading disorders in the *DSM-IV* indicates that the student must perform below levels expected for age and IQ and specifies only sensory disorders as exclusionary:

A. Reading achievement, as measured by individually administered standardized tests of reading accuracy or comprehension, is substantially below that expected given the person's chronologic age, measured intelligence, and age-appropriate education.
B. The disturbance in Criterion A significantly interferes with academic achievement or activities of daily living that require reading skills.
C. If a sensory deficit is present, the reading difficulties are in excess of those usually associated with it.

Although these definitions are used in different areas of practice, they lead to similar approaches to the identification of learning disabilities. Students typically receive IQ and achievement tests, with the IQ test interpreted as an indicator of aptitude against which achievement is compared. Achievement tests in reading, math, and written expression are used because learning disabilities are a heterogeneous group of disorders, but essentially the same definition is applied to different academic domains. In certain settings, especially those outside public schools, this IQ-achievement assessment is supplemented with neuropsychological or cognitive tests of processing skills, consistent with the federal statutory definition of learning disabilities. Unfortunately, this approach stems from definitions and classifications that lack validity, lead to approaches to identification that emphasize diagnosis and not treatment, and have not been associated with good outcomes for children with the characteristics of unexpected underachievement.

In IDEA 2004, major changes are apparent in the regulations addressing children with learning disabilities. Specifically, the 2004 statutes indicated that states could not require districts to use IQ tests for identification. In addition, the 2004 statutes indicated that children could not be identified for special education if low achievement was due to lack of appropriate instruction in reading or math, or to limited English proficiency. When the regulations were released in 2006, school districts were given a choice in identification procedures, permitting either an approach that explicitly incorporated information from an evaluation of the child's instructional response or some form of a discrepancy model that included either an age or IQ- based discrepancy:

> i. The child does not make sufficient progress to meet age or State-approved grade-level standards in one or more of the [8 domains of achievement] when using a process based on the child's response to scientific, research-based intervention; or
>
> ii. The child exhibits a pattern of strengths and weaknesses in performance, achievement, or both, relative to age, State-approved grade-level standards, or intellectual development, that is determined by the group to be relevant to the identification of a specific learning disability, using appropriate assessments.

In addition, regardless of the identification model, the regulations indicated that:

To ensure that underachievement… is not due to lack of appropriate instruction in reading or math, the group must consider, as part of the evaluation…

1. Data that demonstrate that prior to, or as a part of, the referral process, the child was provided appropriate instruction in regular education settings, delivered by qualified personnel; and
2. Data-based documentation of repeated assessments of achievement at reasonable intervals, reflecting formal

assessment of student progress during instruction, which was provided to the child's parents.

There are other components of the regulations that are like those from previous versions of IDEA requiring due process, consideration of exclusionary conditions, and parental notification, but the major changes for those involving learning disabilities involve the flexibility in identification models and the explicit statement of the need for documentation of appropriate instruction. To avoid the proliferation of identification models, other components of the regulations indicated that districts could only adopt models for which the state wrote regulations. The statute and regulations also emphasized the importance of early identification and intervention, even permitting states to use funds from special education to support these activities. The emphasis on response to intervention reflects in part this emphasis, which is further discussed below.

Validity of the Underlying Classifications

Implicit in these definitions is a classification model of learning disabilities as those who show a measurable discrepancy in some, but not all domains of cognitive development, and who are not identified into another subgroup of poor achievers. In these definitions, the discrepancy is quantified with two tests involving aptitude (IQ) and achievement tests. In this model, there is an implicit hypothesis that those who meet an IQ discrepancy definition are different in meaningful ways from those who are underachievers, don't have a discrepancy, and do not meet one of the exclusionary conditions. In fact, research has not supported this model, failing to find systematic differences between those who meet IQ discrepancy criteria and those who are low achievers in reading or math in cognitive functions, behavioral adjustment, achievement, prognosis, response to instruction, and neuroimaging findings.

In response to the lack of evidence for the validity of the model, others have proposed that aptitude measures are unnecessary and that learning disability is synonymous with underachievement, suggesting that students be identified with achievement tests and the exclusionary criteria. This model, however, does not capture the concept of unexpected underachievement. Can underachievers with poor performance attributed to learning disabilities be differentiated from underachievers with poor performance attributed to emotional disturbance, economic disadvantage, or inadequate instruction? In reading, little evidence exists that such subgroups differ on language measures, response to instruction, or neuroimaging correlates.

A third alternative is to add neuropsychological measures to the assessment, representing a multitest discrepancy model. The problem is that there is little evidence that processing measures facilitate diagnosis or treatment planning or add information beyond what would be known by assessing achievement domains. Certainly, there is little evidence that teaching processes (memory, visuospatial skills) leads to better academic outcomes, because such training does not transfer to the academic area.

All three of these models base identification on a single assessment. This practice leads to reliability issues in the assessment of individual students because of the attempt to set a criterion cutoff point on a normal distribution and the small measurement error of the tests themselves. It is no different from diagnosing hypertension on the basis of a single blood pressure assessment, although the reliability of most achievement tests is much higher than a blood pressure assessment. In the absence of a natural break in the distribution of academic skills, measurement error will lead to instability in the identification of learning disabilities because test scores will fluctuate around the cutoff point with repeated testing. In both real and simulated data sets, fluctuations in up to 35% of subjects are found when a single test or discrepancy between two tests is used to identify a cutoff point. This problem is not a major issue for research, which tends to rely on a low achievement classification; on average, children around the cutoff point who may be fluctuating in and out of the class of interest across definitions are not very different. However, the problem for an individual child who is being considered for special education placement or other diagnosis of learning disability is obvious. It is simply not reliable when based solely on a single set of test scores.

Alternative Concepts of Learning Disabilities

Alternatives to traditional approaches to classifying and identifying learning disabilities exist that have a stronger research base and begin to avoid some of the problems with current approaches. These alternatives preserve the concept of unexpected underachievement but focus instead on the child who shows intractability in learning characteristics. Such models stem from a set of seven research-based propositions about learning disabilities:

- Learning disabilities are real.
- The most important markers of learning disabilities are achievement related.
- Learning disabilities are variations on normal development.

- Learning disabilities have their origins in childhood and persist.
- It is simplistic to attribute learning disabilities solely to constitutional factors or to imply that "neurologic dysfunction" can be directly assessed.
- Learning disabilities should not be equated with eligibility for services. Determination of eligibility always requires both the presence of the disorder and a determination of need.
- The most important question is not whether a person has learning disabilities but what to do about it.

Learning Disabilities Are Real

There is strong evidence supporting the viability of learning disabilities as a construct that can be defined and measured. The validity of this classification hypothesis stems from research showing that individuals with learning disabilities reliably differ from individuals without learning disabilities, as well as from individuals with different types across different approaches to definition of learning disability in (1) cognitive correlates, (2) response to intervention, (3) neural correlates, and (4) heritability.

Cognitive Correlates

The cognitive correlates of learning disabilities vary with the area of academic impairment. Thus, individuals who are impaired in word recognition, reading fluency, and reading comprehension can be reliably differentiated on different indices of language. Individuals whose primary problem is with word recognition are largely impaired in phonologic awareness; the most reliable correlate of fluency difficulties is rapid naming. Comprehension difficulties are primarily correlated with difficulties in development of vocabulary and oral language. Individuals can have impairments in each of these areas that are specific, but the impairments also co-occur. For example, individuals with word recognition difficulties (dyslexia) typically have problems with fluency and comprehension. In addition, each of these forms of reading disability can be reliably differentiated from learning disabilities involving specific math disability but no impairment in reading. Individuals with specific math disability typically have impairments in motor and constructional skills, working memory, and problem-solving abilities. It is also important to differentiate individuals who have problems with both word recognition and math from those who have problems with either only reading or only math. Such difficulties reflect more severe problems with oral language and working memory as opposed to simple comorbidity of the two disorders. Less well understood are disorders of written language, because it is not clear whether these people have problems with spelling, handwriting, or text production, and little research has been done that shows that such problems occur independently of other forms of learning disabilities or other disorders, such as attention-deficit hyperactivity disorder (ADHD). Nonetheless, research on the cognitive correlates of learning disabilities support the existence of six academic subgroups.

Response to Instruction

There is clear evidence for subgroup-by-treatment interactions in individuals with different academic forms of learning disabilities. Although this may seem rather obvious, it is not generally acceptable practice to provide math instruction to students with reading difficulties, or vice versa. Where the controversy lies is in terms of tailoring instruction to individuals with different processing difficulties. Here there is little evidence supporting interactions of specific processing difficulties and response to instruction. This does not obviate the evidence for interactions of learning disabilities on the basis of academic types of learning disabilities and response to instruction.

Neural Correlates

The functional neuroimaging correlates of reading and math difficulties in adults are demonstrably different. Individuals with reading difficulties show reliable activation differences indicating impairment of the inferior frontal gyrus, middle and superior temporal gyrus, and angular gyrus in the left hemisphere. The correlates of math processing are different, involving predominantly biparietal areas and left frontal areas depending on the type of math process imaged. Individuals with learning disabilities in math have not been studied, but such studies will be emerging.

Heritability

Reading and math problems are differentially inherited. The genetic constellations responsible for the heritability of these difficulties are not identical. There is some overlap, reflecting the common co-occurrence of reading and math difficulties in the same individual.

The Most Important Markers of Learning Disabilities Are Achievement Related

Difficulty developing academic proficiencies is the most reliable marker of learning disabilities and the part of the disorder that leads to adaptive impairments and disability. Some would argue that individuals with learning disabilities should be identified on the basis of unevenness in

neuropsychological or processing skills, but processing skills are only loosely linked with most forms of learning disability, the exception being the link between phonologic processing skills and dyslexia. Moreover, given that processing skills are assessed as indicators of academic strengths and weaknesses, why measure the former, especially as they are not reliably linked to instruction? Furthermore, we do not know how to measure processing skills for all learning disabilities. Thus, any attempt to define and measure learning disabilities should focus on academic skills, as they are linked to treatment and account for the validity of definitions of learning disabilities.

Learning Disabilities Are Variations on Normal Development

Population-based studies of reading and math in children usually show that these skills are normally distributed. Genetic studies are not consistent with the presence of qualitatively different characteristics for the heritability of reading and math disorders, and the assumption of normal variation is pivotal for this type of research. These observations are important because as a normally distributed trait that exists on a continuum, there are no natural demarcation points that differentiate individuals with learning disabilities from those without them. This means it is difficult to establish firm cutoff points for identifying individuals with learning disabilities in the absence of external criteria, such as response to instruction or some type of functional assessment. The dimensional nature of learning disabilities leads to a host of psychometric factors associated with the use of single cutoff points on a normal distribution, making identification on the basis of a single assessment unreliable. This does not mean that learning disabilities should be equated with low achievement. Rather, low achievement in the absence of some type of external criterion is what makes it difficult to identify individuals who have learning disabilities.

Learning Disabilities Have Their Origins in Childhood and Persist

Learning disabilities in reading and math have origins early in development and persist into adulthood. Children with learning disabilities have similar disabilities as adults in the absence of systematic intervention. In the Connecticut Longitudinal Project, there was no evidence of catching up in the long-term growth of reading ability. Seventy percent of individuals identified with reading disabilities in third grade had reading disabilities as adults. Special education services seem to maintain the child's status but do not close the gap.

"Neurologic Dysfunction" Is a Simplistic Explanation of Learning Disabilities

Despite the evidence for the validity of the construct of learning disabilities, the extrapolation from this body of evidence to the traditional idea that learning disabilities are due to "constitutional factors" or "neurologic dysfunction" is simplistic. Similarly, implying that factors intrinsic to the individual, such as brain dysfunction, can be directly assessed by behavioral tests, neurologic soft signs, and related approaches is misleading. We do not mean that the brain is uninvolved in learning disabilities. Research shows subtle structural differences in the brain that are heritable and make it more difficult to teach people with learning disabilities. However, studies of neural and genetic factors show important interactions with the environment. For example, in the reading area, studies are emerging that show that intensive instruction alters the brain activation patterns characteristic of students with reading disabilities. Such changes do not indicate that learning disabilities are caused solely by environmental factors or that the brain has been repaired. However, they imply the environment plays a much more significant role in the etiology of learning disabilities for many children. Such an observation is entirely consistent with genetic research, which shows that what is inherited is a susceptibility to reading or math proficiency that is moderated by environmental influences. Simply attributing learning disabilities to a static deficit in the brain does not do justice to the rich interplay between intrinsic and extrinsic factors responsible for the evolution of learning disabilities. That the brain was involved was apparent as soon as it was demonstrated that the person could not adequately read or do math.

Learning Disability Should Not Be Equated with Eligibility for Services

The mere presence of learning disabilities does not establish eligibility for special services, such as special education. Many individuals with learning disabilities adapt with relatively minor modifications of their environment. Any determination of eligibility for services needs to be a two-pronged determination that includes both the presence of the disorder as well as the need for a particular type of service or accommodation. A major weakness in defining and measuring learning disabilities is the absence of definitions linked to functional criteria. At what level of

reading ability, for example, does adaptive impairment result? This varies depending on the demands of the environment.

The Most Important Question Is Not Whether a Person Has Learning Disabilities but What to Do about It

Virtually every discussion of learning disabilities poses the question of how to best identify affected individuals. We submit that the most important question is not whether the person has a learning disability but what to do about the achievement and adaptive difficulties associated with it. Too much time and money is often spent trying to make distinctions about whether underachievement is to the result of a learning disability or some other type of problem when the primary concern should be what to do about difficulties in developing adequate reading, math, or writing skills. It is more important to determine whether there are academic deficits that lead to adaptive impairments, implement quick and reliable ways to ensure that academic skills are assessed, and, most importantly, to have interventions appropriate for facilitating skill development in these individuals without concern for putative cause. There is little evidence that students with different causes of underachievement (learning disabled, brain injured, economically disadvantaged) respond differently or require interventions that vary with putative cause insofar as the academic skill component is involved. Those with learning disabilities are likely children and adults who do not respond to instruction.

Models Incorporating Response to Instruction

One approach to dealing with the reliability and validity issues associated with identification is to increase the number of times a child is assessed. This approach would involve much shorter assessments of key achievement skills over time, usually in relation to some attempt at intervention. By linking multiple assessments to intervention, the student's response to instruction can be gauged. Those who are learning disabled are identified in part on the basis of nonresponsiveness to instruction to which most other students respond, thus operationalizing unexpected underachievement as those who are difficult to teach. The assessment component of the response-to-instruction (RTI) model is well developed, representing the use of short 2- to 3-minute probe assessments of reading and math repeated on weekly to monthly regimens and plotted to evaluate growth. Thus, the student who does not respond clearly demonstrates educational need and may need the protection and flexibility provided by IDEA, which led to the incorporation of RTI models in IDEA 2004. Such models were proposed in several recent consensus reports on learning disability identification, including the President's Commission on Excellence in Special Education and a report of the National Research Council that addressed alternative approaches to eligibility. Both reports suggest that one criterion for identification of learning disabilities is lack of response to high-quality instruction, thus putting instruction in the forefront and requiring systematic attempts to instruct the child before providing the learning disabled label. Thus, the student who does not respond clearly demonstrates educational need and may need the protection and flexibility provided by IDEA.

These approaches are not without difficulty. Models based on RTI also involve imperfect measures that include measurement error. However, this problem is reduced because of the use of multiple assessments and the borrowing of precision from the entire collection of data to provide a more precise estimate of the growth over time. There is still a need to identify individual children, as the diagnosis of learning disabilities is based on some criterion score. Thus, there remain issues with defining cut points until these benchmarks are linked to functional outcomes, an issue never really addressed for *any* learning disabilities identification model. It is not unlike attempting to link hypertension and blood pressure in the absence of a link to cardiovascular disease. Models that include RTI have the promise of incorporating functional outcomes because they are tied to instructional response.

Serial assessments bring learning and the measurement of change to the forefront in conceptualizations of learning disabilities. It focuses the definition of learning disabilities on a failure to learn, where learning can be measured more directly. Moreover, the specific instructional elements and the conditions under which they are implemented can be described, providing a clearer basis for the unexpectedness of any failure to learn. Thus, models that incorporate RTI may identify a unique group of children that can be clearly differentiated from other low achievers in terms of cognitive correlates, prognosis, and even neurobiologic factors.

Diagnosis and Treatment

Given the problems with current classification models and approaches to intervention, as well as the lack of efficacy associated with placement in special education, what are the responsibilities of the pediatric practitioner? First, ensure that the child is in good health. This includes consideration of adequate hearing and vision and

elimination of medical disorders that might contribute to the child's difficulties in school. The physical examination is usually noncontributory. There is nothing specific about learning disabilities that warrants medical diagnostic tests. In particular, electrophysiologic and neuroimaging studies are not routinely indicated, nor are other laboratory studies typically conducted because the child is struggling in school. The indicators for these types of studies are the same as for any other child and do not attend on the possibility of learning disabilities.

Second, if the concern is about learning disabilities, focus on evaluations of achievement. The most important aspect of assessment of a child suspected of having a learning disability (or any child struggling in school) is a careful evaluation of the academic domains known to be associated with learning disabilities, which would involve reading accuracy, fluency, and comprehension, computational math, and written language (spelling, handwriting, text generation). These types of skills can be easily screened in the office. If the pediatric practitioner works with psychologists and educators who do assessments, make it clear that the primary concern is achievement and don't encourage parents to invest in costly psychometric assessments. Funds are much better spent on intervention. There is little point in extensive neuropsychological or psychoeducational assessments, as they are unrelated to academic instruction.

Third, be aware of and assess for comorbid conditions. In particular, ADHD commonly co-occurs with learning disabilities, affecting on average about one-half of all children with reading and math difficulties. The pediatric practitioner should ensure that ADHD is evaluated in all children suspected of having learning disabilities. Less frequent comorbidities include speech and language disorders, which should be formerly evaluated by a qualified speech pathologist, as well as emotional difficulties that attend with any school-related problem.

Fourth, be prepared to refer children for intervention in academic areas. Pediatric practitioners should have a network of individuals to whom they can refer children for academic instruction. In this respect, emphasize interventions that involve explicit instruction in the academic domain. Be prepared to discourage families from quick fixes that involve special eye glasses or colored overlays, processing skills (eg, auditory/visual processing, learning styles, central auditory processing, speech sound perception), interventions that address different aspects of ambulation or sensory integration training, eye training exercises, or interventions oriented toward the cerebellum (eg, taking Dramamine or listening to a metronome). The primary focus should be on instruction in the academic area. Interventions of this sort are demonstrably effective for children with academic difficulties if provided with integrity, appropriate content, and intensity. The diagnosis of a learning disability is not as important as ensuring that the child receives some type of instruction.

Fifth, given the models described above, it is important to ensure that the child's progress in intervention is actually assessed. The pediatric practitioner should ask for reports in which progress is formerly assessed. It may be possible to identify nonresponders who would indeed represent children with intractable learning characteristics. In addition, children should not continue with interventions that do not demonstrate efficacy.

Sixth, understand how schools work. It is especially important to be prepared to refer parents to resources that explain the special education process. Any child who may have an academic problem could be considered for special education, but the first approach does not necessarily involve a referral to special education. Many schools have pre-referral interventions or other programs that address children who are struggling with academics. If special education seems appropriate, it is important to understand that this is a complicated legal process that begins with the identification of eligibility and the protection of the rights of individuals with disabilities. Schools do not have to base decisions on assessment information provided by a pediatric practitioner or other outside professional. They are allowed to do their own evaluations. The consideration of eligibility for special education should involve much more than just test scores, including a review of child's history, response to instruction, and consideration of factors that might help explain the child's difficulties. It is especially important to provide information about possible comorbidities or medical conditions that might affect the child's learning, particularly because this may provide an avenue for establishing eligibility through a category other than learning disabilities.

Finally, the most important component of strong pediatric practice regarding learning disabilities is to understand and have access to the knowledge-base concerning learning disabilities. Pediatric practitioners should be prepared to discuss concerns about school functioning with parents. A major error is the idea that children outgrow these sorts of problems or that the concerns will go away. This is rarely the case, and such concerns from a parent will typically be presented to a child practitioner first and should be addressed, not only to allay the parents' concern but also because early intervention is much more effective for academic difficulties. The biggest mistake made by pediatric practitioners with regard to concerns about learning disabilities is waiting until the child is in the latter part of elementary or middle school to begin to address the concerns. There is strong evidence that interventions in the early part of school, or even before school, prevent learning disabilities in many children. Given the poor outcomes

associated with special education, prevention is far more desirable than a lifetime of struggling with reading, math, and writing.

Suggested Readings

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National Association of State Directors of Special Education. Response to Intervention: Policy Considerations and Implementations. Washington DC: Author. www.nasdse.org

Practitioner and Patient Resources

Division for Learning Disabilities (DLD)
1110 North Glebe Road, Suite 300
Arlington, VA 22201-5704 Phone: (703) 620-3660
http://www.teachingld.org/
The DLD is a special interest group of the Council for Exceptional Children (CEC), the largest international professional organization dedicated to improving educational outcomes for individuals with exceptionalities, students with disabilities, and/or the gifted. Working on behalf of persons with learning disabilities and the professionals who work with them, DLD seeks to serve the instructional needs of the 2.8 million school-aged children and youth currently receiving special education services for identified learning disabilities in the United States.

International Dyslexia Association (IDA)
8600 La Salle Road
Chester Building
Baltimore, MD 21286
Phone: (800) ABC-D123
http://www.interdys.org
The IDA focuses on the study and treatment of learning disability, dyslexia legislation, public awareness, research, and education.

Learning Disabilities Association
4156 Library Road
Pittsburgh, PA 15234
Phone: (412) 341-1515
http://www.ldanatl.org
The Learning Disabilities Association of America is a nonprofit organization to advance education and welfare of those of normal intellectual but with perceptual, conceptual, and coordinative disabilities. Resources include books, guides, research results, laws.

National Center for Learning Disabilities
381 Park Avenue South
New York, NY 10016
Phone: (212) 545-7510
http://www.ncld.org
This Web site offers information, resources, referral services, public awareness, policies and legislation, and educational programs.

Council for Exceptional Children
Division of Learning Disabilities
1920 Association Drive
Reston, VA 22091
Phone: (703) 620-3660
http://www.cec.sped.org
International professional organization, advocacy, professional development.

CHAPTER 46

DEVELOPMENTAL DYSPRAXIA

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Developmental dyspraxia is a neurologically based developmental disorder characterized by a deficit in praxis. Dyspraxia is the inability to choose, plan, sequence, and perform gesture movements in the absence of primary sensory or motor impairments in otherwise normal children. It is thought to affect 6% of children. Dyspraxia is not a simple disorder and may be part of the spectrum of several other specific learning and developmental disorders in children. These include specific language disorders, dyslexia, attention-deficit hyperactivity disorder, high-functioning autism, tic disorders, and genetic disorders that include Williams syndrome and Turner's syndrome.

Normal Development of Praxis

Normal praxis follows a developmental continuum with stages characterized by different sets of skills (Table 46-1). The complexity of skilled movements observed at different ages suggests that praxis represents a higher cortical function. Several constructional abilities like assembly, copying, drawing, and other forms of praxis are listed in Table 46-1.

When testing praxis, the child should be asked to perform according to age representational gestures following both verbal command (eg, show me what you need to do to brush you teeth) and on imitation (the reproduction of the gesture carried out by the examiner is required) to exclude comprehension deficits. Visual modality (eg, the child is asked to mime the use of a seen object) or tactile (eg, the child is asked to pick up an object and to show how he would use it) may also be used. Both transitive (hit a nail with a hammer) and intransitive (salute) gestures can be realized. The types of errors can be categorized as production or content. Production errors include spatial and temporal errors. Spatial errors can be subdivided into postural, orientation, and movement errors. Postural errors occur when a child uses part of the body as a tool (eg, pantomiming a key to open a door, the child uses use the finger as the key rather

TABLE 46-1. Normal Development of Praxis According to Age

Age (y,m)	Assembly	Age (y,m)	Drawing	Age (y,m)	Autonomy
0,11	Put block in cup	1,01	Scribble	1,01	Drink from cup
1,03	Build tower of 2 cubes	1,09	Supinate pencil grasp, recognize shapes	1,03	Use spoon, fork
1,08	Build tower of 4 cubes	2,07	Imitate vertical line	1,05	Remove garment
1,11	Build tower of 6 cubes	3,00	Copy —	1,09	Brush teeth with help
2,04	Build tower of 8 cubes	3,06	Copy O, pencil grasp: tripod	1,09	Put on clothing
3,00	Copy 3-cube bridge	3,07	Copy +	1,10	Wash, dry hands
3,03	Copy 4-cube train	3,10	Draw person (3 parts)	2,08	Put on T-shirt
4,02	Copy 3-cube steps (50%)	4,06	Copy □, (demonstrated)	3,06	Prepare cereal
4,06	Copy 4-cube steps	4,08	Draw person (3 parts)	3,05	Brush teeth, no help
		5,02	Copy □	3,06	Dress, no help
		5,03	Copy Δ		

Adapted from Denver developmental scale and Egan visual-motor-integration test.

than the finger and thumb holding the key). Orientation errors occur when a child demonstrates incorrect orientation (when pantomiming cutting a piece of paper in half with an imaginary scissors, the child orientates the scissors laterally or fails to maintain it in a consistent plane). Movement errors occur when a child is instructed to perform a specific movement (eg, a salute), but the child performs the wrong gesture (eg, incorrect rotation of the palm of the hand). Temporal errors include delayed or very slow movements. Content errors could include related or unrelated responses. An example of related response would be pantomime playing of a trumpet when playing a guitar was requested. An unrelated response would be when requested to use scissors, the child pantomime plays a trumpet.

Clinical Signs: Index of Suspicion

The performance of learned motor tasks involves the ability to complete many of the child's activities of daily living. Presenting symptoms may be isolated and include problems with motor control when learning to ride a bicycle, reproducing drawings, or playing with constructional toys, such as puzzles or building blocks (eg, Lego®), and coordination difficulties (eg, learning to tie shoelaces or doing up buttons, and writing). Here is a brief breakdown of findings in children with dyspraxia by age:

Between 0 and 3 years of age:

- Irritability and feeding problems
- Delay in developmental milestones
- Bottom shuffling instead of the crawling stages
- Avoidance of tasks that require good manual dexterity

Between 3 and 5 years of age:

- Difficulty with movements of the mouth and tongue
- Messy eating, prefers to eat with their fingers, frequently spills drinks
- Not playing with constructional toys, such as puzzles or building blocks (eg, Lego®)
- Difficulty with left/right orientation, laterality still not established
- Inability to pedal a tricycle, ride a bicycle, play ball games or sorting games
- Lack of pretend play (such as using a spoon to stir an empty bowl), little interest in "dressing up" or in playing appropriately in a doll house
- Limited concentration, tasks often left unfinished

By 7 years of age:

- Coordination difficulties in dressing (eg, learning to tie shoelaces or doing up buttons)
- Holding a pencil, drawing, or copying a drawing, using scissors, picking up small objects, coordinating knife and fork
- Impaired control of eye movements (necessary for reading) or hand–eye coordination (necessary for writing)
- Limited concentration and poor listening skills
- Slow completion of class work

Classification

Ideomotor dyspraxia is an impairment in the selection, sequencing, and spatial orientation of a requested movement involved in gestures such as saluting, waving goodbye, or playing pretend actions (such as pantomiming the combing of one's hair with an imaginary comb).

In some cases the child cannot gesture normally to command but performs well spontaneously (automatico-voluntary dissociation).

Ideational dyspraxia applies only to impairments of limb movement and denotes a failure to carry out a sequence of movements. It is the inability to demonstrate how to use a common object such as a toothbrush; when writing and sending a letter, the child may seal the envelope before inserting the letter.

Constructional dyspraxia refers to impairment of any type of performance in which parts are put together or articulate to form a single entity or object (assembling blocks to form a design or drawing four lines to form a square or a diamond). It is characterized by misalignment of lines, overwriting when drawing designs, lack of connection between lines, and multiple small strokes when creating a longer line.

Dressing dyspraxia is an inability to perform the relatively complex task of dressing. Preschool children who cannot put on a coat are suffering from dressing apraxia.

Verbal dyspraxia indicates that the child has difficulty with volitional control of nonspeech movement. It is an expressive disorder in which the child is extremely nonfluent.

Developmental dyspraxia manifests itself precisely in the acquisition of complex gestures during the learning of motor skills and the elaboration of sequenced movements involved in gestures. The child seems unable to plan, sequence, and execute the correct movement to perform age appropriate skills in a smooth and coordinated manner at will or on command. The acquisition of new skills and the execution of those already learned will require tremendous effort. The child sometimes may correctly execute very well learned gestures in one context, but will fail to transfer it into a new skill and to generalize learned skills. As a result, the presence of dyspraxic deficits can result in the inability of the child to complete many of the activities of daily living.

Developmental dyspraxia may occur as an isolated symptom or with other cognitive or language dysfunctions

or represent a sign of a more global delay. In some genetic disorders, like Williams syndrome, dyspaxic deficits are greater than language deficit. Few chromosomal abnormalities can also lead to more specific patterns of dysfunction, such as dyspraxia in girls with Turner syndrome.

Dyspraxia may occur in children following neurological injury (eg, prematurity with periventricular brain damage, traumatic brain injury, CNS infectious or epilepsy).

Despite its prevalence in neurological disorders, dyspraxia is often undiagnosed. Dyspraxia is not likely to be a key symptom, and a high index of suspicion is needed to make the diagnosis.

Developmental Dyspraxia and Visuospatial Ability

In children, there is often a prevalence of a chief complaint of impairment on a construction task such as drawing or object assembly and 3-dimensional constructional difficulties (block design). However inadequate visuospatial processing may also interfere with constructional ability leading to visuoconstructional dyspraxia which is specifically found in a substantial proportion of old premature infants with periventricular lesions compromising the optic radiation. In case of pure dyspraxia, the deficiency on a construction task such as spontaneously drawing a geometric figure or with performance of a task such as copying a block design is not related to a visuoperceptual disorder and the provision of a model for copying should improve performance of subjects. In contrast, in visuoconstructional dyspraxia, the gestural performance is usually impaired by the abnormal visuosptial analysis. So the child will perform better with spontaneous than copied drawing. However both isolated visuospatial deficits and visuoconstructional dyspraxia can also lead to similar difficulties with both copied and spontaneous drawing and building blocks, except that children with pure visuospatial impairment do not have praxis deficit (Table 46-2).

Testing

Dyspraxia symptoms are strongly dependent on the age of the child. A wide variety of testing material is requested. Basic and specific tests are required. At first, we must be attentive to the history and to possible etiologies (eg, prematurity, meningitis) because this information will drive the type of testing required to fully characterize the dyspraxia. Quantitative tests are used to assess the intelligence quotient (IQ) score, evaluate visuospatial and constructional abilities, evaluate graphics abilities, and characterize gestural abilities.

In most cases, IQ scores may be characterized by a marked discrepancy between verbal IQ and performance IQ (18 points or more). But this discordance cannot be observed in children with both developmental language disorders and dyspraxia. The general configuration reveals a number of difficulties on tasks involving complex visuospatial organizational skills within the context of somewhat better performance on activities involving some verbal and auditory-perceptual abilities. More specifically, differences are observed in each scale: In the verbal scale, lower scores in math are typical. In the performance scale, there is almost always failure in the block design subtest and sometimes in the object assembly subtest. Poor performance on the coding subtest may indicate an impairment of gestural ability (delays before initiating a movement,

TABLE 46-2. Constructive and Visuospatial Tasks Used for Differential Diagnosis

Tests	Constructional Dyspraxia	Visuoconstructional Dyspraxia	Visuospatial Deficit
Drawing/puzzles	Poor	Poor	Poor
Verbal order	Deteriorated	Improved	Improved
Copying	Improved	Deteriorated	Deteriorated
Kohs block design	Poor	Poor	Variable
Model	Improved	Not improved	Not improved
Verbal explanation	Improved	Improved	Variable
Block design (WISC-III)	Poor	Poor	Variable
Object assembly (WISC-III)	Poor	Poor	Variable
Mazes (WIPPSI-R)	Normal	Variable	Poor
Rey Complex Figure	Poor	Poor	Poor
d2 test	Normal	Poor	Poor
Frostig			
Space positions	Variable	Poor	Poor
Space relations	Poor	Poor	Poor

These tasks are used to analyze the relations between constructional dyspraxia, visuoconstructional dyspraxia, and visuospatial disturbances in children. Adapted from Mazeau, 2003.

slowness of execution, slow handwriting) or difficulty in complex hand-eye coordination. The subtest Maze requires the subject to draw paths through mazes within the limit and provides a measure of planning; these skills may be impaired in children with visuoconstructional dyspraxia, but not in children with pure dyspraxia. Children with visuospatial deficit have also great difficulty on the Maze test. Nevertheless, it is important to account for individual variations.

Evaluation of Visuospatial and Constructional Abilities

Several tests are available for visuospatial evaluation. They evaluate abilities to detect, analyze, and interpret orientations. For example, the Frostig test (to test space relations and space positions), or Brickenkamp's barrage test d2 (to assess sustained attention and visual scanning ability) can be used. For the constructional evaluation, we observe children making constructions with blocks (Kohs block design test) or completing the stick construction test (Goldstein-Sheerer Tests).

Evaluation of Graphic Abilities

Clinically, we observe graphic quality and writing speed. Generally, spontaneous drawings are poorly structured. A test of visual-motor integration (VMI) is also useful in assessing visuoconstructional abilities. First, classic evaluation allows assessment relative to peers. Second, the observation may show difficulty with obliques, absence of global planning, piecemeal strategy with detail juxtaposition, and multiple sheet rotations with badly spaced organization. Bender's test, which involves the reproduction of geometric forms, allows the evaluation of orientation, angles, and relative position indices.

Evaluation of Gestural Abilities

There are tools available to assess gestural abilities. For example, we use the Praxic Abilities Task (Hill), the hand movements subtest from the Kaufman Assessment Battery for Children (K-ABC), the Assess Neuropsychological Development in Children (NEPSY), or the Imitation of gesture without significance test (Test d'imitation de gestes Bergès and Lézine). Complex hand–eye coordination can be measured with the Grooved Pegboard Test.

In conclusion, all these tests allow the examiner to make a definitive diagnosis and to formulate a specific individualized treatment plan. In addition, global neuropsychological evaluation is performed to assess strengths and weaknesses in each child. It is also important to have several tests showing a deficit, that is to say, consistency of results, before giving a diagnosis. This is even more important with young children. We must always remember that children are individuals and their abilities vary over time and in comparison with each other.

Treatment

Dyspraxia can be a lifelong concern. Treatment is designed to promote compensatory skills. Neuropsychologists, occupational therapists, and speech therapists are key to management. Caregivers and teachers should also participate in treatment by helping children divide routines in stages (for example, to get dressed: I must put on my panties, put on my socks, put on my T-shirt, with the tags close to me) and to also assist the child with gestures (for example, do the forms of letters). They can also help with strategies to enhance activities of daily living: preference of Velcro over shoelaces, making an imaginary ball between shoes (half in right and half in left, so the union of the two shoes makes a ball). Failure in drawing or in geometry can also be helped by breaking down the task into several stages. These strategies promote independence and increase self-esteem. Because dyspraxia can take an emotional toll on children, caregivers and teachers must be attentive to cues.

Case Studies

Case Study #1—Loic

An 11-year-old named Loic had difficulty with puzzles and building blocks, delay in riding a bike, and problems with dressing, tying shoes, and using utensils. Past medical history was noncontributory. Results of testing showed: VIQ 98 (math subtest: 8) and PIQ 65 (maze subtest: 1, block design subtest: 5, and object assembly subtest: 5). Loic had more difficulty with copying than with writing from memory (Figure 46-1A). He had poor handwriting and slow writing, difficulty in visual sweeping, deficits in the Barrage d2 testing (errors with orientations), difficulty with embedded drawn, and a deficient Rey Complex Figure test (Figure 46-1B). Loic was diagnosed with visuoconstructional dyspraxia.

Case Study #2—Raphael

A 9-year-old named Raphael had similar presenting complaints as Loic (see above). Past medical history was noncontributory. Results of testing showed: VIQ 108 and PIQ 82 (geometric figure subtest: 2). He had poor handwriting and slow writing, difficulty in visual sweeping, deficits in the d2 Barrage testing (errors with orientations and lines jumped), problems with imitation of gestures without significance, and a deficient Rey Complex Figure test.

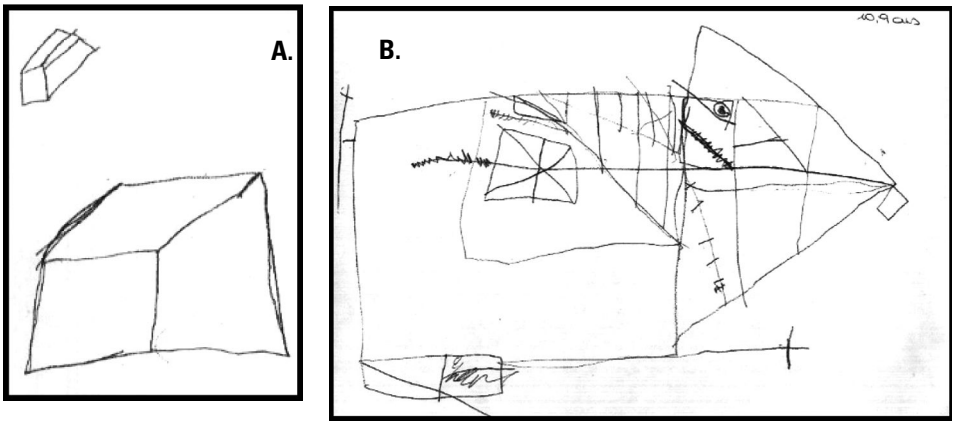

FIGURE 46-1. Loic. *A,* Upper part: copy of a cube. Lower part: spontaneous drawing. The copy is more difficult than the one drawn from memory. *B,* Copy of Rey Complex Figure.

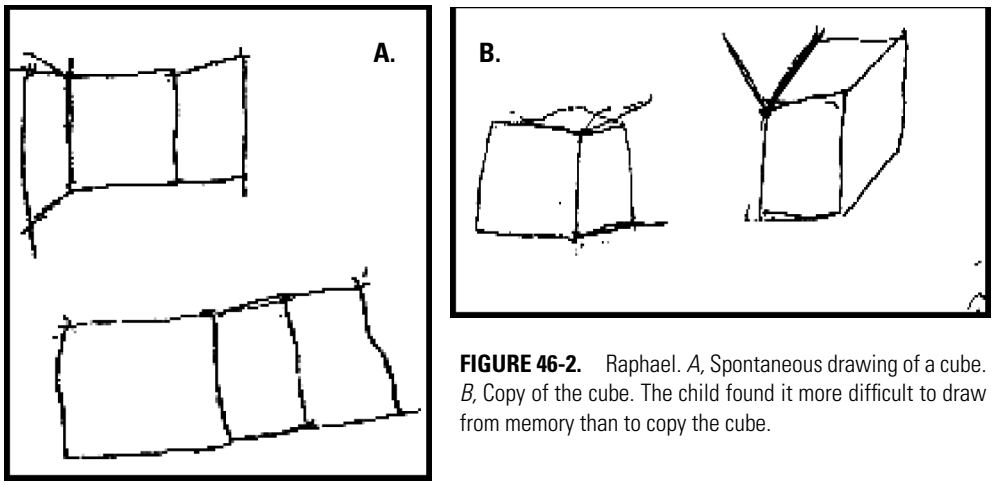

FIGURE 46-2. Raphael. *A,* Spontaneous drawing of a cube. *B,* Copy of the cube. The child found it more difficult to draw from memory than to copy the cube.

In this case study, the child found it more difficult to draw from memory than to copy (for example, Figure 46-2). So, visualization helped him perform the task. Raphael was diagnosed with constructional dyspraxia.

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Practitioner and Patient Resources

Dyspraxia Foundation (DF)
8 West Alley
Hitchin
Hertfordshire SG5 1EG
United Kingdom
http://www.dyspraxiafoundation.org.uk
DF is a UK charity that exists to help people understand and cope with dyspraxia. The organization is a resource for parents, for teenagers and adults who have the condition, and for professionals who help all of them. You can use this site to find out what dyspraxia is, to find out how joining the Dyspraxia Foundation could help you, to get practical information about coping with daily life and what you can do as a parent, and to find links to other useful sites.

Dyspraxia USA NFP
2502 N. Clark St
Chicago, IL 60614
Executive Suite 223
http://www.dyspraxiausa.org
This Web site offers information, resources and public awareness about developmental dyspraxia.

Parents/Caretaker Behavior Questionnaire—Dyspraxia Assessment

Pupil's name:		Date:		
	Never	Occasionally	Often	Always
Poor self-esteem				
Frustration-Sensibility				
Obstinacy				
Easily disorganized				
Poor adaptability				
Avoidance of tasks that require good manual dexterity				
Immature behavior				
Clumsiness				
Inattentive, easily distracted				
Have problems with fine motor skills.				
Difficulties in autonomy learning				
Bumps into everything all the time.				
Continued messy eating, Spills everything.				
Difficulties with cover charge				
Have problems dressing and doing up buttons.				
Tooth brushing disability				
Fine Prehension difficulty				
When writing, grips the pencil very tightly and awkwardly.				
Wiping nose difficulty				
Has problems using stairs, steps				

Chapter 47

Diagnostic Approach to Developmental Delay

Michael Shevell, MD, CM, FRCP(C)

Diagnosing developmental delay requires careful, meticulous, creative attention to the basics of child neurology and the many needs of the patient and family. The actual diagnosis of a developmental delay subtype is not the end point of specialty involvement; rather, it marks the beginning of the efforts to prescribe the proper range of rehabilitative, interventional, and support services required to optimize function.

Developmental delay is a common problem in child health and, as such, is a frequent reason for referral of a child for specialty evaluation by a developmental pediatrician or pediatric neurologist. Developmental delays are a group of related, etiologically heterogeneous, chronic disorders that share as an essential feature a documented disturbance in one or more of the recognized developmental domains: motor (gross or fine), speech/language, cognitive, social, and activities of daily living. Usually, the disturbance needs to be significant, that is, a performance of ≥ 2 standard deviations below the mean on an age-appropriate, norm referenced, standardized developmental assessment. When more than one domain is affected, a global developmental delay exists. When a single domain (motor or speech) is affected, a gross motor delay or a developmental language disorder (developmental dysphasia, specific language impairment) exists. The autistic spectrum disorders (ie, autism syndrome and pervasive developmental disorder) are characterized by a qualitative as well as a quantitative distortion in the acquisition of developmental skills, particularly relating to the social and language domains, with associated, often prominent, behavioral disturbances.

The specialty evaluation of the young child (ie, < 5 years of age) with a suspected developmental delay has a multitude of aims and objectives. These include the following: (1) confirming and classifying the suspected delay, (2) searching for a possible underlying etiology, (3) arranging for the provision of appropriate rehabilitation service interventions, (4) counseling the family regarding the diagnosis, and (5) managing any associated medical or behavioral conditions (eg, spasticity, epilepsy, attentional difficulties, sleep disturbances) th at may detract from the child's full actualization of his or her intrinsic developmental potential.

This chapter describes the elements of the specialty evaluation of the young child with a suspected developmental delay.

History

Much time and effort need to be directed to a careful and detailed history in this particular clinical setting. This begins with a comprehensive family history. The number of children and siblings of the parents; their respective health, developmental, and school (if applicable) attainment status; and the referred child's place in the birth order needs to be ascertained. Open-ended questions regarding the health and developmental status and school attainment of other family members are helpful. Specific examples of neurologic disorders (eg, epilepsy, convulsive disorders, mental retardation) may need to be suggested so parents don't inadvertently fail to recall important relevant conditions. The possibility of parental consanguinity has to be probed as well as any familial neonatal or infantile deaths or maternal pregnancy losses. Ethnic heritage and geographic origin of the family may, in some instances, provide a clue to etiology.

Details regarding the mother's pregnancy and prenatal care with the affected child should be established. Adverse prenatal events, such as per-vaginal bleeding, gestational diabetes, intercurrent infections, or medical conditions, should be discussed. Documentation of maternal prescription medication, tobacco, alcohol, or illicit drug use is necessary. The timing of labor (premature or term), its spontaneous or induced onset, duration, mode of presentation, and means of delivery must be ascertained. Suggestions of difficulties during the delivery process, such as meconium staining or abnormalities in fetal heart monitoring, are relevant. The reason for cesarean section, if any, is important to note. Birth weight, Apgar scores (especially beyond 5 minutes, if early scores are of concern), and the duration of the infant's postnatal hospital stay are important objective parameters. The neonatal course should be probed for any clinical findings, such as seizures, encephalopathy, or feeding difficulties, that suggest early concerns that may lead to a focus on a prenatal or perinatal etiology.

Subsequent to birth, the child's medical history should be ascertained. Hospital admissions, surgical procedures, possible chronic medical conditions, and current medication use need to be documented. Parental socioeconomic (ie, educational attainment, occupation), marital, and custody status, together with existing child-care arrangements, are relevant to establishing a proper social and familial

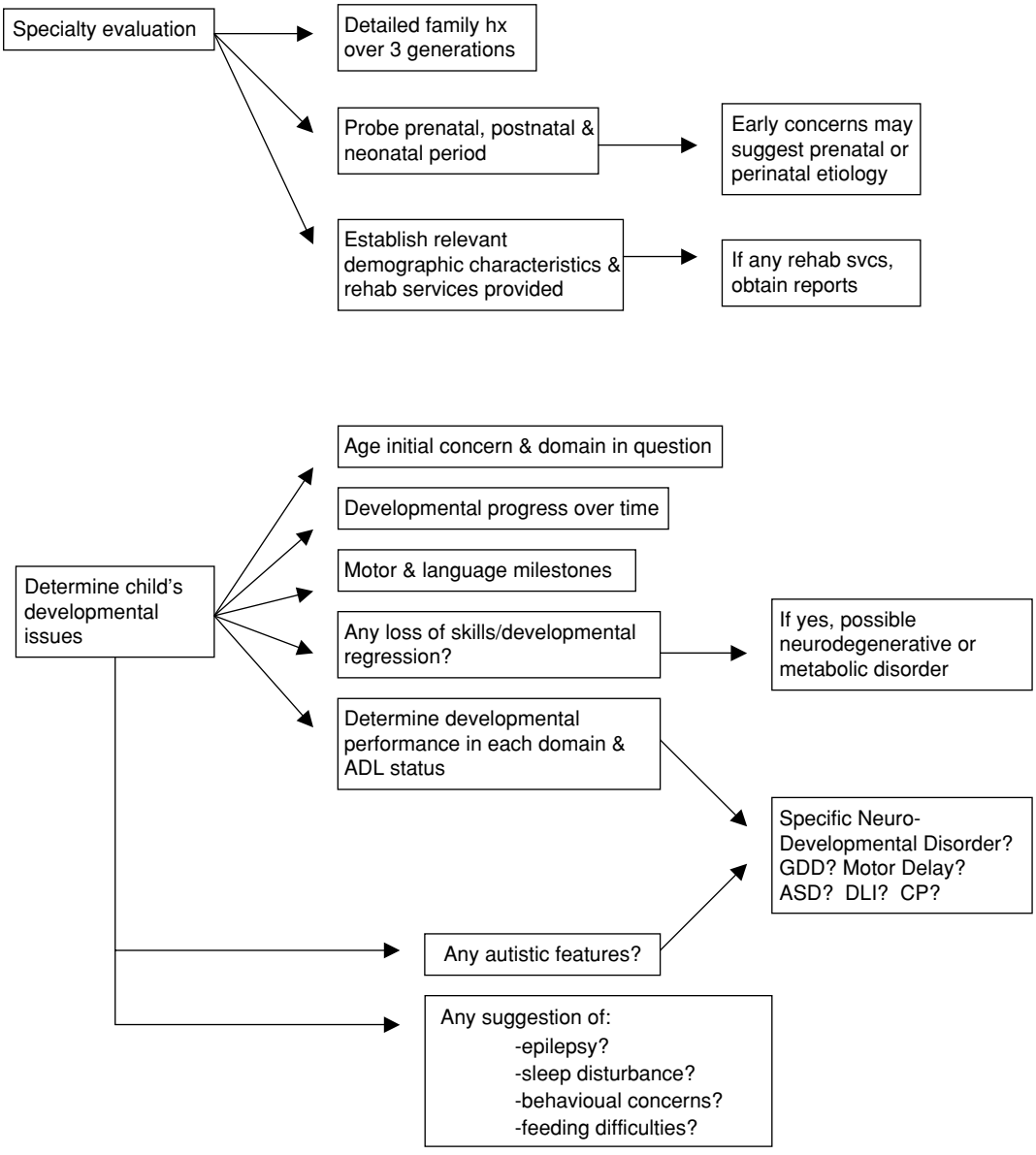

FIGURE 47-1.

context for the child under evaluation. The provision, either previously or currently, of any special services, particularly those of a rehabilitative nature, should be ascertained and relevant reports from these services obtained.

With the above historical background established, the evaluator can then turn to specific developmental issues. The age of initial parental concern and the precise domain (ie, motor, language, social) of original concern should be elicited. Developmental progress in each of the domains should be established. Key sequential motor skills include rolling over, sitting, crawling, pulling up to stand, cruising, and walking independently. Key progressive language skills include cooing, babbling, saying initial words, speaking two- and three-word phrases, and correctly

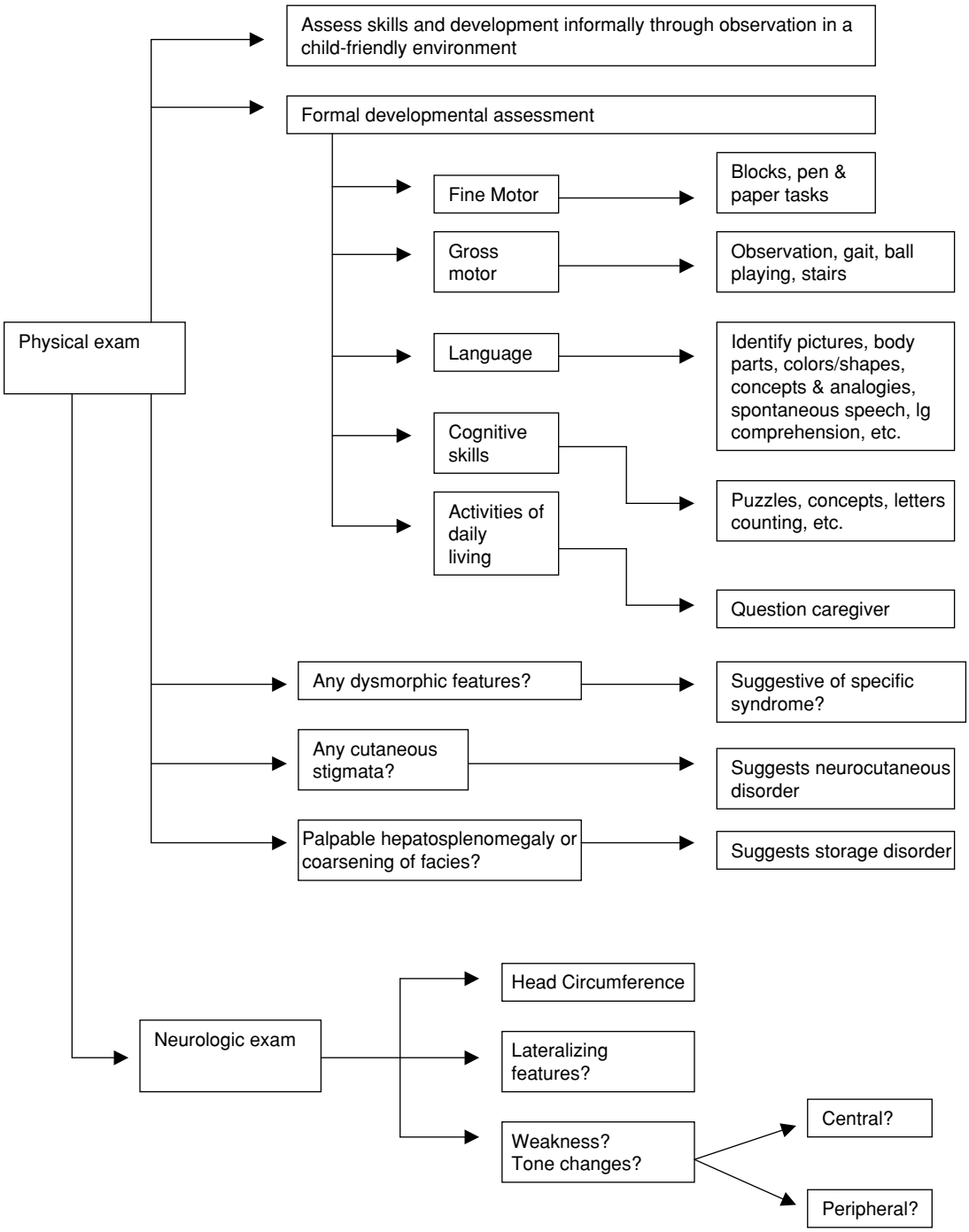

FIGURE 47-2.

using pronouns, plurals, and subject-verb-object sentence structure. Parental recall may often be sketchy and frustratingly elusive, so it may be useful to obtain from the caregiver an idea of the child's capabilities at specific ages (eg, first or second birthday). If the parents have other children, they may phrase their recall for the child of concern by comparing that child's pace of skill acquisition with those of their other children. The possible loss of skills or developmental regression should be specifically asked for, as this may be an important clue to a possible neurodegenerative or metabolic disorder. Current developmental performance in each domain should be ascertained. For the older child, performance of activities of daily living, such as toileting, dressing, feeding, and self-hygiene, is a good barometer of overall developmental attainment. For the older child with motor concerns, copying and writing skills, running, riding a tricycle, and going up and down stairs are a good index of status. For the language-impaired child, assessment of comprehension and a grasp of body parts, colors, shapes, objects and their uses, and simple analogies provide a good idea of linguistic attainment. The possible presence of any autistic features, such as poor eye contact, emotional inappropriateness, desire for sameness, repetitive behaviors, lack of pretend play and appropriate social interaction should be specifically sought. Given their frequency among children with developmental delays, the possible presence of coexisting paroxysmal behaviors suggestive of epilepsy, disruptive sleep disturbances, ongoing behavioral concerns, and feeding difficulties also should be specifically searched for.

Physical Examination

The physical examination is an integral part of the diagnostic evaluation of the delayed child. The examination may alternatively suggest a specific syndrome due to the observation of a constellation of particular findings, confirm a diagnostic suggestion apparent on history taking, or document findings that suggest an increased likelihood of an etiologic yield on subsequent laboratory testing.

Much of the neurodevelopmental examination takes place by observation during the extended history-taking described above. Therefore, a child-friendly environment is necessary, with provisions made for the availability of age-appropriate playthings, including blocks, picture books, crayons, paper, simple puzzles, stuffed animals or dolls, and balls. Through the child's interaction with this environment, the manipulation and use of toys, expression of curiosity in the surroundings, grasp of language, imaginative play skills, and personal and social interactions can be assessed by the observer in a detached and nonthreatening manner. This playtime can take place while the young child sits on the lap of a reassuring caregiver or, for the older ambulatory child, in a child-sized chair or at a table set up in the examining room. Before proceeding to the assessment's necessary formal aspects, it is crucial that the evaluator establish a rapport with the young child. The reassuring physical proximity between child and caregiver should be maintained when at all possible. The child needs to know what to expect by being told what will happen next. The sequence of the examination needs to be fluid and adaptable to immediate opportunities and, if possible, direct physical manipulation of a body part by the examiner deferred to the end.

This observation of spontaneously expressed developmental skills is complemented by a more formal developmental assessment that permits accurate documentation of the child's current developmental status in all relevant domains. Fine motor skills are best assessed by the use of blocks and pen/paper tasks and gross motor skills by observation, gait analysis, and ball playing. Language is assessed by the child's ability to identify pictures, body parts, colors, and shapes and to explore concepts and analogies. Spontaneous speech and storytelling by the child provides a means of assessing vocabulary and grammatical and semantic capabilities. Comprehension skills can be tested by following progressively more complex commands conveyed by the examiner or caregiver. Cognitive skills can be evaluated by the child's grasp of puzzles and such concepts as small/big, short/long, open/close, and under/over, as well as simple counting skills. Activities of daily living are best assessed by questioning the caregiver; however, observation of how the child dresses and undresses may be instructive in the examining room.

Particularly relevant aspects of the general physical examination include current height and weight measurements and an understanding of their evolution over time and a careful search for possible dysmorphic features. Dysmorphology needs to be considered within the context of ethnic and familial variation. The skin must be examined in detail to search for possible stigmata of a neurocutaneous disorder, such as café-au-lait spots or hypopigmented macules and an underlying myelodysplasia that may manifest itself overtly simply by a cutaneous abnormality over the spine. Storage disorders commonly manifest by palpable hepatosplenomegaly in addition to a coarsening of facies.

An essential element of the neurologic examination is obtaining a head circumference (occipitofrontal), which is then plotted to yield an age-appropriate percentile. Documented microcephaly (< 2%) or macrocephaly (> 98%) mandates the obtaining of prior measurements and plotting these values over time. In addition in the setting of microcephaly or macrocephaly, parental head circumference measurements should be obtained and plotted.

Formal neurologic assessment includes a search for nystagmus, facial paresis, excessive drooling, dysphagia, or dysarthria. Visual fields should be ascertained by confrontation as well as pupillary responses to light. Office screening for a primary sensory impairment (either visual or auditory) as well as a funduscopic examination is necessary, which may be limited because of a patient's age and lack of cooperation. Motor examination focuses on the detection of any asymmetries or lateralizing features with respect to bulk, strength, tone, stretch reflexes, and plantar responses. The quality of limb movements also should be appreciated and any dyskinesias (eg, dystonia, athetosis, chorea, tremor, dysmetria) documented. Gait should be assessed if the child is ambulatory and described in detail if abnormal. Arising from a squatting position or a supine posture on the floor (Gowers' sign) is a good test for proximal weakness. Running down an adjacent hallway, ascending or descending stairs, standing on one foot and hopping (if possible), copying simple figures, and catching/throwing/kicking a ball provide a good assessment of dexterity, coordination, and motor planning skills.

Laboratory Investigations

Laboratory investigations in this setting are directed at establishing a possible etiology underlying the child's specific developmental delay. This etiology may or may not be apparent at the end of the clinical assessment. Thus, laboratory testing may be directed by findings on history or examination (ie, confirmatory) or undertaken on a screening basis to detect a previously unsuspected etiology. Laboratory testing needs to be selective, as extensive nondirected testing is neither feasible nor justified on the basis of medical indications, invasiveness, or costs. Several possible investigations and their diagnostic values are depicted in Figure 47.3.

Determining an underlying etiology is important for many reasons. It imparts an understanding of the pathogenesis to the family, answering their "need to know why." It also may have implications with respect to an accurate estimation of recurrence risk if genetic factors are found to be at play, which may subsequently involve parental testing. It also allows for more accurate prognostication of what can be expected for the child. A specific etiologic diagnosis may also modify ongoing medical management or programmatic follow-up (eg, tuberous sclerosis, neurofibromatosis). A diagnosis also empowers family members by providing them with sufficient information to act on their child's behalf and brings closure to the first stages of dealing with having a child with developmental delay.

Etiologic yield and appropriate laboratory testing is highly dependent on the specific subtype of childhood developmental delay under consideration. Recent retrospective and prospective studies have shown that more often than not an underlying etiology can be determined in the situation of global developmental delay. Three quarters of etiologies in cases of global developmental delay are accounted for by four diagnostic categories: (1) cerebral dysgenesis, (2) hypoxic-ischemic encephalopathy, (3) antenatal toxin exposure (ie, alcohol or drugs), and (4) chromosomal abnormalities (including fragile X). Clues to the successful etiologic determination on the basis of history and physical examination include documentation of antenatal toxin exposure, microcephaly, and focal motor findings. The presence of any autistic features is a negative predictor of successful etiologic yield. The yield of karyotyping is the same whether it is done for screening or when a condition is suspected because of dysmorphic features. In contrast to karyotyping, neuroimaging is three times more likely to identify an etiology if one is suspected clinically (ie, microcephaly, focal findings).

Routine metabolic testing for an extensive list of inborn errors of metabolism cannot be justified. However, given the implications of their ascertainment, for reasons of treatment, prognosis, and recurrence risk, diagnostic vigilance for these disorders must be maintained. Clinical situations that should prompt careful consideration for metabolic testing include family history, parental consanguinity, documented developmental regression, episodic decompensation, suggestive dysmorphology, involvement of nonectodermal derived organ systems, and suggestion of white matter involvement.

In the setting of a child with a global developmental delay, the following recommended testing has been put forward. Lead testing should only be done on those children with identifiable risk factors for excessive lead exposure. Similarly, testing for thyroid hormone status should target those in whom newborn screening was not undertaken or in whom specific systemic features of hypothyroidism are present. Metabolic screening is indicated in the context of no prior newborn universal screening or historical or physical examination findings that are suggestive of a possible metabolic etiology. These findings include parental consanguinity, prior fetal or child loss, history of episodic decompensation, developmental regression, dysmorphic features, or hepatosplenomegaly. Karyotyping (high resolution) is recommended routinely even if there are no dysmorphic features, as well as fragile X mental retardation (FMR-1) molecular genotyping. Fluorescent in situ hybridization (FISH) studies are reserved for those situations in which the delay is unexplained or a specific syndromic diagnosis is suspected. Complementary genomic hybridization (CGH), while promising, cannot yet be routinely recommended. MECP2 testing is recommended in both girls and boys with severe, as yet unexplained,

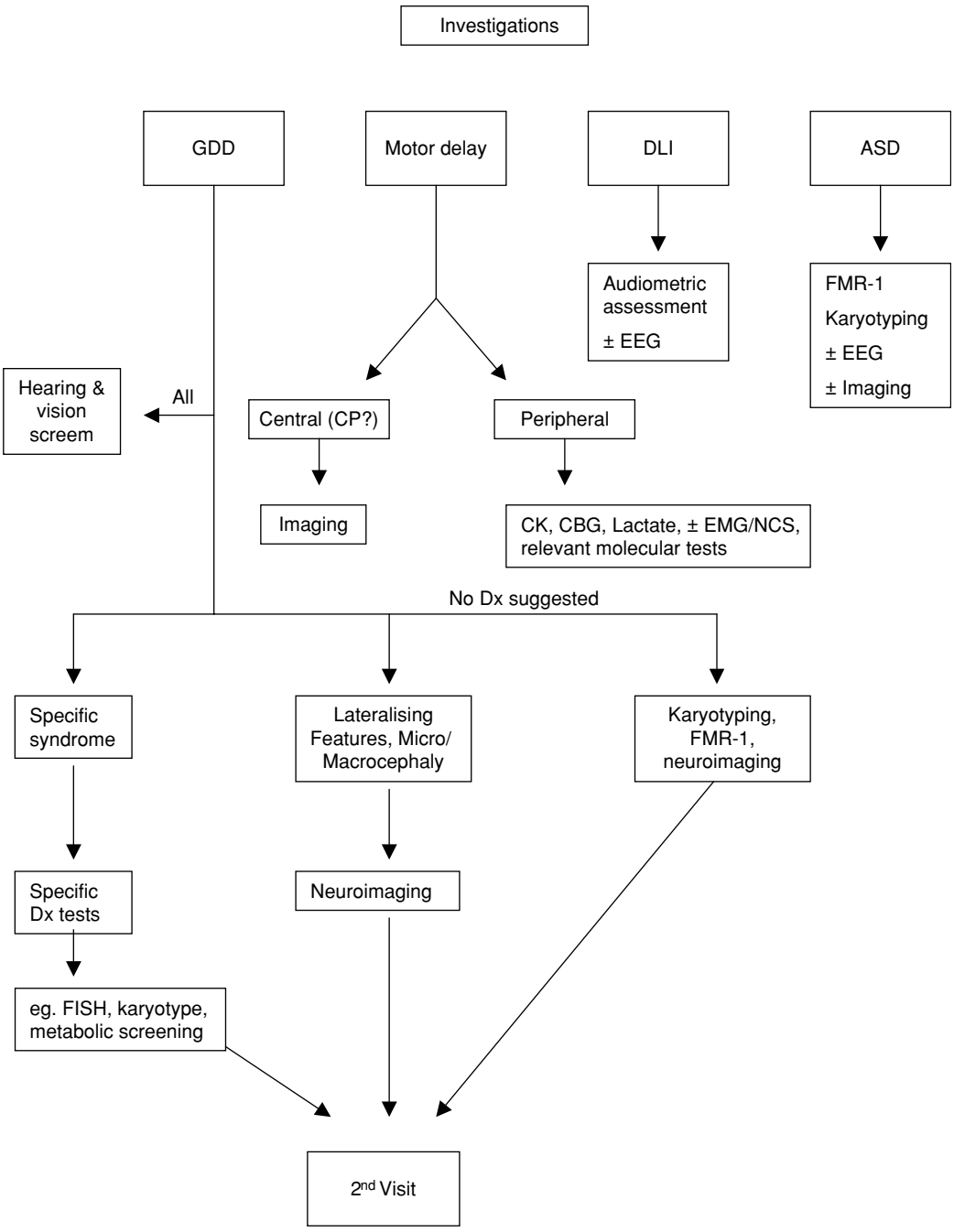

FIGURE 47-3.

mental retardation. In the setting of large somatic features both Prader-Willi syndrome and Sotos syndrome should be suspected with the former tested initially by FISH study and the latter by bone age testing. Obtaining an electroencephalogram (EEG) is not useful from a diagnostic point of view and should be pursued only if there is a suggestion of seizures or a specific epilepsy syndrome. Routine neuroimaging is recommended, with magnetic resonance imaging preferable to computed tomography, especially in the context of documented physical findings. All children with a global developmental delay should undergo hearing and vision assessment.

With respect to the child with a single-domain developmental delay, there is a marked dichotomy to etiologic

yield. The child with restricted motor delay is more likely than not to have an underlying etiology that can be determined. This is especially so if physical findings, such as weakness, asymmetry, and tone or reflex changes are demonstrable. Once again, specific laboratory testing has to be directed by findings on history or physical examination. These findings, if present, should allow for classification of underlying etiology into either a central or peripheral origin. If central, imaging of the brain is indicated. If peripheral, studies targeting muscle/nerve integrity should be pursued (ie, creatinine kinase, serum acid-base status and lactate levels, electromyography/nerve conduction studies). The situation is markedly different among children with a developmental language disorder. An underlying etiology is rarely appreciated (< 5% of cases), despite careful evaluation. Laboratory testing in this clinical situation can be restricted routinely to detailed audiometric assessment and perhaps EEG if there is a suggestion of a possible acquired epileptic aphasia (Landau-Kleffner syndrome). Clinical features that are suggestive of this include objective loss of previously acquired language skills and behavioral disturbances. EEG should include, when feasible, a sleep study.

With reference to the child with an autistic spectrum disorder, recommended testing presently consists of karyotyping and an FMR-1 molecular genotype, especially if there is coexisting mental retardation, a positive family history, or suggestive dysmorphic features. Similarly, as for global developmental delay, metabolic testing should be undertaken only if there are suggestive clinical or physical examination features. At present, an EEG is not routinely recommended in the setting of an autistic spectrum disorder, but only if seizures are suspected or if there is regression such as a significant loss of social and communication function, which raises the possibility of Landau-Kleffner syndrome. At present, routine neuroimaging is not indicated for autistic spectrum disorder, even in the setting of macrocephaly.

Other Health Professionals

The diagnostic evaluation of the delayed child by a developmental pediatrician or child neurologist is not a solo or stand-alone effort. Other health professionals with disparate yet complementary expertise need to be consulted to ensure a complete and thorough evaluation and to ensure that appropriate services are provided to the affected child. The high frequency of primary sensory impairments in this population requires careful consideration of audiometric and ophthalmologic assessments. The developmental concerns profiled following history and physical examination will mandate referrals, where appropriate, to occupational therapy (fine motor, activities of daily living), physical therapy (gross motor), speech language pathology (language), or psychology (cognition, social, behavioral). These professionals possess the skills to apply standardized assessments that objectively document the child's developmental deficits in a way that is far more rigorous than what can be done in the standard office examination described above. Furthermore, these professionals assume responsibility for ensuring the implementation of appropriate goal-directed therapeutic interventions that optimize the child's functional capabilities. They also serve as information sources for available community based resources. Additionally, specific care needs (eg, feeding, respite care, financial) may mandate the involvement of nursing care and social services. From a medical perspective, the suggestion of a genetically based etiologic diagnosis should prompt the involvement of a genetics consultant, especially in this era of increasingly esoteric laboratory testing (eg, FISH, molecular genotyping, imprinting analysis, comparative genomic hybridization) to confirm a particular suspected genetic diagnosis.

Second Visit

A second patient visit with the specialist is an integral part of the diagnostic assessment of the young child with a developmental delay. The timing of this visit should be 4 to 6 months after the original visit. Developmental progress should be ascertained to rule out a progressive encephalopathy (ie, neurodegenerative process). Results of laboratory investigations should be reviewed, as well as the evaluations of the other professionals involved. The specialist should combine and integrate these reports and then counsel the parents regarding the precise nosology (ie, developmental delay subtype) of their child's disability and the determination, or lack thereof, of an underlying etiology. The current provision of rehabilitation support services should be determined, and if lacking relevance to the needs of the child, the sources and means of obtaining such services should be discussed. Family concerns (i.e. sleep, behavior, feeding) should be elicited and addressed directly as they can often be overlooked when focusing on the medical aspects of developmental delay, though they may be of paramount importance to the family. Developmental progress in the interim should be highlighted and implications regarding future prognosis discussed. For the child nearing school age, educational (ie, schooling) options will need to be enumerated and their appropriateness for the particular child addressed.

Suggested Readings

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Shevell MI, *Sherr E. Global developmental delay and Mental retardation* in Pediatric Neurology: Principles & Practice (4th Ed). *K.Swaiman, S. Ashwal, D. Ferreiro (eds) Mosby Elsevier, Philadelphia, 799–820, 2006* Srour M, Mazer B, Shevell MI. Analysis of clinical features predicting etiologic yield in the assessment of global developmental delay. Pediatrics 2006; 118:139–145.

Practitioner and Patient Resources

National Association for Child Development
The Weber Center
2380 Washington Blvd, 2nd Floor
Ogden, UT 84401
Mailing address:
PO Box 380
Huntsville, UT 84317
Phone: (801) 621-8606
E-mail: info@nacd.org
http://www.nacd.org

The National Association for Child Development is an international organization of parents and professionals dedicated to helping children and adults reach their full potential. Founded in 1979 by internationally recognized educator and lecturer Robert J. Doman Jr, NACD designs very specific home neurodevelopmental programs for infants, children, and adults.
http://www.med.umich.edu/1libr/yourchild/devdel.htm

Family Resource Services, Inc.
PO Box 1146
Magnolia, AR 71754
E-mail: dorothy@frs-inc.com
http://www.frs-inc.com
An autism and developmental disabilities resource catalog.

Chapter 48

Children at Risk: Social Disadvantage and Neurodevelopmental Functioning

Michael E. Msall, MD

Both biological and social risks are increasing for preschool developmental challenges in communication, learning, and social skills. The complex neurologic pathways involved in these disorders require a biopsychosocial approach that promotes literacy, problem solving, and social successes.

The 20th century has seen major advances in reducing infant mortality, decreasing malnutrition, and controlling infectious diseases. However, there are large social and community threats to the complex developmental processes underlining school and social success. Such threats include poverty, low parental education and unemployment, inadequate housing, parental mental illness, domestic violence, child abuse and neglect, and neighborhood crime. In order for children to enter kindergarten healthy and ready to learn and become adults who will make positive contributions to society, we must effectively prevent these threats. The purpose of this chapter is to review the interplay of social risks on developmental processes essential for communicative, cognitive, and educational achievements of children from families living in poverty and facing the challenges of low socioeconomic status (SES).

Definition of Poverty

It must be emphasized that defining poverty is complex since it involves external factors that contribute to low SES (eg, the job market, physical environment) as well as factors associated with social capital (eg, parental health, education, ability to engage their children in developmental learning activities). The classical definition of poverty is based on assumptions regarding food costs relative to basic needs and is based on gross income and family size. As of 2006, the Federal Poverty Level for a 3-person household is a pretax income of $16,600 per year or less and for a 4-person household a pretax income of $20,000 per year or less.

Definition of SES

Most scholars and researchers agree that defining the term SES can be complex and difficult since there has never been complete consensus on its exact definition across health, economic, and social programs. Some tie SES with household income because it allows access to material resources as well as the social capital of family members. However, studies that look exclusively into household income use the word poverty and nonpoverty (or poor and nonpoor) rather than high SES and low SES. It is worth noting that in general, measurement of SES not only includes family income but also parents' educational

attainments, family structure (eg, marital status), and neighborhood conditions. Duncan and Magnuson explain that "SES refers to one's social position as well as the privileges and prestige that derive from access to economic and social resources." For example, historically, nursing, social work, and teaching were viewed as jobs that were paid poorly compared with workers employed at an automobile plant. However, these jobs require both a college education and the knowledge of essential resources of health, education, and community service. Although the monetary compensation of nursing, social work, and teaching have been less than that of an auto worker, individuals with these occupations are considered professionals and therefore are seen to be at a higher SES than individuals working at an automobile plant.

SES can also be influenced by race and immigration status or vice versa. According to Palfrey, 34% of black children, 30% of Hispanic children, and 10% of Caucasian children come from families "whose total income is below poverty." Studies on ethnicity and poverty (or SES) showed that "poverty status had a greater impact on access to learning materials than did ethnicity." Bradley notes that across all ethnic groups, nonpoor mothers were more likely than poor mothers to speak and engage their children verbally and in conversation. In addition, European American families and Asian American families received higher ratings than did African American and Hispanic families in appropriate developmental, learning, and educational activities.

Effects of Poverty and SES on Children

Many studies suggest that the effect of poverty and SES on child development has the most impact during preschool years. Conditions linked to poverty include premature birth with low birth weight, failure to thrive (ie, failure to gain weight at the anticipated rate during the first two years of life), lead poisoning, and parents with complex physical, mental, or developmental impairments. These conditions are also overrepresented among children in foster care, a group both economically and socially disadvantaged. It is important to remember that in most cases, cognitive, health, and behavioral outcome affected by poverty and low SES also affect one another, thereby increasing the long-term suboptimal outcomes for these children.

Cognitive Development

Despite the fact that there is no working consensus on exactly how, and to what extent, the experiences of childhood influence adult life, several researches point out that "effects of poverty on children's cognitive development occur early" (Brooks-Gunn and Duncan, 1997), and the duration of poverty plays a substantial role in children's cognitive development. This is particularly true for the duration of poverty whereby low income throughout ages from birth to seven years exhibits the highest correlation with low rates of high school completion and college enrollment. On a similar note, Bradley has noted that indicators of SES (both physical and social) were strongly and significantly related to cognitive outcomes throughout infancy and middle childhood. Evidence suggests a particularly strong relationship between SES and verbal skills and SES and developmental learning experiences. Bradley notes that children from low-SES background disproportionately lack access to cognitively stimulating resources and activities such as books, cassette tapes, educational toys, visits to the museum, and related parent-child learning activities. Thus, longitudinal and community research teams have elegantly summarized that "early childhood emerges as the stage in which both income and social capital matter the most."

Neighborhood conditions (eg, accessibility to day care, museums, library, playgrounds, health-care facilities, and after-school programs) also have a large affect on child development. Brooks-Gunn and Duncan contend that "Living in neighborhoods with high concentration of poor people is associated with less provision of learning experiences in the homes of preschoolers, over and above the links seen between family income and learning experiences." Poor (or extremely poor) neighborhoods are also often characterized by social disorganization such as crime, unemployed adults, and high dropout rates from high school. These population approaches have resulted in several ongoing analyses by KIDS Count (2002), the Future of Children (2001), the National Academy of Science (2000), and the Carnegie Foundation (1983). These reports emphasized that in the United States, there are substantial numbers of children who encounter multiple accumulative adverse risk across key developmental periods and enhance vulnerability for long-term adverse outcomes.

Several indicators of these risks for children living in the United States are highlighted in Table 48-1.

In order to understand what mechanisms might be involved in children's early learning, communicative interactions between parents and children were comprehensively analyzed by Hart and Risley (1980). In middle class families, children receive verbal input exceeding 30,000,000 words by age 3 with 83% being educational and positive in content while 17% were negative and disciplinary in content. In contrast, children from poor African American families had received inputs of 10,000,000 words by age 3 with 29% being educational and positive in content while 21% were negative and disciplinary. These differences were manifested in less verbal abilities, lower IQ, and poorer educational achievement throughout childhood.

TABLE 48-1. Epidemiology of Early Psychologic Risks (2000)

Children under 6 years in poverty	
African Americans	48%
Hispanics	43%
Caucasians	15%
In deep poverty*	13%
African Americans in deep poverty*	33%
Psychosocial risks	
Parents with < high school education	25%
Single moms	22%
Teenaged moms	38%
Maternal mental health disorder	5%
Children in foster care	2%
Children who are homeless	0.5%
Biomedical risks	
Low birth weight	7%
Very low birth weight (<1,500 g)	1%
Genetic malformations	3%
Illicit substance exposure†	10%
No prenatal care	5%
Prenatal exposure to tobacco	>20%
Prenatal exposure to alcohol	10%
Childhood failure to thrive	5%
Childhood lead level	5%
Chronic early childhood impairments	2%
Developmental risks	
Developmental motor delay‡	5%
Developmental language delay‡	20%
Global developmental delay‡	10%

*Deep poverty = 50% below poverty line.
†Includes cocaine, heroin, and marijuana.
‡Standard scores of more than 1.5 SD below the mean for age.

Health

Low-SES, especially poverty, has negative affects on children's health. Palfrey writes that "According to parents' reports, 62% of poor children have excellent or very good health, versus 90% of children from non-poor families. Activity limitations for children aged 5–17 with chronic conditions is reported for 10% of poor children, compared with 7% non-poor children." Some of these differentials across the domains of motor, self care, communicative and learning, and behavioral functional domains are highlighted in Table 48-2.

Many poor children do not receive the same preventative, prenatal or early childhood services as their nonpoor counterparts and are more likely to be undernourished, under immunized, receive less medical and dental care, and sustain periods of time without health insurance. Poor children also encounter environmental hazards such as lead poisoning, tobacco exposure, and air pollution more frequently.

One of the most prominent conditions in which poverty and low SES adversely affect children is premature birth (delivered prior to 37 weeks gestation) and low birth weight (less than 2,500 g or 5 pounds, 8 ounces), which contributes significantly to childhood preschool disability and educational challenges. The majority of the infants born preterm also have low birth weight. In 2003, 67% of low birth weight babies were preterm. The other 33% were small for gestational age reflecting suboptimal intrauterine growth. Although international studies have revealed that women who are poor and socially disadvantaged have the highest rates of premature births and low birth weight children, the complex pathways of stress, inadequate nutrition, preeclampsia, gestational diabetes, prenatal exposures, and social support have not led to the discovery of biologic markers or sustained interventions that reliably decrease these risks to children.

TABLE 48-2. Poverty and Moderate/Severe Functional Limitations in School Age Children

Functional Limitation	Above Poverty	Below Poverty
Motor	2.2/1000	2.4/1000
Self-care	4.7/1000	6.5/1000
Communication	23/1000	34/1000
Learning	61/1000	100/1000

Child abuse and neglect can also pose a threat to the long-term and the short-term well being of infants and children. This epidemic of adverse caretaking environments occurs across all levels of society, but children living in poverty are disproportionately represented. Recent studies have identified adults who have not completed high school, live at or below poverty level, and experience depression as having increased likelihood of becoming abusive or neglectful toward their children. Rates of depression are also significantly higher among mothers from low SES background and add to the complexity of less educational achievement, lower income, and being a single parent. While death is viewed as the worst outcome possible for child abuse and neglect, a spectrum of neurologic outcomes as well as adverse developmental, behavioral, and educational outcomes frequently occur.

Behavioral

Low SES is considered to impact behavioral problems and disorders in children and adolescents such as attention deficit-hyperactivity disorder, depression, anxiety, and substance abuse. Brooks-Gunn and Duncan argue that "poor children suffer from emotional and behavioral problems more frequently than do non-poor children." Their study shows that "children in persistently poor families had more internalizing behavior problems than children who had never been poor." These disorders of anxiety, depression, and post traumatic stress are both underrecognized and poorly managed in current community settings.

Domestic violence, and concurrent child abuse and neglect, is one of the many channels in which poverty and low SES influence children's behavioral health. The behav-

ioral outcomes of children who had been victims of abuse and neglect include aggression, anxiety, depression, juvenile delinquency, drug use, and gang membership. Studies show that children who experience abuse or neglect are more likely to engage in violence, suffer health problems, and/or become child abusers themselves. Thus, the risk for children is not limited to the first generation.

Intervention and Assistance

If one considers that there are 20 million preschoolers 0 to 5 years old in the United States experiencing combinations of serious indicators of social disadvantage in conjunction with the biologic risks listed in Table 48-3, then one begins to understand that on a population level, it is critically important to understand results from model interventions. We will highlight lessons learned from neonatal outcome studies of extreme prematurity, the preschool results from the Infant Health and Developmental Program, and the importance of human capital in early childhood with respect to positive adult outcomes.

TABLE 48-3. Prevalence of Early Childhood Disorders and Risks for Children 0–5 years (Population: 20 Million)

	Rates Per 1,000	Number of Children
Neurodevelopmental disorders		
Cerebral palsy	2.5	50,000
MR (IQ < 50–55)	5	100,000
Communicative disorder	5	100,000
Autism	2	40,000
Hearing loss (>50db)	2	40,000
Visual loss (<20/200)	0.5	10,000
Technology dependent	1	20,000
Any ND disorder	20	400,000
Neurologic and genetic disorders		
Down syndrome	1	20,000
Fragile X	1	20,000
Fetal alcohol	1	20,000
Neonatal encephalopathy	7.5	150,000
Epilepsy	5	100,000
Spina bifida	0.5	10,000
Muscular dystrophy	0.5	5,000
Congenital heart disease	7	140,000
Any congenital disease	30	600,000
Biomedical risk		
Elevated lead	5	100,000
Prenatal drug exposure	100	2,000,000
Prenatal tobacco exposure	200	4,000,000
Prenatal alcohol exposure	200	4,000,000
LBW (<2,500 g)	70	1,400,000
VLBW (1,000–1,499 g)	10	200,000
ELBW (<1,000 g)	1	20,000
Psychologic risk		
Parent education < high school	250	5,000,000
Children in poverty	250	5,000,000
Teen parents	100	2,000,000
Child abuse-neglect	10	200,000

LBW = low birth weight; VLBW = very low birth weight; ELBW = extremely low birth weight.

Lesson 1: Kindergarten Readiness After Extreme Prematurity

Between 1983 and 1986 an evaluation of strategies to manage respiratory distress syndrome was undertaken in 194 preterm infants less than 28 weeks gestation. In all, 26% of the mothers had received betamethasone for more than 24 hours prior to delivery to stimulate endogenous surfactant production, 46% received surfactant replacement in the delivery room prior to the first breath, and 28% did not receive surfactant replacement or maternal prenatal steroids. This was a very high risk cohort with a mean birth weight of 885 g and a mean gestation of 26.5 weeks. More than 1 in 5 (21%) died. High-risk neonatal morbidities included bronchopulmonary dysplasia in 65%, intraventricular hemorrhage 3 or 4 in 8.4%, and severe retinitis of prematurity in 11%. Neurodevelopmental impairment rates were high with 5% of survivors having cerebral palsy, 10% having mental retardation, 1% being blind, and 5% having multiple neurodevelopmental impairments. Functional assessment at kindergarten entry revealed that all but 4% of survivors were able to walk, were able to communicate in sentences, do not require diapers, and were able to perform feeding and dressing tasks. Among the 21% of survivors with any neurodevelopmental impairments, 94% understood requests, 87% walked, 84% talked in sentences, and 81% were able to perform basic feeding, dressing, and toileting tasks. Thus, the majority of survivors (79%) were free of major neurodevelopmental disorders. Among the survivors with major neurodevelopmental disorders, the overwhelming majority (>80%) were competent in basic functional tasks. However, at kindergarten entry, only 50% of the survivors did not require any special education resources, 42% required some special education supports such as physical, occupational, speech, or behavioral therapies. One in 11 of survivors required intensive special education supports such as smaller class size, extensive rehabilitation services, assistive technologies, classroom personal assistants, or counseling services. Though biomedical risks of parenchymal brain injury, retinopathy of prematurity, and sepsis predicted neurosensory impairments, poverty, minority status, and male gender substantially increased the risk of requiring special education services. Thus, even in the modern era of neonatology with aggressive use of prenatal steroids, caesarian deliveries, and surfactant replacement, comprehensive interventions will be required for vulnerable children in early childhood.

Most researchers seem to agree that there is no "magic bullet" that will cure the adverse affects of low SES or poverty.

Hertzman and Wiens write that "many of the most promising social interventions are rather modest in character." They suggest different programs targeting infancy, preschool period, and preadolescence. Emphasis on developing both cognitive and noncognitive (eg, motivation, perseverance, and tenacity) skills will increase the chances of success in life. Current intervention programs include home visiting, early start, early intervention, and Head Start, which in the United States target only a portion of the vulnerable children. Model programs integrate health, development, and education, as well as family support, teach self-efficacy, and provide ties to legal and social advocates for basic needs. The developmental interventures emphasize parents as partners and emphasize the use of daily routines to enhance communication, exploration, and relationship learning. Several meta-analyses of model studies have demonstrated the effectiveness of comprehensive intervention programs in reducing suboptimal health, mental retardation, behavioral problems, delinquency, and high school dropout rates. As the purpose of this chapter includes children at dual risk, I will now highlight lessons learned from the Infant Health and Development Program (IHDP) and the Iowa orphanage study.

The IHDP Study

The IHDP was a multicenter study designed to evaluate the effects of early intervention on health and developmental outcomes of low birth weight survivors. Almost 1,000 (N = 985) premature low birth weight infants from Boston, Dallas, Little Rock, Miami, New Haven, New York, Philadelphia, and Seattle were recruited between the years 1985 and 1986. Of the study population, 37% weighed 2,001 to 2,500 g, 37% weighed 1,501 to 2,000 g, and 26% weighed less than 1,501 g. In all, 377 were randomly assigned to the intervention group, while the other 608 were assigned to the follow-up only group (ie, control group). Throughout the duration of the program, children from both groups were given medical care and received a series of developmental and social assessments. The IHDP standard care for all control children also included developmental and rehabilitation referrals to early intervention and community providers when delays were detected.

The IHDP intervention group consisted of quality home visits and center-based early childhood full-day education using a validated developmental curriculum. The home visits began at neonatal discharge, and the center-based early childhood educational experience began when the infants were 1 year of age. Both home visiting and early educational interventions lasted until the children were 3 years of age.

The home visits were conducted on a weekly basis during the first year and biweekly in years 2 and 3. The home visiting lessons consisted of relationship-based learning with a focus on enhancing communication skills and facilitating parent problem solving for child behavior stressors and family challenges. The center-based interventions operated 7 to 9 hours a day and 5 days a week with children encouraged to attend a minimum of 4 hours per day. Staff to children ratio was 1:3 between 12 and 23 months and 1:4 for ages 24 to 36 months. The curriculum was centered on games and activities that addressed cognitive, fine motor, language, gross motor, social, and self-help skills.

A 3 year follow-up of both intervention and control groups revealed substantial differences in the percentage of children with borderline ($IQ \leq 85$) and impaired ($IQ \leq 70$) intellectual performance. Among children with the highest participation rates, 1 in 13 had cognitive impairments. In contrast, 2 in 5 children with the lowest participation rates had cognitive impairments. In addition, the program's greatest impact occurred among children whose mothers had low IQs. Approximately 40% of children from the control group whose mothers had cognitive disability had mental retardation at age 3 compared with 15% of intervention children whose mothers also had cognitive disability.

The assessment on cognitive, behavioral, and health status of the participants at 3 years of age showed that children in the intervention group had significantly higher scores on the intelligence test and receptive vocabulary test than those in the control group. The intervention group also scored lower on reported behavior problems than the control group. Among children who survived birth weights less than 1,500 g, the mean Stanford Binet IQ of the intervention group was 88 compared with 80 in the controls. These scores increased to 92 and 82 among the very low birth weight survivors without cerebral palsy. Among children who survived birth weights less than 1,000 g, the scores were 87 and 80, respectively, with scores of 93 and 85 when extremely low birth weight survivors without cerebral palsy were assessed.

Overall, the short-term conclusion of the IHDP intervention was that psychosocial mental retardation could be prevented among children at dual jeopardy because of prematurity and parents with cognitive disability.

Medical and Social Risks and Impact on Kindergarten Costs

Both biologic and SES factors affect prenatal, neonatal, and postnatal outcomes of infants, and these results in turn affect the cost of education at kindergarten entry. Although appropriate early intervention programs can significantly reduce the number of children requiring special education because of missed prevention opportunities, students who enter school with challenges in development cost an estimated 2.3 times more than the cost of students who

are healthy and ready to learn. A study on the relationship between excess educational costs and infant and maternal risk factors demonstrated the importance of both biologic and social risks on these costs. Among the two groups with the highest rates of neonatal intensive care (low birth weight and congenital malformations), increased kindergarten cost was $19.3 million per year. Among children born to families living in poverty or whose parents were young (teens) or with low maternal education, there were $129 million in excess cost associated with providing special education services. Further analysis demonstrated that if the number of low birth weight infants (1.5–2.5 kg) could be reduced by 9%, then $1 M could be saved; if the female high school dropout rate was decreased by 3%, then $1 M could be saved; and if poverty could be reduced by 10%, then $8.3 M could be saved. In order to demonstrate what the long-term impact of adverse social environments for vulnerable children, lessons from the Iowa orphanage study need to be described.

Adverse Early Child Environments During the Great Depression

Initially conducted in the 1930s, this study by Harold M. Skeels followed 25 children (13 in the experimental group and 12 in the contrast group) who became wards of the orphanage following court procedures due to parents' inability to provide for basic child needs or because of severe neglect and/or abuse. All children came from homes that had low social, economic, occupational, and intellectual levels. The children in the experimental group were lower in early cognitive scores (mean IQ of 64.3) compared with those in the contrast group (mean IQ of 86.7) and were considered to be mentally retarded at the beginning of the study. The experimental group was transferred from the orphanage to an institution where there were women with mild mental retardation. These women became caregivers to these children. In addition, child learning opportunities were provided including play, books, swings, and tricycles. The children in the experimental group started attending nursery school as soon as they could walk and participated in activities such as music, singing, dancing, movies, and Sunday chapel services. It is important to note that apart from intellectual stimulation and individualized attention, 9 of the 13 children in the experimental group had a specific adult who cultivated an intense one-to-one relationship with the child. The children in the contrast group remained in the orphanage where interaction with adults occurred only during feeding, dressing, and toileting. The children had very little or no access to toys or outdoor play equipment.

The duration of the study was from 6 months to 52 months. Children in both groups were given standardized developmental tests throughout the study. By the end of the experimental period, the children in the experimental group showed a gain from 7 to 58 points in their intelligence test. Skeels points out that those children "who experienced the more intense personal relationships made greater gains than those who were limited to general interactions." However, children in the contrast group lost anywhere from 9 to 45 points. The results of the first follow-up (2.5 years after the experimental period) demonstrated that the mean IQ of the experimental group was 95.9, while the IQ of the contrast group was 66.1.

The follow-up of adult achievement of the subjects also showed remarkable results. All the 13 children in the experimental group became self-supporting middle-class adults who showed no signs or history of antisocial or delinquent behavior or needing ongoing psychiatric support. Eleven of them had married and had families of their own. However, only two of the 11 living subjects in the contrast group had married, and four of the subjects were either institutionalized or unemployed. The rest, with one exception, were working in poorly paying and low status jobs. Thus, the Skeels study demonstrated the critical importance of the social capital of a concerned, caring, and consistent adult caregiver and early childhood learning. Even in the severe constraints of monetary resources, this investment had a dramatic impact on educational outcomes and adult well being.

Conclusion

This review has highlighted the comprehensive supports that are required for children at risk to optimize health, development, and educational status. Without these broad-based community strategies, missed opportunities will occur and lead to increased and unacceptably high risks for educational underachievement and combinations of medical, developmental, and behavioral impairments. If resources are scarce, then prioritizing services for young children living in poverty and ensuring 100% capture of children who are low birth weight, have neurologic or genetic impairments, or have early developmental delays are required. Only in this way can the dual risk of adverse health and adverse social risk be ameliorated so that the impact is not exponential on achieving learning and behavioral competencies.

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CHAPTER 49

CEREBRAL PALSY

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The term cerebral palsy (CP) is used to designate a mixed group of motor disorders caused by static injury to the developing brain. This chapter provides rationale and strategies for a comprehensive, goal-directed approach to caring for patients who have CP that focuses on four main areas: (1) communication and education, (2) mobility, (3) physical fitness, and (4) independence.

Although the type of brain injury and the nature and severity of the motor abnormalities vary among individuals, all patients with cerebral palsy (CP) have a chronic disorder of movement or posture that presents early and continues throughout life. Children with CP are at increased risk for associated abnormalities, including visual impairments, hearing loss, speech and language delays, epilepsy, nutritional disturbances and failure to thrive, mental retardation, learning difficulties, depression, and other behavioral problems. The desired outcome is for each patient to reach his or her highest potential in life. This requires attention to multiple factors (Figure 49-1).

Communication and Education

Recognizing the Problems

Communication and education are, by far, the most important and most neglected priorities for the child with cerebral palsy. The threat to a child's educational and intellectual future begins the moment they are diagnosed with an irreversible brain injury (eg, periventricular leukomalacia, intraventricular and intracerebral hemorrhage, and hypoxic-ischemic encephalopathy). All too often, physicians make predictions about an infant or child's long-term outcome on the basis of a brain imaging study, leaving parents with the impression that their child will have severe physical, intellectual, and psychosocial limitations. These "experts" instantly dash parents' hopes and alter the way in which parents interact with their infant or child. Parents who give up in despair are likely to limit their interactions with their at-risk children, thereby depriving both the child and themselves of the much-needed emotional and psychosocial stimulation. Thus, delivering bad news badly to parents can have a profound and long-lasting negative impact on the outcome of the child's condition that extends well beyond the structural damage to the child's brain.

The disabled child faces a seemingly endless mountain of obstacles that he or she must overcome to succeed in the classroom and in life. Many school buildings and classrooms are not accessible to students with motor impairments. Limited motor skills may prevent these youngsters from exploring their environment and keeping up with their peers. They may be inappropriately placed in classes with much younger children who are closer to their level of motor ability rather than their level of cognitive development. Children who are not mobile get left out of group activities unless they have personal assistance in the classroom and on the playground. Children who are struggling to sit in their chair without falling may not be able to pay attention to their teacher's story or instructions or may be unable to perform tasks with their hands. Many children with CP have impaired fine motor skills, and for them, a simple writing exercise becomes a chore. These children are at high risk of falling behind by not completing assignments. They may be labeled as "slow" and be expected to do less or simpler work than their classmates. As the curriculum becomes more difficult, school becomes a test of sheer physical endurance, a marathon that turns into hours of extra work at home, exhausting the child and parents as they struggle to try to catch up.

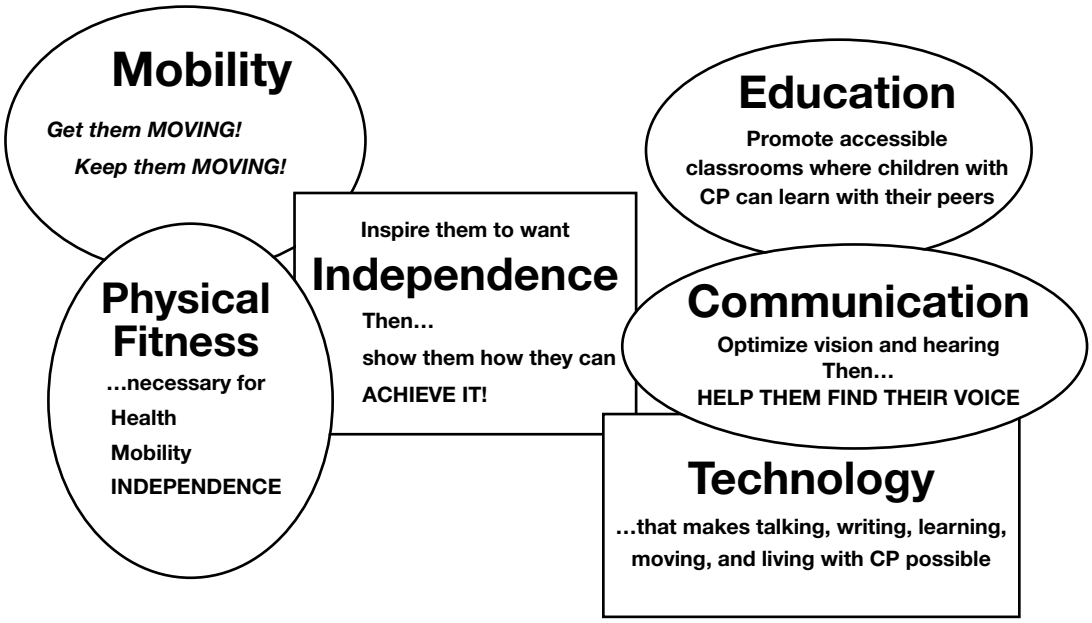

FIGURE 49-1. Key factors in managing cerebral palsy (CP).

The physical barriers that impede a child's educational progress pale in comparison with the psychosocial barriers. In short, the societal expectation for the average child with CP is that he or she will fail to achieve at the same level as his or her able-bodied peers. The greater the motor impairment, the more cognitively impaired and less capable he or she is judged to be. Children who are very verbal and determined may be the exception if they are fortunate enough to have teachers who are able to devote the time required. However, children who are unable to speak or have difficulty speaking due to slow or dysarthric speech may never have the chance to show the world what they have to offer.

The prejudice that most individuals with CP are intellectually subnormal is fueled by the low and even dismal performances of these children on standardized tests of cognitive function. On the basis of these measures, roughly 50% of children with CP are classified as mentally retarded. However, these tests do not accommodate for the motor and speech difficulties and the slowed response time of children with cerebral palsy. The resultant inability to complete entire portions of these tests leads to a lower developmental quotient (DQ) or intelligence quotient (IQ) score. This is especially true in toddlers and young children because developmental scores are linked primarily to the attainment of motor milestones. Ironically, neuropsychologists and educators will counsel parents that these tests are not optimal and may not accurately reflect their child's abilities. Why then do these tests continue to be used to determine a child's "appropriate" placement in school or to limit entry into regular classrooms? Insisting that children with CP prove they are capable of passing tests intended for children with "normal" motor abilities is as ludicrous as using oral examination questions to evaluate children who are hard of hearing or asking children who are visually impaired to pass a written test with pencil and paper. It should be obvious that we cannot know the intellectual capacity of children with motor disabilities (or any child) if we do not give them the chance to tell us what they know. The system continues to assume that these children cannot tell us what they know because their intellect is flawed rather than recognizing and repairing the flaws in the testing and in the educational system itself.

Finding Solutions

Optimizing Communication

Communication is essential to our very quality of life. Communication allows us to relay our most basic needs and wants, to tell people when we are hungry, thirsty, ill, or in pain. For any child to be able to learn effectively, he or she must have the opportunity and the means to communicate. Communication requires the ability to gather information from one's environment through visual, auditory, and tactile senses. Children with CP are at high risk for visual and hearing difficulties that, left untreated, will impede their ability to communicate and to learn. Every child with CP should be evaluated by a trained pediatric ophthalmologist who understands the special risks to vision associated with CP and will look carefully for abnormalities in visual acuity, eye tracking, and binocular vision. Early recognition and treatment of

visual problems can make an enormous difference in the long-term outcome for the child. Similarly, every child who has delayed speech must be evaluated by a trained pediatric audiologist and, if necessary, an otolaryngologist to correct treatable causes of hearing loss.

Children with speech abnormalities should be enrolled early in aggressive speech and language therapies. Physical therapy to strengthen truncal musculature also can improve volume and rate of speech. However, it is important to recognize the substantial number of patients with CP whose motor impairments severely limit their ability to speak. These children must be offered alternative means of communication that will allow them to express themselves as quickly and as energy-efficiently as possible. Although individuals of any age can benefit tremendously from augmentative communication, ideally, these patients should be identified early (between 2 and 3 years of age) so that they can learn to communicate before formal schooling begins. Parents should be reassured that use of a communication device will not thwart a child's chances for continued improvement in speech and that the device may, in fact, improve the chances.

Fitting a child with an appropriate communication device requires a specialized team of experts, including occupational and speech therapists who are familiar with a wide variety of communication devices and switch technologies. These experts must be willing and able to evaluate even the child with the most severe motor disabilities. Patients frequently need to be observed using several different devices and switches to determine the system best suited for them. For example, whereas one child may be able to point to icons on a touch screen, another child may need a switch (activated by hand, elbow, or head turning) and a scanning program to make choices. Still another child may do best with an infrared head pointer. It is important to choose a device that is adaptable and may be upgraded so that the child can use it in the present but also continue to use it as he or she gains increasing language skills. These communication devices are prohibitively expensive, and individuals or families may be able to afford only one or two chances at acquiring technology that their child needs for a lifetime.

Unfortunately, simply obtaining a specialized device does not ensure that an individual will have the chance to communicate. Despite the increasing availability of newer and faster devices, there is an alarming paucity of experts who know how to program the various machines, who are familiar with the latest software, and who have the time to train patients and their parents. As a result, expensive and much-needed equipment sits unused. In response, many parents attempt to become as "expert" as they can at their child's device and take on the responsibility of being their child's teacher.

Optimizing Education with Accessible Classrooms and Computer Technology

Overcoming the barriers to learning in the classroom requires common sense and the coordinated efforts of parents, teachers, school officials, and physicians. Exchanging stairs for ramps or elevators, widening doors and desk sizes to accommodate children in wheelchairs, improving classroom seating systems for children with poor trunk stability, and providing aides to assist children who need them are some examples of where to begin. Computer technology has the potential to level the playing field for the children with motor and speech impairments and to allow them to compete in the classroom at a level commensurate with their true cognitive abilities. Augmentative communication devices can be used for both verbal and written communication. Adapted computers with voice-activated software, touch screens, one-hand keyboards, and other modifications are available to allow children access to learning, regardless of their motor limitations.

Despite advances and adaptations in computer hardware and software, this powerful technology is useless if it never reaches the child. The physician's role is to facilitate the child's access to computers, communication devices, and the classroom. To do this, it may be necessary to write very specific orders to be carried out by the teachers and school therapists, such as "Please provide Johnny with full-time access to his communication device at school and send it home with him on evenings and weekends" or "Johnny needs to use the computer for 80% of his written work due to his limited fine motor skills." Speech and occupational therapy goals in the classroom should focus on creative ways to ensure the child's success in using the computer or communication device. Although it is desirable to improve the patient's fine motor skills and ability to use a pen or pencil, this should not supersede the more important goal of ensuring the best possible chance at an education for the child.

Mobility

Mobility, the ability to move around in one's environment, is a major determinant of a person's level of independence (Figure 49-2). By definition, mobility is reduced in individuals with CP. The child with CP can expect fluctuations in mobility over time, associated with weight gain and linear growth; the general tendency is for individuals with CP to become less mobile as they reach adulthood. The cost of not moving (ie, being sedentary) is high and includes progressive deformity, contractures, chronic pain, severe bone loss and fracture, scoliosis, hip dislocation, reduced cardiovascular fitness, atherosclerotic disease, obesity, and depression. Preventing immobility requires a concerted

FIGURE 49-2. Mobility is important to independence in cerebral palsy.

effort to help patients remain as active as possible by optimizing biomechanics, tone management, strength, balance, and physical fitness. It is also important to recognize that assisted mobility (crutches, canes, walkers, and manual and powered wheelchairs) can greatly augment a person's mobility and independence.

Biomechanics

Several strategies are available to promote optimal biomechanics, including stretching, weight bearing, orthotics and bracing, serial casting, botulinum toxin (BTX) injections, and orthopedic surgery. A more detailed discussion of biomechanics in CP has been published elsewhere (see Suggested Readings).

Tone Management

The management of spasticity and other tone abnormalities is a primary focus for many physicians who treat patients with CP. Too often, tone reduction alone is the goal. This loses sight of the primary goal: to improve and maximize function. The pharmacologic and surgical approaches to spasticity and movement disorders associated with CP best address the "positive symptoms"—hyperreflexia, clonus, and increased tone. These symptoms are clinically evident due to the chronic loss of inhibition. The "negative symptoms" (ie, underlying weakness and loss of agility) that represent the loss of central nervous system function are least responsive to medications and surgery and often the most disabling of the motor symptoms associated with CP. Thus, it is pivotal to determine whether the positive symptoms are the source of the patient's functional impairment. In addition, it must be recognized that, at times, spasticity may, in fact, assist in function. For example, increased tone in a patient's weak legs may provide an antigravity effect that allows them to stand.

The treatment approach to patients with CP has changed dramatically during the past several years as treatment options have greatly expanded. Specific therapies are reviewed in detail in Chapter 50, "Spastic Paresis." An individualized and comprehensive approach to each patient has never been more important. Initial and periodic evaluations by an interdisciplinary team, educated in each of the treatment options, offers the best approach to meet the ever-changing needs of the patient with CP. The decision regarding the appropriateness of a given modality and when and in conjunction with what other treatment option it should be used is based on multiple factors. The patient's age, complicating medical issues (ie, seizures, pain, and rapid development of contractures), and prior response to therapy help direct decision making. Familial and societal factors include compliance and cost factors.

Oral medications, most commonly baclofen, tizanidine, and benzodiazepines, have been extensively used in patients with CP. Although studies have shown a reduction in spasticity, the cognitive and sedative side effects often overshadow any improvement. The emphasis on maximizing cognition is the focus of this chapter and must be kept in clear sight. Oral medications have best been used in the treatment of spasms and sleep disturbance and as an adjunctive in seizure disorders. Their use as a modality for tone reduction is only modest and rarely sufficient.

BTX is well recognized as being effective in reducing tone in specific, focal muscle groups. BTX offers a directed, selective therapy with minimal side effects. Patients tolerate the procedure well and typically benefit for 3 to 4 months. BTX also can be used in conjunction with other modalities.

Intrathecal baclofen therapy provides multisegmental or generalized tone reduction by means of a delivery system consisting of a refillable pump, catheter, and a telemetry programmer that can noninvasively modify the dosage and delivery regimen. The advantages include an effective dosage at a fraction of the oral dose, thus reducing the cognitive side effects. The patient experiences a generalized reduction in spasticity, predominantly in the lower extremities. The upper extremity effect is influenced by the level of the catheter tip, with efficacy increasing as it moves from the lower to upper thoracic area. The literature supports a reduction in spasticity as well as functional improvements.

Selective dorsal rhizotomy has received renewed interest as a treatment option. Although the optimal patient selection criteria remain under dispute, the consensus points to the use of the modality in a select group of patients: mildly diparetic patients, 8 years old or younger, with good underlying strength. Multiple articles continue to debate the merits as well as the disadvantages of the technique.

Strength and Balance

Improving strength and balance requires hard work. Goal-directed physical therapy is important but should be considered adjunctive to a daily home exercise program. In fact, one of the goals of the physical therapist should be to help the patient develop a wide variety of exercises and activities to do at home to strengthen specific muscle groups, improve balance (sitting, standing, static, and dynamic), and maintain and improve muscle or tendon length. Sports and aerobic exercise should be included as part of this daily routine. Patients who comply with a home program get more out of their physical therapy sessions because the therapists are able to work on more complicated motor skills and challenge patients in ways they do not have time to do if entire therapy sessions are spent on stretching. Weight training and resistive exercises build muscle mass and, with proper supervision, can be safely performed by cooperative older children and adolescents without worsening their spasticity. Relatively recent modalities that have been adopted from sports medicine include electrical stimulation of the muscles, which may augment the effects of a muscle-strengthening program in patients with CP.

Physical Fitness

Cardiovascular fitness is vital to the health and wellbeing of the human mind and body. This fact holds true for humans with or without disabilities. Cardiovascular disease and the complications associated with a sedentary lifestyle can strike anyone, and it stands to reason that those who have motor disabilities are at higher risk for these illnesses because they are more likely to be sedentary. The good news is that having a motor disorder and being physically fit are not mutually exclusive. There is a wide and increasing variety of sports and athletic activities (eg, swimming, water aerobics, therapeutic horsemanship, basketball, soccer, snow and waterskiing, dance, and martial arts) that are adaptable and available to individuals with CP. Moreover, many of these activities also promote overall strength and improve balance. Regular aerobic conditioning not only protects one's health but also increases energy levels and endurance. For those with CP, having the physical stamina to move can mean the difference between dependence and independence.

Independence

Independence, the ability to make one's own choices in life and pursue one's own dreams, is the ultimate goal for any child, including persons with disabilities. For individuals with CP, independence often seems elusive and unattainable; the obstacles hindering their success are numerous and daunting and extend far beyond the motor disorder and other associated impairments that they live with. Communication and education, mobility, physical fitness, and goal-directed therapies geared at strengthening and at teaching activities of daily living are all important tools to assist patients in becoming independent. However, none of these interventions will make a truly significant impact unless we work to create a world in which all children are permitted to thrive to their greatest potential, a world in which "accessibility" applies to buildings, doorways, and sidewalks, as well as to all the opportunities life has to offer.

Suggested Readings

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Nelson KB, Grether JK. Causes of cerebral palsy. Curr Opin Pediatr 1999;11:487–91.

Rapp CE Jr, Torres MM. The adult with cerebral palsy. Arch Fam Med 2000;9:466–72.

Tilton AH. Management of spasticity in children with cerebral palsy. Semin Pediatr Neurol 2004;11:58–65.

O'Shea M. Cerebral palsy. Semin Perinatol. 2008 Feb;32(1):35-41.

Practitioner and Patient Resources

Augmentative and Alternative Communication Connecting Young Kids (YAACK)
http://aac.unl.edu/yaack/
YAACK is a comprehensive, practical, and easy-to-use guide to augmentative and alternative communication that focuses on three important areas: how to get started, choosing an augmentative communication system, and teaching.

Simplified Technology for Children with Disabilities
www.lburkhart.com/main.htm
Web links for assistive technology and augmentative communication.

Variety Clubs International
350 5th Avenue, Suite 1119
New York, NY 10118
Phone: (212) 695-3818
Fax: (212) 595-3857
http://members.ozemail.com.au/~bworth/bashvc.htm
Local chapters around the world provide funding for essential medical equipment and programs for children with disabilities.

United Cerebral Palsy (UCP)
1660 L Street NW, Suite 700
Washington, DC 20036-5602
Phone: (800) 872-5827
http://www.ucpa.org
UCP is a national organization with local affiliates in virtually every state. The mission of UCP is to advance the independence, productivity, and full citizenship of people with cerebral palsy and other disabilities.

Shriners Hospitals for Children
2900 Rocky Point Drive
Tampa, FL 33607-1435
Phone: (800) 237-5055
http://www.shrinershq.org
A network of 22 orthopedic Shriners hospitals across the country where children (up to 18 years) receive orthopedic care free of charge.

CHAPTER 50

SPASTIC PARESIS

TERENCE S. EDGAR, MD, FAAP, FAACPDM, FAAEM

The disabling features of central nervous system injury are due to paresis, soft tissue contracture, and muscle overactivity. A multidisciplinary team experienced in the use of the different treatment modalities available is most likely to achieve optimal patient management. Clearly formulated treatment goals and a thorough understanding of the potential benefits, indications, and complications of these therapies are imperative.

Spastic paresis, a significant cause of disability and handicap, frequently represents a major challenge to the management of patients with various neurologic disorders. Disruption in the central execution of voluntary motor command results in paresis. This is accompanied by gradual lesion and activity dependent adaptive changes within the higher centers, the spinal cord, and the soft tissues involved in movement. As a consequence of these events, an abnormal sensitivity to muscle stretch develops in the paretic body part. A classic feature is an increased muscle response to phasic stretch, which invariably follows the rule that the higher the velocity of stretch, the more increased is the reflex. This observation led to the definition of spasticity as a velocity-dependent increase in the stretch reflex.

Motor function in patients with spastic paresis is subjected over time to three fundamental insults:

1. The neural insult itself, which causes paresis, ie, reduced voluntary motor unit recruitment.
2. The relative immobilization of the paretic body part, which causes adaptive shortening of the muscles left in a shortened position and joint contracture.
3. Muscle overactivity, ie, reduced ability to relax the muscle.

Paresis

Paralysis or paresis is defined as decreased voluntary motor unit recruitment. An injury can disrupt central voluntary motor command at various "levels" within the central nervous system. The highest level can be considered two functional units. The first unit provides the spatial and temporal representation of the movement. A mental representation of the movement is created. This is assumed to involve the posterior parietal and prefrontal cortex. Lesions disrupt accuracy of movement with excessive motor hesitation (motor apraxia). These patients are not paretic. The second functional unit generates the voluntary drive or motivation to move. This most likely involves the medial frontal-subcortical (anterior cingulate) circuits.

The middle level of motor command corresponds to the actual programming in time and space of the various muscle contractions and relaxations required to accomplish the intended movement. This involves the anterior part of the supplementary motor area, which has reciprocal connections with the prefrontal cortex and the basal ganglia. It also involves the cerebellum. Patients with disturbances of movement preparation typically exhibit acceleration deficits. For example, in cerebellar dysfunction, there is increased movement size due to delayed antagonist contraction, resulting in hypermetria. Disturbance of movement preparation does not result in paresis.

The lower level of central voluntary motor command is the execution of the movement itself, which is disrupted in patients who develop spastic paresis. Once the movement has been conceived, decided, and planned, the plan is executed centrally by the primary motor area (Brodman area 4), centrum semiovale, internal capsule, and corticospinal tract. Peripheral execution is via the lower motor neuron, neuromuscular junction, and muscle. A lesion in any of the central execution areas disconnects the concept will and program of the movement from its effectors and disrupts

the access of the volitional command to the lower motor neuron. The failure of central voluntary activation of motor units is associated with the following:

1. A loss of normally functioning motor units in the spinal cord.
2. Failure to recruit high threshold motor units
3. Failure to modulate the motor discharge rate during attempts to increase voluntary force

The decrease in recruitment and firing rate results in increased fatigability, compounded by greater difficulty in isolating contraction to a muscle group.

Effects of Immobilization and Disuse

Paresis leaves the affected muscle immobilized. Most situations of joint immobilization place one of the muscles around the joint in a shortened position, resulting in a reduction in the longitudinal tension of the muscle (muscle unloading). The postunloading muscle contracture in spastic paresis is characterized by muscle atrophy, a shortening and loss of sarcomeres, and the accumulation of connective tissue and fat. The loss of normal weight bearing or counterresistance activity results in a reduction of bone mineralization.

Muscle Overactivity

As a result of both the paralyzing lesion and the paresis related disuse, adaptive sprouting occurs at both the supraspinal and the spinal level. The consequences of these plastic changes include the gradual emergence of abnormal and often excessive reflex responses to peripheral inputs such as cutaneous stimuli or muscle stretch. These abnormal reflex responses contribute to global muscle activity.

Disruption of primary execution pathways leads to increased task-related activation in regions not normally involved with direct execution of movement, eg, supplementary motor cortex, cingulate motor area, premotor cortex. In addition, there is increased reliance on undamaged brainstem descending pathways (rubro-, vestibulo-, reticulo-, and tectospinal tracts). Both mechanisms are a source of abnormal supraspinal descending drive that contributes to the muscle overactivity.

Types of Muscle Overactivity

In order to develop a treatment strategy, it may be useful to group the different types of muscle overactivity into two categories, depending on whether they are characterized by prominent stretch sensitivity (Table 50-1). The stretch sensitive forms of muscle overactivity include spasticity, spastic dystonia, and spastic cocontraction, which are distinguished by their primary triggering factor, ie, phasic muscle stretch, tonic muscle stretch, and volitional command, respectively.

TABLE 50-1. Different Types of Muscle Overactivity

Type	Trigger	Disabling
Stretch-sensitive		
Spasticity	Phasic stretch, at rest	–
Spastic dystonia	Tonic stretch, at rest	+
Spastic cocontraction	Voluntary command plus tonic stretch	+
Not stretch sensitive		
Pathologic extrasegmental cocontraction (synkinesis; chorea; athetosis)	Voluntary command	+
Cutaneous and nociceptive reflexes	Cutaneous stimulation	+

- *Spasticity*: it is measured at rest and is defined as a velocity-dependent increase in the stretch reflex, in the absence of volitional activity. As such, it is not a particularly disabling form of overactivity.
- *Spastic dystonia*: conceptualize spastic dystonia as an inability to rest the muscle. It alters the resting posture, contributes to disfigurement, and is virtually a constant feature in patients with spastic paresis.
- *Spastic cocontraction*: it opposes voluntary movement and contributes to impairment in active function. There is inappropriate antagonist recruitment triggered by the volitional command on an agonist. A classic example is the active flexion of the proximal and distal interphalangeal joints observed with attempted voluntary finger extension in patients with spastic hemiparesis.

Patient Evaluation

The presenting features of spastic paresis include as follows:

1. Symptomatic manifestations of UMN dysfunction, including pain, stiffness, clonus, flexor, and extensor spasms, and disfigurement, as well as effortful movement, slowness, and incoordination;
2. Problems of passive function, including personal care and positioning issues. Patients experience problems with dressing, personal hygiene and bathing, difficulty toileting and caring for the perineal region, and problems with skin integrity;
3. Problems of active function, including limb use and mobility issues. The examiner should be particularly interested in reach, grasp, transport, and release in the upper limbs. In the lower extremities, active problems

of UMN dysfunction can interfere with mobility, including problems with transitional movements, transfers, and gait (eg, advancement, clearance, and upright stability).

Clinical assessment of impairment (ie, spasticity and contractures) includes evaluation of the following:

- passive and active range of motion
- strength and endurance
- posture and mobility
- motor control
- function/disability

To effectively manage spasticity, it is important to appreciate the changing character of the motor disability with growth and maturation. Normal joint motion requires coordination and balance of agonist and antagonist muscles, and spasticity is inherently a failure of reflex modulation. If opposing muscles controlling a joint exhibit differential tone or spasticity, shortening or contracture occurs in the agonist muscle. The agonist muscle shortens, and longitudinal growth is inhibited. The antagonist muscle is invariably weak and becomes elongated. This imbalance of dynamic and static forces (Table 50-2) results in the generation of common UMN patterns (Table 50-3).

In developing a treatment paradigm, it is important to bear in mind that impairment constitutes only one dimension of disablement. To develop a realistic management plan, assessment of functional limitations (eg, dressing), disability, and societal limitations need to be considered. Successful treatment can only occur in the context of the patient's and family's expectations and values.

TABLE 50-2. Clinical Phenomena Associated With the UMN Syndrome

Dynamic phenomena
Exaggerated velocity-dependent stretch reflexes (spasticity)
Clonus
Abnormal posturing
Flexor and extensor spasms
Synergy patterns
Babinski sign
Exaggerated cutaneomotor reflexes
Clasp-knife phenomenon
Slow, effortful, and uncoordinated movements
Loss of balance and trunk control
Static phenomena
Muscle contracture
Muscle stiffness
Stiffness of other soft tissues (eg, skin, blood vessels)
Loss of range of motion
Joint and capsular stiffness

TABLE 50-3. Common UMN Patterns

Upper limb
Adducted internally rotated shoulder
Flexed elbow
Pronated forearm
Flexed wrist
Clenched fist
Thumb-in-palm
Lower limb
Flexed hip
Adducted thighs
Flexed knee
Equinus foot with associated varus or valgus
Hyperextended hallux

Current Treatment Options

Several treatment options are available to manage spasticity, and more than one option can be used (Figure 50-1). A complementary approach to the treatment of spasticity is encouraged and may include physical, pharmacologic, and surgical interventions. It is not uncommon to use physical and occupational therapies in combination with botulinum toxin (BTX) injections, intrathecal baclofen (ITB) therapy, and timed orthopedic interventions. A rational approach to therapy can be developed on the basis of the proposed pathophysiology and receptor–neurotransmitter interactions. Realistic and clearly defined goals should be established before initiating treatment.

Oral Pharmacotherapy

Oral medications may be of benefit in the treatment of painful spasms, disrupted sleep, and dystonia, but their use in the management of generalized spasticity has been disappointing. With the possible exception of diazepam and dantrolene, there is little evidence that oral medications can meaningfully reduce tone. The nonselective action is seen in all muscle groups and centrally, with frequent cognitive side effects. A detailed description of drugs is found in Table 50-4.

Baclofen

Baclofen is a structural analogue of γ-aminobutyric acid (GABA). It enhances Renshaw cell activity and appears to block the polysynaptic and monosynaptic afferents in the spinal cord by binding to GABA-B receptors. Its mechanism of action may be as a direct inhibitory neurotransmitter or through hyperpolarization of the afferent nerve terminals. Penetration of the blood-brain barrier is very poor, with more than 90% of the absorbed drug remaining in the systemic circulation. Oral baclofen is particularly useful for symptomatic problems, such as flexor spasms, stiffness, and pain in

Table 50-4. Pharmacotherapy for Spasticity

Generic Name	Trade Name	Web Site	Dosage Forms	Usual Doses	Mechanisms of Action
Baclofen	Lioresal®		Tablets: 10 mg, 20 mg	Age < 2 yr, 2.5 mg PO q8h, maximum 20 mg/d; age 2–7 yr, 5 mg PO q8h, maximum 40 mg/d; age > 8 yr, 5 mg PO q8h, maximum 60 mg/d; dose titration at 7 d intervals to effective dose	GABA agonist—inhibits transmission of reflexes at the spinal cord level
Clorazepate	Tranxene® C-IV		Tablets: 3.75, 7.5, 11.25, 15, and 22.5 mg; capsules: 3.75, 7.5, and 15 mg	Adult: 7.5 mg PO bid, increase weekly by 7.5 mg to maximum 90 mg/d given in divided doses; age 9–12 yr: 3.75 mg PO bid, increase weekly by 3.75 mg not to exceed 60 mg/d in divided doses	Facilitates the actions of GABA
Clonazepam	Klonopin®	www.rocheusa.com/products/klonopin	Tablets: 0.5, 1, and 2 mg	0.1–0.3 mg/kg/d PO divided bid or tid	Facilitates the actions of GABA
Diazepam	Valium®; Valrelease®		Tablets: 2, 5, and 10 mg; solutions: 1 and 5 mg/mL; sustained release capsule: 15 mg	Adult: 2–10 mg PO bid to qid; child: 0.05–0.1 mg/kg PO bid to qid (maximum 0.8 mg/kg/d)	Facilitates the actions of GABA
Clonidine	Catapres®, Catapres-TTS®		Tablets: 0.1, 0.2, and 0.3 mg; transdermal patch: 0.1, 0.2, and 0.3 mg/d, change every 5–7 d	5–10 μg/kg/d PO divided q 8–12 h	Centrally acting α_2-adrenergic agonist that increases presynaptic inhibition of motor neurons
Tiagabine	Gabitril®		Tablets: 4, 12, 16, and 20 mg	Adult: 32–56 mg/d divided bid–qid (start with 4 mg/d PO, adjust weekly); child: 0.1 mg/kg/d increase to 0.5 mg/kg/d	Inhibits neuronal and glial uptake of GABA
Tizanidine	Zanaflex®		Tablet: 4 mg	Adult: initial dosing 4 mg PO q8h PRN, may increase to maximum 36 mg/d; child: age < 10 yr, initial dosing 1 mg PO qhs; age > 10 yr, 2 mg PO qhs, maintenance 0.3–0.5 mg/kg/d divided qid	Centrally acting α_2-adrenergic agonist that increases presynaptic inhibition of motor neurons
Gabapentin	Neurontin®		Capsules: 100, 300, and 400 mg; tablets: 600 and 800 mg; suspension: 250 mg/5 mL	Adult: 900–3,600 mg PO divided tid to qid; child: up to 60 mg/kg/d divided tid to qid	Unknown
Dantrolene	Dantrium®		Capsule: 25 and 100 mg	Adult: 25 mg/d PO, increase every 4–7 d to maximum 400 mg divided into 4 doses per day; child: age > 5 y, 0.5 mg/kg PO bid, increase every 4–7 d to maximum 400 mg divided into 4 doses per day	Interferes with calcium ion release from sarcoplasmic reticulum of skeletal muscles
Injectable					
Baclofen	Lioresal®		Intrathecal injection: 0.2 mg/mL (for test doses mix with preservative-free normal saline to concentration 50 μg/mL)	Test doses, continue to desired effect or 100 μg—day 1, 50 μg/1 mL; day 2, 75 μg/ 1.5 mL; day 3, 100 μg/2 mL test dose given over 24 h via pump; usual doses are 300–800 μg/d via implanted pump	GABA agonist—inhibits transmission of reflexes at the spinal cord level
Botulinum A toxin	Botox®	www.botox.com	Injection: 100 units/vial;	1–3 units/kg for small muscles, 3–6 units/kg for large muscles, maximum 15 units/kg (or 400 IU) for all muscles per treatment. Treatments usually need to be repeated at 2–6 mo intervals	Blocks neuromuscular conduction by inhibiting releaseof acetylcholine

Table 50-4. Pharmacotherapy for Spasticity (continued)

Generic Name	Precautions	Side Effects	Drug Interactions
Baclofen	Avoid use in renal failure, intracranial bleeding, stroke, diabetes, seizure disorders, and peptic ulcer disease and when spasticity is used to maintain posture or balance. Avoid abrupt withdrawal.	Drowsiness, weakness, dizziness, headache, nausea, vomiting, hypotension, constipation, confusion, insomnia, and urinary frequency	Any drugs that share CNS depressant effects; worsening of diabetic control with oral drugs or insulin; combination with tricyclic antidepressants increases muscle hypotonia; combination with MAOIs increases CNS depression and hypotension
Clorazepate	Hypersensitivity, preexisting CNS depression, uncontrolled pain, narrow angle glaucoma. Avoid abrupt withdrawal.	Tachycardia, fatigue, sedation, tolerance, dry mouth, constipation, urinary retention, weakness, depression, ataxia, impaired coordination, memory impairment, and blurred vision	Increased effects seen with other CNS depressants, alcohol, and cimetidine
Clonazepam	Hypersensitivity, severe liver disease, and narrow angle glaucoma. Avoid abrupt withdrawal.	Tachycardia, fatigue, sedation, tolerance, dry mouth, constipation, urinary retention, weakness, depression, ataxia, impaired coordination, memory impairment, and blurred vision	Increased effects seen with other CNS depressants
Diazepam	Hypersensitivity, preexisting CNS depression, uncontrolled pain, and narrow angle glaucoma. Avoid abrupt withdrawal.	Tachycardia, fatigue, sedation, tolerance, dry mouth, constipation, urinary retention, weakness, depression, ataxia, impaired coordination, memory impairment, and blurred vision	Increased effects seen with other CNS depressants, alcohol, SSRIs, and cimetidine
Clonidine	Avoid in patients with cerebrovascular disease or coronary insufficiency. Adjust dose with renal dysfunction. Avoid abrupt withdrawal.	Hypotension, dizziness, sedation, nausea, vomiting, depression, dry mouth, constipation, and hepatotoxicity	β-blockers may potentiate bradycardia and may increase the rebound hypertension of withdrawal
Tiagabine	Use with caution in patients with hepatic disease.	Sedation, dizziness, memory impairment, emotional lability, headache, abdominal pain, and anorexia	Increased effects seen with other CNS depressants. Enzyme-inducing drugs such as phenytoin or phenobarbital may increase the clearance of tiagabine. Valproic acid can displace tiagabine from protein-binding sites.
Tizanidine	Avoid in renal or hepatic dysfunction.	Hypotension, dizziness, sedation, nausea, vomiting, depression, dry mouth, hepatotoxicity, hallucinations, and psychotic-like symptoms	Alcohol and oral contraceptives may increase concentrations. Tizanidine would be additive in causing hypotension if used with antihypertensive agents.
Gabapentin	Avoid in patients with severe renal dysfunction. Avoid abrupt withdrawal.	Somnolence, dizziness, ataxia, nystagmus, weight gain, rash, nausea, vomiting, blurred vision, tremor, slurred speech, peripheral edema, dyspepsia, and hiccups	Decreased absorption of gabapentin when taken with antacids
Dantrolene	Avoid with cardiac, pulmonary, or liver disease and when spasticity is used to maintain posture or balance. Avoid sunlight.	Drowsiness, dizziness, light-headedness, fatigue, rash, diarrhea, nausea, vomiting, muscle weakness, and respiratory depression	Increased toxicity when used in combination with estrogens, CNS depressants, MAOIs, phenothiazines, clindamycin (neuromuscular blockade), verapamil, and warfarin
Injectable			
Baclofen	Avoid use in intracranial bleeding, stroke, diabetes, or seizure disorders and when spasticity is used to maintain posture or balance. Avoid abrupt withdrawal.	Drowsiness, weakness, dizziness, headache, nausea, vomiting, hypotension, constipation, confusion, insomnia, urinary frequency, seizures, paresthesias, blurred vision, hypotonia, coma, hypertension, and dyspnea	Any drugs that share CNS depressant effects
Botulinum A toxin	Presence of fixed contractures	In one trial: 3% incidence of leg weakness, leg or calf pain, and falling; 1% incidence of fatigue, unstable gait, malaise, ankle inversion injury, pain at injection site, lethargy, tingling in back, foot callus, and urinary incontinence. Also, risk of infection, rash, allergic reactions, and flu-like symptoms	Potentiate neuromuscular blockade with aminoglycosides; chloroquine antagonizes the onset of paralysis

CNS = central nervous system; GABA = γ-aminobutyric acid; MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor.

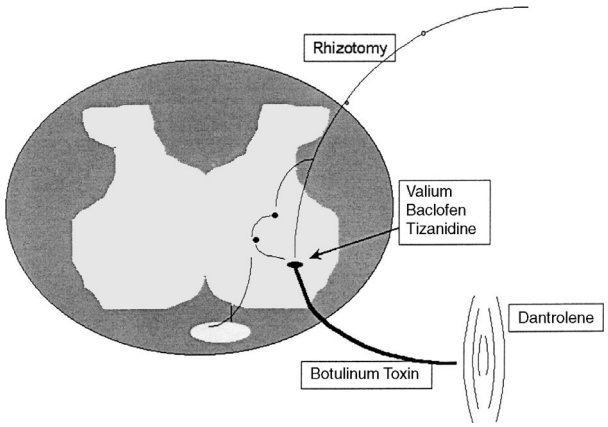

FIGURE 50-1. Points of Treatment.

patients with spinal cord injury (SCI) and demyelinating myelopathies (DMs).

Dosing in children is as follows:

- Start with 2.5 mg qhs and titrate to tid or qid every 7 days
- In older patients, initiate treatment with 5 mg bid
- Suggested maximum dose (adjusted to efficacy and patient tolerance):
  - 20 mg/d if <2 years
  - 40 mg/d if 2 to 7 years
  - 60 mg/d if >8 years

Side effects may include sedation, drowsiness, fatigue, and exacerbation of existing weakness. Acute baclofen withdrawal may precipitate hallucinations, seizures, and psychosis.

Diazepam

Benzodiazepines exert their antispasmodic action through GABA-A receptors. In the spinal cord, diazepam appears to increase presynaptic afferent inhibition and depress mono and polysynaptic transmissions. There is evidence for enhanced postsynaptic inhibition in the reticular formation. Diazepam is useful in SCI, DM, and cerebral palsy (CP), but the sedation and cognitive side effects limit its use in stroke and traumatic brain injury. It is particularly useful in children with painful spasms that produce insomnia.

Dosing is as follows:

- Infants: starting dose 1 mg qhs
- Young adults: starting dose 5 mg qhs
- Maximum dose in children is 0.8 mg/kg/d, divided q 6 to 8 hourly.

Tizanidine

Tizanidine is an imidazole derivative, related to clonidine, with agonist action at both spinal and supraspinal α_2-adrenergic receptors. It reduces aspartate and glutamate release from the presynaptic nerve terminals of the spinal interneurons and appears to have antinociceptive properties. It may be particularly useful in nighttime spasms, pain, and clonus. Sedation is a significant limiting factor in achieving adequate dosing, which is compounded if the medication is administered with food.

Dosing is as follows:

- Target dose is 0.3 to 0.5 mg/kg/d
- The short half-life requires qid dosing or used as a single dose to treat nighttime spasms and pain.
- <10 years of age: start at 1 mg qhs and increase at weekly increments to a qid dosing as tolerated.
- <10 years of age: start at 2 mg qhs and increase at weekly increments to a qid dosing as tolerated.

Hepatotoxicity occurs in ±5% of patients. Liver enzymes should be monitored.

Dantrolene

This is a potentially underused treatment, particularly in the nonambulatory patient. It is unique among antispasmodic agents in that it acts peripherally at the level of the muscle fiber rather than the spinal cord. Dantrolene uncouples electrical excitation from contraction by inhibiting the release of calcium from the sarcoplasmic reticulum. It is useful for symptomatic relief, especially clonus, in all types of UMN insults. Because it may significantly exacerbate weakness, it should be used with caution in DMs and in ambulatory patients with CP.

Dosing is as follows:

- Start at 0.5 mg/kg qhs and increase to 2 to 4 times per day at 4-day intervals.
- Then increase by 0.5 mg/kg to a maximum of 3 mg/kg (the maximum adult dose is 400 mg/d).

The incidence of hepatotoxicity is low (<5%). Do a baseline liver function test before starting dantrolene and monitor throughout treatment.

Other Agents

Tiagabine inhibits the reuptake of GABA, thus theoretically increasing GABA levels in the synapse. There is weak evidence that tiagabine may be of benefit in the symptomatic management of spasticity, particularly in patients with coexisting seizures. Cyproheptadine is a 5-hydroxytriptamine receptor antagonist that may neutralize spinal and supraspinal serotonergic excitatory inputs. Gabapentin may be of some use in treating painful spasms, but its effectiveness in treating spasticity is questionable.

Neuromuscular Blockade

Two preparations of BTX are available in the United States, Type A (BTX-A, BOTOX) and Type B (BTX-B, MyoBloc). Binding of the neurotoxins to specific fusion proteins blocks binding of the acetylcholine-containing vesicle to the nerve terminal; thus preventing depolarization at the neuromuscular junction. A process of synaptic repair and

rehabilitation reverses the action of BTXs on the cholinergic synapses.

The therapeutic goal of neuromuscular blockade in patients with spastic CP (as achieved with BTX injections) is the complete or partial paralysis of specific target (agonist) muscles affecting a specific spastic joint while leaving the antagonist muscle unaffected. As a result, joint forces will become more balanced, and a functional passive range of motion will be restored. However, elimination of spasticity in itself may not necessarily result in improved performance of that particular muscle group but may, instead, expose the negative impairments of the agonist/antagonist muscle pair (eg, loss of strength or dexterity). For this reason, BTX injections should be accompanied by an aggressive physiotherapy (PT) program that increases muscle strength and dexterity as a means of improving the performance of everyday activities.

BTX-A is both safe and well tolerated. Mild discomfort occurs at the injection site, lasting 5 to 10 minutes. Side effects are rare; occasionally, patients will report a mild myalgia. Response is seen within 3 to 4 days after injection and is maintained usually for 3 months or longer.

The primary criterion for identifying patients who are potential candidates for BTX is the presence of either persistent or dynamic hypertonia in the absence of significant fixed deformity, regardless of the anatomic site or distribution of palsy:

- In the upper limb, indications for treatment include persistent thumb-in-palm or thumb adduction, wrist posture preventing effective hand use, or tight elbow flexion. Tone in the shoulder extensors or external rotators can significantly limit functional mobility and responds well to BTX therapy.
- In the lower limb, indications include a dynamic equinus persistent throughout the gait cycle, knee hyperextension secondary to overactive plantar flexors, a dynamic knee flexion angle >20° during the gait cycle or interfering with gait, or significant scissoring or adduction at the hips.

In either upper or lower limbs, relative muscle weakness may be a contraindication for BTX-A therapy and should be thoroughly assessed.

BTX-A is dispensed as a freeze-dried powder in vials containing 100 U of toxin. The freeze-dried product must be stored at 4°C and reconstituted with 0.9% preservative-free saline before use. The reconstituted product should be used within 4 hours of preparation. Dosing of BTX-A is based on the number of units of toxin; guidelines for dosing are as follows:

- Total maximum dose administered per visit: less than 15 U/kg or 400 U.
- Number of injection sites per muscle: two to four for gastrocnemius, medial hamstrings, and quadriceps (extended knee); one to two for all other muscles.
- Dose range per large muscle per visit: 3 to 6 U/kg.
- Dose range per small muscle per visit: 1 to 3 U/kg; maximum dose per injection site, 50 U, requiring dividing the total planned unit dose per muscle into equal volumes per injection site.
- Reinjection intervals should exceed 3 months.

Dose modifications for BTX-A injections can be made on the basis of the patient's physical status, muscle size and/or function, and the results of clinical evaluation.

Following BTX injections, PT and occupational therapy (OT) should focus on improving range of motion, strength, and functional movement, including gait and/or functional hand use. Serial casting and functional electrical stimulation may be used to enhance progress. Recommended frequency of PT or OT is 30 to 45 minutes two to three times per week.

ITB

ITB is a technique whereby very low doses of baclofen can be infused into the subarachnoid space around the spinal cord with effective potentiation of GABA-modulated inhibition of spasticity. Administration of ITB produces 10-fold higher levels of baclofen in the lumbar cerebrospinal fluid (CSF) than that achieved with oral baclofen. ITB is cleared by rostral blood flow, resulting in a 4-fold greater concentration of baclofen in the lumbar CSF than that measured at the cervical level. This reduces the risk of respiratory suppression but also results in reduced efficacy on upper extremity spasticity.

There are essentially two groups of patients that should be considered for ITB therapy:

1. Ambulatory patients whose gait is adversely affected by increased muscle tone, with disruption of normal movement patterns, but who have fair to good trunk and proximal strength. Associated dyskinetic movements are not a contraindication.
2. The nonambulatory patient with severe generalized spasticity that interferes with function, ease of care, and quality of life. Muscle spasms and significant contractures may be present.

The patient must have failed oral antispasmodics and weigh at least 30 lbs, with good social support and motivated caregivers.

Prior to pump placement, the family is provided with a video and detailed information regarding ITB therapy. Arrangements are then made for an ITB trial with 50 to 100 μg of ITB administered by lumbar puncture. During the trial, at least a one-point change on the Ashworth scale is required before the patient is deemed a successful candidate. It is important to consider not only changes in tone but also changes in posture, balance, and transfers. Discernment is required, particularly in those patients with significant axial-proximal weakness. These patients are at significant risk for the development of scoliosis and loss of functional

mobility when tone is decreased. It is imperative that clearly defined goals are established prior to pump placement.

Currently, the most effective system for administering ITB is the SynchroMed infusion pump (Medtronic, Minneapolis, MN). This disc-shaped pump is 3 inches in diameter and 1 inch deep. It contains a peristaltic pump, a battery with an operational life of 5 to 7 years, a reservoir for baclofen, and electronic controls that permit regulation of the pump by telemetry. These features permit easy dose adjustment according to the patient's activities. For example, a bolus may be programmed prior to awakening, making it easier to dress. During the course of the morning using a lower rate can be considered to optimize posture while sitting in the classroom, with increased rates in the afternoon and evening.

Following pump placement, ITB therapy is initiated by continuous infusion, with adjustment of baclofen dosage as necessary to obtain maximal functional benefit. One month after pump placement, an aggressive PT program is initiated with the goal of increasing strength and optimizing function. Patients return for pump refills every 2 to 3 months.

Potential side effects of ITB include hypotonia, somnolence, nausea or vomiting, headaches, and dizziness. Overdose could lead to respiratory suppression. Although extremely rare, acute baclofen withdrawal is potentially a life-threatening event and requires aggressive management. Patients initially present with pruritis, increased tone, and spasms. Malignant hyperthermia, with rhabdomyolysis, consumptive coagulopathy, and vasomotor collapse, may develop. This syndrome needs to be treated aggressively, ideally with reinitiation of ITB therapy. However, if this is not possible, using a midazolam infusion (acts on GABA-B receptors) and/or a dantrolene infusion (to minimize rhabdomyolysis) can be considered. Admission to an intensive care unit is strongly advised. This complication can largely be avoided by providing patients with rectal valium (Diastat), which is kept at home in the event of an acute ITB withdrawal. There should be a low threshold to its use, particularly in a patient presenting with pruritis or severe exacerbation of spasms.

PT and OT following ITB pump placement focuses on range of motion, positioning, and mobility and/or functional training, incorporating gait if the patient is ambulatory. Strengthening of trunk muscles and muscle groups antagonistic to spastic muscles is crucial to optimizing patient outcomes when patients have independent mobility at any level. Orthotic needs are assessed and modifications made, depending on the patient's level of function postplacement.

Surgical Interventions

Selective Dorsal Rhizotomy

It involves the cutting of approximately 50% of the dorsal roots, decreasing proprioceptive and exteroceptive drive on the α-motor neuron. The result is a reduction in muscle tone in the lower extremities, with improved sitting posture and gait. The ideal candidate is a child 3 to 8 years of age with near-normal lower extremity strength, who has not developed fixed contractures and in whom the alteration of tone will lead to the desired improvement in function. The presence of associated dyskinetic movements is a contraindication to surgery. After rhizotomy, intensive OT and PT programs are initiated, targeted at restoring and ultimately surpassing the patient's presurgical level of functional mobility, and independence in activities of daily living.

Orthopedic Surgery

Orthopedic interventions remain a crucial element in the rehabilitation of patients with spasticity. Surgery is used to treat both the static and dynamic consequences of UMN injury.

Treatment of the dynamic forces includes as follows:

- tendon lengthening
- intramuscular lengthening
- muscle release
- tendon transfer
- neurectomy

Treatment of the static forces includes as follows:

- release of soft tissue or capsule contractures
- lengthening of contracted muscle
- correction of bone and joint deformities
- excision of heterotrophic bone

Orthopedic intervention is indicated if a patient is not demonstrating improvements with conventional stretching, BTX and/or serial casting, myofascial release, or dynamic splinting to improve range of motion. Orthopedic referral should be considered if:

- misalignment cannot be corrected with orthoses
- a positive femoral anteversion test is observed with palpation
- a >25° knee flexion contracture is present in supine knee extension
- instability of the hips is present

A comprehensive review of orthopedic interventions is beyond the scope of this chapter (see suggested readings).

Outcome Measures and Assessment Tools

The Gross Motor Function Measure is a good assessment tool for demonstrating incremental progress for a child with CP. Many of the test items are activities requiring control of disassociated movement, so the test allows the

clinician to track changes in quality of movement as well as changes in functional skill level. The Pediatric Evaluation of Disability Inventory can be used for children 6 months to 7 years old and is particularly useful for assessing the more severely impaired child. This measure emphasizes self-care and social aspects more than other pediatric outpatient assessment tools do.

Using the Tardieu scale at initial and subsequent clinic visits is an excellent mechanism for assessing patient response to and need for spasticity intervention measures over time. In the Tardieu scale, R1 is designated as the initial point of resistance in range. R2 is designated as the maximum range of motion available. R1 focuses on the dynamic component of spasticity, whereas R2 is more indicative of the static component. The Ashworth scale is an alternative tool for tonal assessment. The scale ranges from 1 to 5, with a score of 1 reflecting normal tone and 5 indicating that the affected part is maintained in rigid flexion or extension. Goniometric measurement is useful for providing an objective assessment of limitations in range of motion and evaluating progress. Quantification of spasm frequency using the spasm scale may be a useful measure for assessing response to intervention, especially for those patients with a severe startle reflex.

Orthotics

The purpose of orthotics is to provide support for body structures that do not have inherent appropriate biomechanical support from the patient's own musculoskeletal system. Orthotics may be used to improve upper and lower extremity functions and are selected on the basis of the patient's function and range of motion.

Patients with mild upper extremity spastic patterns of movement usually benefit from an appropriate splint that blocks the spastic pattern, promoting a more normal pattern of grasp and reach. Patients with spasticity requiring lower extremity orthotics most often benefit from the use of an "inhibitory" orthosis. Trim lines and types of lower extremity orthotics are selected on the basis of analysis of the structure and function of the limb in the swing and stance phases of gait. The brace should be the least restrictive possible while providing optimal alignment.

Suggested Readings

Booth MY, Yates CC, Edgar TS, Brandy WD. Serial casting vs combined intervention with botulinum toxin A and serial casting in the treatment of spastic equinus in children. Pediatr Phys Ther 2003;15:216–20.

Coffey RJ, Edgar TS, Francisco GE, et al. Abrupt withdrawal from intrathecal baclofen: recognition and management of a potentially life-threatening syndrome. Arch Phys Med Rehabil 2002;83:735–41.

De Lissovoy G, Matza LS, Green H, et al. Cost-effectiveness of intrathecal baclofen therapy for the treatment of severe spasticity associated with cerebral palsy. J Child Neurol 2007;22:49–59.

Edgar TS. Oral pharmacotherapy of childhood movement disorders. J Child Neurol 2003;18 Suppl 1:S40–9.

Practitioner and Patient Resources

American Academy for Cerebral Palsy and Developmental Medicine
6300 N. River Road, Suite 727
Rosemont, IL 60018-4226
Phone: (847) 698-1635
http://www.aacpdm.org
Excellent educational resource for health professionals and patients.

United Cerebral Palsy Association
1660 L St., NW
Washington, DC 20036-5602
Phone: (800) USA-5-UCP
http://www.ucpa.org
Excellent patient resource site. Their mission is to advance the independence, productivity, and full citizenship of people with cerebral palsy.

CHAPTER 51

NEURODEGENERATIVE DISORDERS

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Children with neurodegenerative disorders pose a diagnostic challenge to the child neurologist. A simplified paradigm for diagnostic evaluation is presented based on detailed history, selected physical findings, ophthalmologic examination, and data from magnetic resonance imaging of the brain.

Neurodegenerative Disorders with Cognitive Decline

Neurodegeneration refers to the loss of neurons from the central or peripheral nervous systems. Neurodegenerative disorders are diseases produced by this progressive loss of nerve cells, usually on the basis of genetic mutations that compromise neuronal health. The evolving sophistication of molecular biology has made it possible to identify the mutations associated with many degenerative disorders. These mutations are referred to as the disorder's genotype. The clinical manifestations of this genotype are dependent on a number of factors, including the remainder of the individual's genetic constitution and the status of nervous system development at the time of disease onset. As such, the same gene deletion may produce markedly different clinical presentations in affected individuals, even within the same family. These clinical signs and symptoms are the disorder's phenotype, which may involve both central and peripheral nervous system dysfunctions, in addition to changes in the development and function of other organ systems. This chapter deals with those neurodegenerative disorders of childhood that result in a loss of cognitive function (dementia) and advances a diagnostic approach that is heavily dependent on nonneurologic signs and symptoms in concert with data from magnetic resonance imaging (MRI) of the brain. The infrequency of each neurodegenerative disorder of childhood, typically on the order of 1/10,000 to 1/500,000 of population, renders a vast experience with these disorders impossible for most clinicians. As such, a systematic approach for evaluating these disorders relying on a limited number of clinical and radiological guideposts is recommended.

Variable Clinical Presentation of Cognitive Decline

Neurodegenerative disorders are not diagnosed on the basis of a specific biochemical or genetic defect. These disorders are diagnosed clinically in the child who sustains a decreased rate of developmental skills acquisition. Developmental progress ultimately plateaus, a state that is frequently followed by a loss of previously acquired developmental skills. Figure 51-1 demonstrates the course of degenerative disorders graphically. Child (A) maintains a normal neurodevelopmental profile. Developmental milestones are acquired stably and at appropriate chronological ages. Child (B) has mental retardation. Stable developmental progress is made, although milestones are met at twice the expected chronological age. Child (C) sustains a decrease in the normal rate of acquisition of developmental milestones, followed by a developmental plateau. This child has a degenerative disorder, despite the absence of developmental regression. Child (D) sustains a similar slowing of developmental skill acquisition but has a "classic" neurodegenerative disease involving subsequent loss of developmental skills. Child (E)

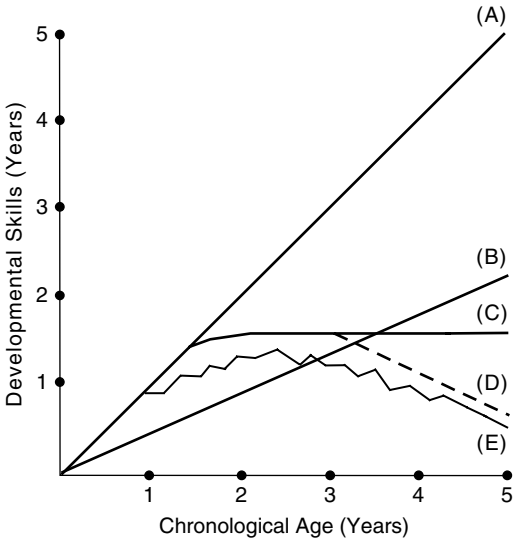

FIGURE 51-1. Graphic representation of childhood development.

demonstrates that loss of developmental skills may not be continuous. Rather, a saltatory loss of skills is seen in some children. Paroxysms of developmental regression may be triggered by catabolic stress in the form of illness or injury. Regardless of clinical course, neurodegenerative disorders may be mistaken for mental retardation or psychiatric disturbance at disease onset. A careful developmental history with attention to persistent developmental stasis and/or cognitive regression will ultimately define the presence of a neurodegenerative disorder.

History and Physical Examination Are Essential

The availability of DNA-based testing has greatly improved diagnostic accuracy for many neurodegenerative disorders. However, these tests have also revealed a much broader phenotypic range for many neurodegenerative diseases than initially recognized, in addition to demonstrating poor correlations between genotype and phenotype in many disorders. While awaiting the development of an accurate DNA screening battery for these diseases, the child neurologist is faced with a transitional period in diagnostic technologies. Many degenerative disorders continue to be diagnosed by enzyme assay or histological analysis, while DNA-based testing continues to evolve. This often mandates the performance of multiple diagnostic tests, completed in a profusion of specialty laboratories. These factors render the assessment of children with degenerative disorders confusing, logistically challenging, and expensive. As such, a simplified and directed approach for evaluating these children is imperative.

The diagnostic process begins with a detailed family history (pedigree), as inheritance patterns are specific to each disorder and may focus the evaluation. This history should include ethnicity as many degenerative disorders are specific to particular ethnic groups, in addition to questions regarding consanguinity as this increases genetic risk and suggests an autosomal recessive disorder. History regarding affected family members should include a broad review of signs and symptoms, as marked intrafamilial phenotypic variation may be seen with some degenerative disorders. Screening neurologic examinations should be performed on available family members to look for unrecognized neurologic signs.

A detailed neurologic examination is essential when evaluating the child affected with a degenerative disorder. Attention to features of central nervous system dysfunction (dementia, seizures, spasticity, dystonia, chorea) and their association with signs of peripheral nervous system degeneration (weakness, neuropathy) may significantly narrow the child's range of potential diagnoses. Of equal importance, however, is the child's general physical examination. Abnormalities of head size, skin and hair changes, hepatic and/or splenic enlargement, skeletal changes (dysmorphism), and ocular pathology may be used to guide the clinician through a complex array of diagnostic possibilities.

A Flowchart to Simplify the Diagnostic Evaluation of Neurodegenerative Disorders

Figure 51-2 is a flowchart that directs the clinician to specific diagnoses of neurodegenerative disease on the basis of the affected child's physical examination, in concert with ophthalmologic examination and data from MRI of the brain. Although Figure 51-2 is complicated, the reader should not despair. By working through a limited number of major decision points, the differential diagnostic possibilities for a given patient are greatly reduced. At the top of the flowchart (see Figure 51-2), conditions are listed that may mimic neurodegenerative disorders of childhood that are potentially treatable or have genetic implications. See Table 51-1 for a more detailed listing of these conditions. In an effort to reduce the visual complexity of Figure 51-2 and the accompanying Table 51-2 regarding ocular pathology, an effort has been made to minimize redundant use of diagnoses. As such, if a degenerative disorder is uniformly detected by visceromegaly during the initial decision points of Figure 51-2, it may not appear in Table 51-2 even if some patients manifest ocular pathology. Regrettably, some conditions, such as mitochondrial disorders, demonstrate such extreme phenotypic variability that they appear in multiple locations within Figure 51-2. The number next to each degenerative

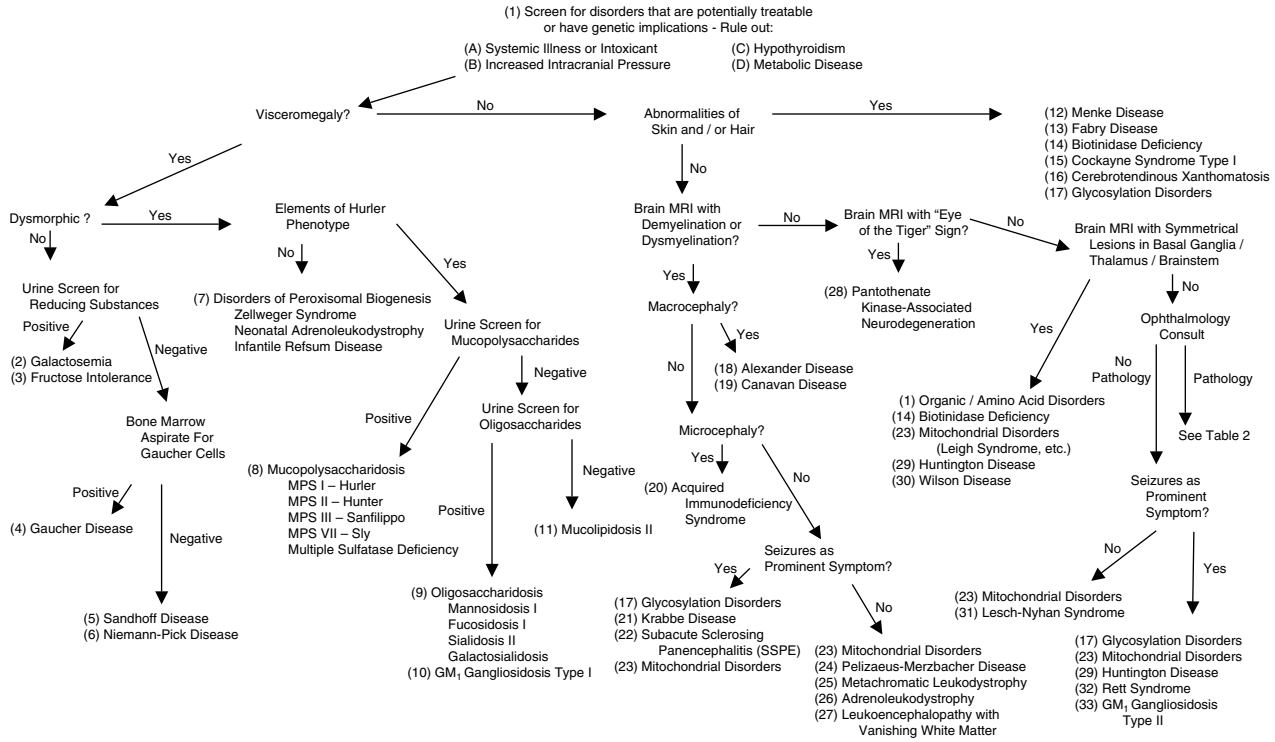

FIGURE 51-2. Evaluation of neurodegenerative disorders of childhood with cognitive decline (dementia).

TABLE 51-1. Conditions That May Mimic Neurodegenerative Disorders in Childhood

Drug intoxication—prescription or illicit
Lead intoxication
Renal failure
Hepatic failure
Respiratory failure
Sleep disorder
Endocrine disorders
Nutritional deficiencies
Chronic central nervous system infection
Cerebrovascular disorders
Rheumatologic disorders/vasculitis
Multiple sclerosis
Epilepsy
Brain tumor
Increased intracranial pressure
Trauma/abuse
Psychiatric illness
Autism

disorder in Figure 51-2 refers to a concise disease summary in the Appendix of this chapter. Included in each summary is the numeric designation for Online Mendelian Inheritance in Man (MIM#). This number permits the reader to access continually updated information regarding each neurodegenerative disorder via the Internet.

Gray Matter versus White Matter

As indicated in Figure 51-2, data from MRI of the brain serves as a critical branch point in the diagnostic process for neurodegenerative disorders of childhood. This is particularly true of an MRI revealing demyelination or dysmyelination of the brain's white matter. Yet, this branch point may be confounded over the first years of life by variations in the natural process of myelination that are evident by MRI. As such, it is the purview of the neurologist to interpret white matter changes by MRI in the context of the patient's clinical presentation. On the basis of progression of signs and symptoms early in the course of a degenerative disorder, inferences can be made regarding the predominant pathology—gray matter (neurons) versus white matter (oligodendrocytes and the myelin sheath). Table 51-3 presents the signs and symptoms associated with disorders of gray matter and white matter. This differentiation can only be pursued early in the course of a neurodegenerative disorder, as both gray and white matter diseases have similar clinical findings at end stage. White matter changes on brain MRI in the young child presenting with typical findings of a white matter disorder should clearly be treated with greater importance as the diagnostic evaluation unfolds.

The Importance of Diagnosis in Neurodegenerative Disorders

If the neurodegenerative disorders of childhood produce an inexorable decline in cognition and systemic health, why is rapid and accurate diagnosis of these disorders important? First, a precise diagnosis permits counseling of the child's family regarding disease causation and prognosis. This frequently assuages parental feelings of guilt and permits the family to frame realistic neurodevelopmental expectations for the child. Further, the genetic risks associated with the disorder can be reviewed. This is particularly important in pediatric practice, as the patient's family often has plans for further children. Beyond the risk of recurrence associated with the disorder, the availability of prenatal testing for many degenerative diseases affords the family an additional level of reproductive planning. For the patient, a specific diagnosis may prompt attempts at therapeutic intervention. Some neurodegenerative disorders can be stabilized or improved with specific therapies, and symptomatic treatment may be applied more effectively if the disease process is known. Given the progressive nature of degenerative disorders, prompt diagnosis is critical to optimizing the effectiveness of therapeutic endeavors. Finally, a diagnosis permits further exploration of the pathophysiologic mechanisms linking genotype to resultant phenotype. This research furthers our understanding of developmental neurobiology and holds the promise of more effective treatment for children with neurodegenerative disorders in the future.

Appendix: Neurodegenerative Disorders of Childhood with Cognitive Decline (Dementia) by Number from Figure 51-2

1. Screen for disorders that are potentially treatable or have genetic implications:
   a. Any serious systemic illness or intoxicant may be associated with impairment of cognitive function. (see Table 51-1)
   b. Review head circumference data and elicit history regarding symptoms of increased intracranial pressure. Excessive head growth may be secondary to hydrocephalus, while decreased head growth may indicate craniosynostosis. Both conditions may be treated neurosurgically.
   c. Check serum thyroxine (T4) and thyroid-stimulating hormone (TSH) to rule out hypothyroidism.
   d. In the absence of clinical findings directing the examiner to a specific disorder, check fasting plasma amino acids, ammonia, lactate, pyruvate, and acyl-carnitine profile; in concert with urine organic acids, amino acids, and fatty acid oxidation screen. Disorders of amino acid and organic acid metabolism and energy production defects demonstrate marked phenotypic variability that may preclude bedside diagnosis. Effective pharmacologic or dietary interventions are available for selected disorders.

2. Galactosemia (Classic)

   Genetics: Autosomal recessive

TABLE 51-2. Ocular Pathology in Selected Neurodegenerative Disorders

Corneal clouding
Mucopolysaccharidoses I (8)
Mannosidosis I (9)
Mucolipidosis II (11)
Fabry disease (13)
Mucolipidosis IV (34)
Cataract
Galactosemia (2)
Zellweger syndrome (7)
Fabry disease (13)
Cockayne syndrome type I (15)
Cerebrotendinous xanthomatosis (16)
Kayser-Fleischer ring
Wilson disease (30)
Retinal pigmentary degeneration
Disorders of peroxisomal biogenesis (7)
Cockayne syndrome type I (15)
Glycosylation disorders (17)
Mitochondrial disorders (23)
Pantothenate kinase-associated neurodegeneration (28)
Mucolipidosis IV (34)
Neuronal ceroid lipofuscinosis (35)
Cherry red spot
Sandhoff disease (5)
Niemann-Pick disease (6)
Sialidosis type II (9)
GM_1 gangliosidosis type I (10)
GM_2 gangliosidosis (36)
Sialidosis type I (37)
Optic atrophy (early in disease course)
Zellweger syndrome (7)
Biotinidase deficiency (14)
Canavan disease (19)
Krabbe disease (21)
Pelizeaus-Merzbacher disease (24)
Adrenoleukodystrophy (26)
Infantile neuroaxonal dystrophy (38)

TABLE 51-3. Clinical Presentation of Neurodegenerative Disorders of White Matter versus Disorders of Gray Matter

White Matter	Gray Matter
Early: Spasticity/Babinski signs	Cognitive decline
Peripheral neuropathy	Seizures
Optic nerve atrophy	Retinal degeneration
Ataxia	Ataxia
Late: Cognitive decline	Spasticity/Babinski signs
Seizures	

Signs/Symptoms: Onset—neonatal with milk feeds/hepatomegaly/jaundice/vomiting/diarrhea/failure to thrive/lethargy/hypotonia/tense fontanelle/sepsis/cataracts

Treatment: Lactose-free diet

Prognosis: Improved, but persistent cognitive > motor impairments/verbal apraxia/tremor/ataxia/ovarian failure

Biochemical Defect: Galactose-1-phosphate uridyltransferase

Testing: Screen for reducing substances in urine/Enzyme assay in erythrocytes/Molecular genetic testing available—chromosome 9p13 (MIM # 230400)

3. Hereditary Fructose Intolerance

   Genetics: Autosomal recessive

   Signs/Symptoms: Onset in infancy following feeds containing fructose or sucrose/hepatomegaly/jaundice/vomiting/lethargy/seizures/hypoglycemia—episodes may be fatal

   Children surviving infancy: Failure to thrive/vomiting/hepatomegaly/hepatic failure/renal failure/seizures/bleeding diatheses/avoidance of sweets/ingestion of fructose or sucrose may produce hypoglycemia, encephalopathy, shock—may be fatal

   Treatment: Fructose-free diet

   Prognosis: Normal development/variable hepatic dysfunction with early treatment

   Biochemical Defect: Aldolase B

   Testing: Urine screen positive for reducing substances/aldolase B assay in hepatocytes/molecular genetic testing available—chromosome 9q22 (MIM# 229600)

4. Gaucher Disease

   Disorder: Gaucher Disease Type II

   Genetics: Autosomal recessive—no ethnic predilection

   Sign/Symptoms: Onset < 6 months/splenomegaly > hepatomegaly/spasticity/head retraction/oculomotor abnormalities/rapid dementia/dysphagia/respiratory problems

   Treatment: Symptomatic/enzyme replacement/substrate reduction

   Prognosis: Death by 2 to 4 years

   Biochemical Defect: Glucocerebrosidase

   Testing: Gaucher cells in bone marrow aspirate/enzyme assay in leukocytes/molecular genetic testing available—chromosome 1q21 (MIM# 230900)

   Disorder: Gaucher Disease Type III

   Genetics: Autosomal recessive—increased incidence in Scandinavians

   Signs/Symptoms: Onset of visceromegaly in infancy/onset neurologic symptoms in late childhood/slowly progressive dementia/horizontal supranuclear gaze palsy/myoclonus/seizures/spasticity/bone marrow failure/bone lesions/interstitial lung disease

   Treatment: Enzyme replacement/substrate reduction/bone marrow transplant

   Prognosis: Death in early adult life

   Biochemical Defect: Glucocerebrosidase

   Testing: Gaucher cells in bone marrow aspirate/enzyme assay in leukocytes/molecular genetic testing available—chromosome 1q21 (MIM# 231000)

5. Sandhoff Disease

   Genetics: Autosomal recessive

   Signs/Symptoms: Onset 3 to 6 months/hepatosplenomegaly/exaggerated startle response/irritability/weakness/hypotonia evolving to spasticity /blindness/cherry red spot/nystagmus/seizures/skeletal changes/macrocrania > 1 year of age

   Treatment: Symptomatic

   Prognosis: Death by 3 to 5 years

   Biochemical Defect: Hexosaminidase A and B

   Rare phenocopy with G_{M2} activator protein deficiency (normal hexosaminidase levels)

   Testing: Enzyme assay in leukocytes or fibroblasts/molecular genetic testing available—chromosome 5q13 (MIM # 268800)

6. Niemann-Pick Disease

   Disorder: Niemann-Pick Disease Type A

   Genetics: Autosomal recessive—increased incidence in Ashkenazi Jews

   Signs/Symptoms: Onset < 3 months/hepatomegaly > splenomegaly/feeding problems/failure to thrive/lymphadenopathy/pulmonary infiltrates/hypotonia evolves into spasticity/dementia onset at 6 to 12 months/visual failure/cherry red spot in 50%

   Type B: Primarily visceral symptoms/may have later neurologic involvement in childhood through adult years

   Treatment: Symptomatic

   Prognosis: Death usually at 2 to 3 years

   Biochemical Defect: Sphingomyelinase

   Testing: Enzyme assay in leukocytes or fibroblasts/molecular genetic testing available—chromosome 11p15 (Type A MIM# 257200/Type B MIM # 607616)

   Disorder: Niemann-Pick Disease Type C

   Genetics: Autosomal recessive—no ethnic predilection

Signs/Symptoms: Onset early childhood through adolescence/visceromegaly/supranuclear vertical gaze palsy/ataxia/tremor/dysarthria/slowly progressive dementia/behavior problems/spasticity/dystonia/seizures/cataplexy

Neonatal onset: Severe hepatic and/or pulmonary dysfunction/hypotonia > some with dementia, spasticity, ataxia, and death < 5 years > others resolve neonatal symptoms with onset of neurological symptoms at 3 years/onset of dementia by 6 years/death in teens

Adult onset: Prominent psychiatric symptoms with subtle evolving dementia

Treatment: None/symptomatic

Prognosis: Death in second to third decade

Biochemical Defect: Intracellular cholesterol and lipid processing

Testing: Filipin staining of cultured fibroblasts reveals lysosomal accumulation of unesterified cholesterol/molecular genetic testing available—chromosome 18q11-12 (Type C1 MIM# 257220), and chromosome 14q24 (Type C2 MIM# 607625)

7. Disorders of Peroxisomal Biogenesis—Zellweger Syndrome (ZS)/Neonatal Adrenoleukodystrophy (NALD)/Infantile Refsum Disease (IRD):

   Genetics: Autosomal recessive

   Signs/Symptoms: Onset < 1 month/hepatomegaly/high forehead/large fontanelles/broad and flat nasal bridge/shallow supraorbital ridges/full cheeks/epicanthal folds/high-arched palate/poor visual fixation/corneal or lens opacities/retinal pigmentary degeneration/hearing loss/hypotonia/seizures/failure to thrive/cerebral dysgenesis/profound cognitive impairment

   Treatment: Symptomatic

   Prognosis: ZS death < 1 year NALD death < 3 years IRD death—late childhood to teens

   Biochemical Defect: Failure of peroxisomal biogenesis

   Testing: Screen–elevated plasma very long-chain fatty acids/confirmatory assays for phytanic acid, pipecolic acid, bile acid intermediates, and plasmalogens/absence of peroxisomes by electron microscopy in fibroblasts or liver biopsy/molecular genetic testing available—multiple PEX gene loci (ZS MIM# 214100/NALD MIM# 202370/IRD MIM# 266510)

8. The Mucopolysaccharidoses

   Disorder: Mucopolysaccharidosis (MPS) I (Hurler)

   Genetics: Autosomal recessive

   Signs/Symptoms: Onset < 1 year/hepatosplenomegaly/scaphocephaly/macrocephaly/coarse facies/corneal clouding/deafness/dysostosis multiplex/growth failure/airway obstruction/heart disease/hernias/may develop hydrocephalus

   Treatment: Symptomatic/bone marrow transplant/enzyme replacement

   Prognosis: Death < 10 years

   Biochemical Defect: α-L-iduronidase

   Testing: Screen with urine for increased heparan sulfate and dermatan sulfate/enzyme assay in leukocytes or fibroblasts/molecular genetic testing available—chromosome 4p16 (MIM# 607014)

   Disorder: MPS II (Hunter)

   Genetics: X-linked recessive

   Signs/Symptoms: Onset at 2 to 4 years/milder Hurler phenotype/no corneal clouding/ivory-pebbled skin patches on truck and proximal limbs

   Treatment: Symptomatic/bone marrow transplant/enzyme replacement

   Prognosis: Death at 10 to 20 years

   Biochemical Defect: Iduronate sulfatase

   Testing: Screen with urine for increased heparan sulfate and dermatan sulfate/enzyme assay in leukocytes or fibroblasts/molecular genetic testing available—chromosome Xq28 (MIM# 309900)

   Disorder: MPS III (Sanfilippo)

   Genetics: Autosomal recessive

   Signs/Symptoms: Onset < 5years/neurological > visceral/developmental delay prior to onset of rapidly progressive dementia/aggressive behaviors/hyperactive/insomnia/seizures/spasticity/mild hepatosplenomegaly/corneal clouding rare/skeletal and facial abnormalities mild and late

   Treatment: Symptomatic/bone marrow transplant

   Prognosis: Death usually < 20 years

   Biochemical Defect:

   Type A: heparan-N-sulfatase (chromosome 17q25)

   Type B: N-acetyl-α-D-glucosaminidase (chromosome 17q21)

   Type C: acetyl-CoA: α-glucosaminide-N-acetyltransferase (chromosome 8p11)

   Type D: N-acetylglucosamine-6-sulfatase (chromosome 12q14)

   Testing: Screen with urine for increased heparan sulfate/enzyme assay in leukocytes or fibroblasts/molecular genetic testing available (Type A MIM# 252900/Type B MIM# 252920/Type C MIM# 252930/Type D MIM# 252940)

   Disorder: MPS VII (Sly)

   Genetics: Autosomal recessive

Signs/Symptoms: Onset—birth to early childhood/ Hurler features of variable severity/dementia in some—static mental retardation in others

Treatment: Symptomatic/bone marrow and liver transplant

Prognosis: Variable—death neonatal period through adult life

Biochemical Defect: β-glucuronidase

Testing: Screen with urine for increased heparan sulfate, dermatan sulfate, and chondroitin-4, 6-sulfate/enzyme assay in leukocytes or fibroblasts/molecular genetic testing available—chromosome 7q21 (MIM# 253220)

Note: MPS I-S (Scheie)/MPS IV (Morquio)/MPS VI (Maroteaux-Lamy) are not typically associated with dementia

Disorder: Multiple sulfatase deficiency

Genetics: Autosomal recessive

Signs/Symptoms: Onset 12 to 18 months/hepatomegaly > splenomegaly/milder Hurler features/variable developmental delay followed by rapidly progressive dementia/spasticity/peripheral neuropathy/neonatal icthyosis

Treatment: Symptomatic

Prognosis: Death in early to late childhood

Biochemical Defect: Posttranslational modification of multiple sulfatases

Testing: Screen with urine for increased sulfatides, mucopolysaccharides, and oligosaccharides/enzyme assay for multiple sulfatase deficiencies in cultured fibroblasts/molecular genetic testing available on a research basis—sulfatase modifying factor 1 gene on chromosome 3p26 (MIM# 272200)

9. Oligosaccharidosis

Disorder: Mannosidosis I

Genetics: Autosomal recessive

Signs/Symptoms: Onset—infancy/Hurler phenotype/ spoke-like lens opacities/corneal clouding/gingival hypertrophy/recurrent respiratory infections

Type II: Onset < 10 years/milder phenotype/slowly progressive

Treatment: Symptomatic/bone marrow transplant

Prognosis: Death usually < 10 years

Biochemical Defect: α-mannosidase

Testing: Screen with urine for increased mannosyloligosaccharides/enzyme assay in leukocytes or fibroblasts/molecular genetic testing available—chromosome 19cen-q12 (MIM# 248500)

Disorder: Fucosidosis I

Genetics: Autosomal recessive

Sign/Symptoms: Onset—infancy/Hurler phenotype/ rapidly progressive dementia leading to decerebration/ recurrent respiratory infections

Type II and III: Onset < 3 years/milder phenotype/ slower progression/angiokeratoma

Treatment: Symptomatic/bone marrow transplant

Prognosis: Death < 10 years

Biochemical Defect: α-l-fucosidase

Testing: Screen with urine for increased fucosyloligosaccharides/enzyme assay in leukocytes or fibroblasts/ molecular genetic testing available—chromosome 1p34 (MIM# 230000)

Disorder: Sialidosis II (Mucolipidosis I)

Genetics: Autosomal recessive

Signs/Symptoms: Onset—birth to 10 years/coarse facies/ gingival hypertrophy/dysostosis multiplex/ hepatosplenomegaly/inguinal hernias/ataxia/myoclonus/seizures/ vision loss/cherry red spot

Neonatal onset: May be associated with hydrops fetalis

Juvenile/adult onset: Prominent myoclonus/ataxia/ seizures/angiokeratoma

Treatment: Symptomatic

Prognosis: Variable—death infancy to adult life

Biochemical Defect: α-neuraminidase

Testing: Screen with urine for increased sialyloligosaccharides/Enzyme assay in leukocytes or fibroblasts/ molecular genetic testing available—chromosome 6p21 (MIM# 256550)

Disorder: Galactosialidosis

Genetics: Autosomal recessive

Signs/Symptoms: Same as Sialidosis II (above)—overlap of descriptive clinical literature likely

Treatment: Symptomatic

Prognosis: Variable—death infancy to adult life

Biochemical Defect: Protective protein/cathepsin A—deficiency produces combined loss of α-neuraminidase and β-galactosidase activities

Testing: Screen with urine for increased sialyloligosaccharides/combined enzyme assay in lymphocytes or fibroblasts/molecular genetic testing available—chromosome 20q13 (MIM# 256540)

10. GM_1 Gangliosidosis Type I

Genetics: Autosomal recessive

Signs/Symptoms: Onset < 2 months/hepatosplenomegaly/coarse facies/edema/hypotonia evolving to spasticity/acquired microcephaly/hyperacusis/seizures/

failure to thrive/kyphosis/contracture/short hands/ cherry red spot in 50%

Treatment: Symptomatic

Prognosis: Death usually < 2 years

Biochemical Defect: β-galactosidase

Testing: Urine may have increased galactosyloligosaccharides/enzyme assay in leukocytes and fibroblasts/molecular genetic testing available—chromosome 3p21 (MIM# 230500)

11. Mucolipidosis II (I-Cell Disease)

Genetics: Autosomal recessive

Signs/Symptoms: Onset < 1 year/Hurler phenotype/gingival hypertrophy/developmental plateau by 18 months then progressive dementia/recurrent pulmonary infection/progressive cardiac dysfunction

Type III: Onset and severity of Hurler features related to degree of residual enzyme activity—childhood through adult onset with variable prognosis

Treatment: Symptomatic

Prognosis: Death usually < 10 years

Biochemical Defect: N-acetylglucosamine-1-phosphotransferase

Testing: Enzyme assay in leukocytes or fibroblasts/ molecular genetic testing available—chromosome 12q23 (Type II MIM# 252500/Type III MIM# 252600)

12. Menkes Disease

Genetics: X-linked recessive

Signs/Symptoms: Onset < 3months/hair sparse, wiry and pale/skin lax and pale/facies—full cheeks with micrognathia and high-arched palate/hypothermia/ hypotonia evolves to spasticity/rapidly progressive dementia/seizures/myoclonus/angiopathy with subdural hematoma

Treatment: Symptomatic/early subcutaneous copper injection

Prognosis: Death usually < 3 years

Biochemical Defect: Abnormal copper transport/ reduced activity of copper-dependent enzymes

Testing: Screen for reduced serum copper and ceruloplasmin levels/copper transport studies in fibroblasts/ Molecular genetic testing available—chromosome Xq12-q13 (MIM# 309400)

13. Fabry Disease

Genetics: X-linked recessive

Signs/Symptoms: Onset—late childhood to early teens/ angiokeratoma/hypohydrosis/acral pain and paresthesia/corneal or lens opacities/renal failure/heart disease/ stroke/cognitive regression of later onset secondary to cerebrovascular disease

Heterozygous females: May manifest symptoms later in life

Treatment: Symptomatic/enzyme replacement therapy

Prognosis: Death in mid-adult life due to renal and cardiac failure

Biochemical Defect: α-galactosidase A

Testing: Enzyme assay in leukocytes or fibroblasts/ molecular genetic testing available—chromosome Xq22 (MIM# 301500)

14. Biotinidase Deficiency

Genetics: Autosomal recessive

Signs/Symptoms: Onset < 3 months/rash—eczematoid or seborrheic/alopecia/cutaneous candidiasis/ conjunctivitis/seizures—myoclonic/hypotonia/ataxia/ optic atrophy/hearing loss/paroxysmal lethargy and vomiting/associated organic aciduria

Treatment: Biotin supplementation

Prognosis: Resolution of symptoms with early treatment—may prevent mental retardation

Biochemical Defect: Biotinidase

Testing: Enzyme assay in serum, leukocytes, or fibroblasts/molecular genetic testing available—chromosome 3p25 (MIM# 253260)

15. Cockayne Syndrome Type I

Genetics: Autosomal recessive

Signs/Symptoms: Onset < 2 years/photosensitive rash/ growth failure with cachetic appearance/ acquired microcephaly/retinal pigmentary degeneration/cataracts/spasticity/peripheral neuropathy/sensorineural deafness/ataxia/tremor/neuroimaging revealing leukodystrophy and calcification

Type II: Severe connatal involvement

Treatment: Symptomatic

Prognosis: Death in second to third decade

Biochemical Defect: Transcription-coupled DNA repair

Testing: DNA repair assay of UV light-exposed fibroblasts/molecular genetic testing available—chromosome 5q12 (MIM# 216400)

Cerebrotendinous Xanthomatosis

Genetics: Autosomal recessive

Signs/Symptoms: Onset—early childhood to teens/ tendon xanthomas in teens—achilles tendon > elbow, hand, knee, and neck/cataracts/slowly progressive dementia—may have prominent psychiatric symptoms/spasticity/ataxia/seizures/peripheral neuropathy

Treatment: Chenodeoxycholic acid/HMG-CoA reductase inhibitors

Prognosis: Death in mid to late adult life

Biochemical Defect: Sterol 27-hydroxylase

Testing: Elevated plasma and tissue (xanthoma) cholestanol/enzyme assay in fibroblasts/molecular genetic testing available—chromosome 2q33 (MIM# 213700)

17. Congenital Disorder of Glycosylation (CDG) Type Ia

Genetics: Autosomal recessive

Signs/Symptoms: Onset—infancy /supragluteal and suprapubic fat pads/lipoatrophy/inverted nipples/facial dysmorphism/esotropia/hypotonia/failure to thrive/hepatopathy/nephrosis/mid-to-late childhood—seizures and stroke-like events/teens—progressive ataxia, neuropathy, and retinal pigmentary degeneration

Treatment: Symptomatic

Prognosis: 20% die in infancy/Remainder—disabled adults with moderate mental retardation/ataxia/skeletal deformity/progeria

Biochemical Defect: Phosphomannomutase 2

Testing: Screen for abnormal transferrin glycoforms by isoelectric focusing/enzyme assay in leukocytes or fibroblasts/molecular genetic testing available—chromosome 16p13 (MIM# 212065)

This is the most commonly reported disorder of N-linked glycosylation—many other types are described in small numbers of patients—monitor *Gene Reviews* for evolving information.

18. Alexander Disease—Infantile

Genetics: Autosomal dominant/primarily sporadic due to de novo mutation—males > females

Symptoms: Onset < 2 years/megalencephaly/frontal bossing/developmental plateau followed by dementia/spasticity/seizures/ataxia/may have hydrocephalus

Juvenile and adult form: slowly progressive dementia/bulbar and pseudobulbar signs/spasticity/seizures/ataxia

Treatment: Symptomatic

Prognosis: Death < 10 years

Biochemical Defect: Glial fibrillary acidic protein (GFAP) mutation

Testing: White matter abnormalities by brain MRI/molecular genetic testing available—chromosome 17q21 and 11q13 (MIM# 203450)

19. Canavan Disease—Infantile

Genetics: Autosomal recessive—increased incidence in Ashkenazi Jews

Signs/Symptoms: Onset 3 to 6 months/megalencephaly/hypotonia evolves to spasticity/tonic spasms/choreoathetosis/seizures/feeding problems/optic atrophy/blindness

Treatment: Symptomatic

Prognosis: Death < 10 years

Biochemical Defect: Aspartoacylase

Testing: White matter abnormalities by brain MRI (may precede clinical symptoms)/urine screen for increased N-acetyl aspartate/enzyme assay in fibroblasts/molecular genetic testing available—chromosome 17pter-p13 (MIM# 271900)

20. Acquired Immunodeficiency Syndrome (AIDS)

Genetics: Acquired—vertical transmission

Signs/Symptoms: Onset < 10 years/behavioral change/school problems or attention-deficit hyperactivity disorder may precede slowly progressive dementia/spasticity/acquired microcephaly/rigidity/ataxia/tremor/myoclonus

Treatment: Symptomatic/antiretroviral agents

Prognosis: Variable

Biochemical Defect: None—retroviral infection

Testing: HIV DNA polymerase chain reaction study for children < 2 years (eliminates confounding effect of maternal antibody)/2 + years of age—ELISA HIV antibody test with confirmatory Western blot

21. Krabbe Disease—Infantile (Globoid Cell Leukodystrophy)

Genetics: Autosomal recessive

Signs/Symptoms: Onset 3 to 6 months/irritability/fever/rigidity—opisthotonus/spasticity—may have depressed reflexes due to neuropathy/early developmental stasis followed by rapidly progressive dementia/seizures/optic atrophy/blindness

Late-onset forms: Onset 1 year to adult/slower progression/spasticity/ataxia/neuropathy/blindness/survival years to decades

Treatment: Symptomatic/bone marrow transplant

Prognosis: Death < 2 years

Biochemical Defect: Galactocerebroside-β-galactosidase

Testing: Enzyme assay in leukocytes and fibroblasts/molecular genetic testing available—chromosome 14q31 (MIM# 245200)

22. Subacute Sclerosing Panencephalitis

Genetics: Acquired measles infection

Signs/Symptoms: Onset 2 to 10 years postmeasles infection/behavioral change/school problems—followed by myoclonic epilepsy/rapidly progressive dementia/spasticity/ataxia/choreoathetosis/blindness/terminal coma and opisthotonus

Treatment: Symptomatic/isoprinosine/ribavirin/intrathecal or intraventricular interferon

Prognosis: Death < 3 years postonset without treatment

Biochemical Defect: None—infectious

Testing: Cerebrospinal fluid studies for elevated rubeola antibody

23. Mitochondrial Disorders

A heterogeneous group of disorders resulting from defects in cellular energy metabolism. In infants and young children, the majority of these disorders are secondary to autosomal recessive mutations of nuclear DNA. Think of these disorders when confronted with a patient who has multiorgan system failure in concert with neurological dysfunction affecting both the central and peripheral nervous systems.

Signs and symptoms that may be seen in early childhood include hypotonia/weakness/respiratory distress/apnea/feeding problems/vomiting/gastrointestinal dysmotility/seizures/ myoclonus/paroxysmal encephalopathy/sudden infant death/spasticity/dystonia/ataxia/ophthalmoplegia/retinal pigmentary degeneration/deafness/neuropathy/ hepatic dysfunction—may have hepatomegaly/cardiomyopathy/renal tubular dysfunction/craniofacial dysmorphism/developmental brain anomalies.

Signs and symptoms are reflective of defects in pyruvate or carnitine metabolism, the mitochondrial electron transport chain, or fatty acid oxidation. Abnormalities on screening metabolic studies vary according to which metabolic pathway is involved.

Screening studies include lactate and pyruvate in blood, urine, and cerebrospinal fluid/plasma carnitine and acylcarnitine/urine fatty acid oxidation screen/urine organic acids/serum glucose/serum ammonia/serum transaminases/serum ketones/serum creatine kinase/arterial blood gas/serum anion gap/MRI brain.

Definitive diagnosis may require muscle biopsy for histology, immunohistochemistry, and oxidative phosphorylation analysis. Cultured fibroblasts may be required for assay of pyruvate metabolism and fatty acid oxidation studies. Molecular genetic testing is available for selected mitochondrial disorders.

The phenotypic variability associated with these disorders in early childhood results in an absence of well-delineated mitochondrial syndromes in this age group. One exception to this statement is Alpers-Huttenlocher syndrome:

Alpers-Huttenlocher Syndrome

Genetics: Autosomal recessive/sporadic

Signs/Symptoms: Onset < 24 months/abrupt onset mixed—myoclonic epilepsy (intractable)/developmental delay followed by rapidly progressive dementia/ blindness/hypotonia evolves to spasticity/variable hepatic dysfunction

Treatment: Symptomatic

Prognosis: Death < 2 years postonset

Biochemical Defect: Mitochondrial DNA polymerase γ/other disorders of mitochondrial function

Testing: Molecular genetic testing available—chromosome 15q25 (nuclear gene mutation producing mitochondrial dysfunction)/Some require liver or muscle biopsy for evaluation of mitochondrial function (MIM# 203700)

In later childhood and the teen years, patients may present with the signs and symptoms noted above, in addition to "classic" mitochondrial disease syndromes. These include

Leigh Syndrome: Onset usually < 2 years/paroxysmal respiratory abnormalities/oculomotor abnormalities/blindness—optic atrophy/cranial nerve deficits/hypotonia evolves to spasticity/saltatory cognitive regression—may follow episodes of acute illness/dystonia/choreoathetosis/ataxia/neuropathy

Genetics: Autosomal recessive/X-linked recessive/mitochondrial (MIM# 256000)

Kearns-Sayre Syndrome: Onset < 20 years/progressive ophthalmoplegia/ptosis/retinal pigmentary degeneration/hearing loss/heart block/weakness/ataxia/short stature

Genetics: Mitochondrial (MIM# 530000)

Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like Episodes:

Onset < 10 years/stroke-like episodes/paroxysmal encephalopathy/headaches/vomiting/deafness/seizures/weakness/short stature

Genetics: Mitochondrial (MIM# 540000)

Myoclonic Epilepsy with Ragged Red Fibers: Myoclonus/seizures/ataxia/deafness/weakness/short stature

Genetics: Mitochondrial (MIM# 545000)

Neuropathy, Ataxia, and Retinitis Pigmentosa: Sensory or sensorimotor neuropathy/ataxia/retinal pigmentary degeneration/weakness/spasticity

Genetics: Mitochondrial (MIM# 551500)

Leber Hereditary Optic Neuropathy: Painless, subacute loss of central vision/most bilateral/monocular progresses to involve other eye over weeks to months/acute disk swelling with tortuous retinal vessels/may improve with residual centrocecal scotoma/may be associated tremor or neuropathy

Genetics: Mitochondrial (MIM# 535500)

Treatment: Beyond symptomatic treatment, therapy with dietary modulation, medications, and nutraceutical supplements is disease specific. These therapies are attempts to rectify aberrant metabolic pathways and frequently have little clinical data supporting their use.

24. Pelizaeus–Merzbacher Disease

    Genetics: X-linked recessive

    Signs/Symptoms: Onset < 2 months/rotary and pendular nystagmus (may be asymmetric)/developmental plateau < 6 months followed by dementia/optic atrophy/titubation/stridor/dysphagia/hypotonia evolves to spasticity/ataxia/dystonia/choreoathetosis/microcephaly/short stature/seizures

    Carrier females: May be symptomatic

    PLP1 null form: No nystagmus/mild spasticity/peripheral neuropathy

    Treatment: Symptomatic

    Prognosis: Death in childhood to late adult life

    Biochemical Defect: Biosynthesis of proteolipid protein

    Testing: Molecular genetic testing available—chromosome Xq22 (MIM# 312080)

25. Metachromatic Leukodystrophy—Late Infantile

    Genetics: Autosomal recessive

    Signs/Symptoms: Onset 12 to 24 months/gait abnormalities/weakness/hypotonia evolves to spasticity—deep tendon reflexes frequently depressed due to neuropathy/limb pain/strabismus/nystagmus/dysarthria/dysphagia/seizures/optic atrophy

    Juvenile and Adult Forms: Onset 4 to 12 years/initial symptoms frequently cognitive and behavioral/dementia/spasticity/peripheral neuropathy/dysarthria/ataxia/tremor/dystonia/choreoathetosis/seizures/survival 10 to 20 years

    Treatment: Symptomatic/bone marrow transplant—response variable

    Prognosis: Death < 7 years

    Biochemical Defect: Arylsulfatase A

    Rare SAP-1 activator protein deficiency—seen primarily with juvenile form

    Testing: Urine screen for increased sulfatide excretion (normal in arylsulfatase A psuedodeficiency state)/enzyme assay in leukocytes or fibroblasts/molecular genetic testing available—chromosome 22q13 (MIM# 250100)

26. Adrenoleukodystrophy (ALD)

    Genetics: X-linked recessive—intrafamilial variation in phenotype

    Signs/Symptoms: Onset 3 to 10 years/behavior change/school problems/spasticity (may start hemiplegic)/blindness/optic atrophy/deafness/seizures/adrenal insufficiency/melanoderma

    Teen and Adult Forms: May present with similar symptoms

    Adrenomyeloneuropathy: Primary teen and adult phenotype/progressive spastic paraparesis/proprioceptive sensory loss/sphincter problems/sexual dysfunction/ adrenal insufficiency/20% with cognitive regression

    Carrier Females: May present with milder variant

    Isolated Adrenal Insufficiency: Primarily in childhood—may develop adrenomyeloneuropathy in later life

    Treatment: Symptomatic/steroid replacement/dietary restriction of VLCFA plus Lorenzo's oil—may be neuroprotective/bone marrow transplant

    Prognosis: Death < 5 years postonset

    Biochemical Defect: Deficient ALD protein—a peroxisomal membrane transport protein

    Testing: Elevated very long-chain fatty acids in plasma or fibroblasts/molecular genetic testing available—chromosome Xq28 (MIM# 300100)

27. Leukoencephalopathy with Vanishing White Matter

    Genetics: Autosomal recessive

    Signs/Symptoms: Onset—early childhood/spasticity/ataxia/optic atrophy/seizures/course may be chronic progressive or episodic—paroxysmal encephalopathy may be triggered by illness or head trauma

    Severe Connatal Variants: Microcephaly/visceromegaly/contractures/cataracts

    Adolescent and adult-onset variants: Disease progression slower

    Treatment: Symptomatic

    Prognosis: Death several years postonset

    Biochemical Defect: Mutation in gene for subunit of eukaryotic translation initiation factor eIF2B

Testing: Vanishing white matter by MRI/molecular genetic testing available—subunit 1 on chromosome 12/subunit 2 on 14q24/subunit 3 on 1p34/subunit 4 on 2p23/subunit 5 on 3q27 (MIM# 603896)

28. Pantothenate Kinase-Associated Neurodegeneration (Hallervorden-Spatz)

    Genetics: Autosomal recessive

    Signs/Symptoms: Onset < 15 years/retinal pigmentary degeneration—loss of peripheral fields/dystonia (orofacial and limb)/rigidity/choreoathetosis/dysarthria/spasticity/deterioration may be episodic

    Atypical variants: Later onset—slower progression/dysarthria/psychiatric symptoms prominent

    Treatment: Symptomatic

    Prognosis: Death in second to third decade

    Biochemical Defect: Pantothenate kinase with resultant iron accumulation in basal ganglia

    Testing: "Eye of the tiger sign" by brain MRI/molecular genetic testing available—chromosome 20p13-p12 (MIM# 234200)

29. Huntington Disease—Juvenile

    Genetics: Autosomal dominant—children involved in 7% of affected families Majority with affected father—may not be symptomatic at onset of child's illness

    Signs/Symptoms: Onset 5 to 21 years/dementia with prominent psychiatric symptoms/Parkinsonian rigidity and bradykinesia/dysarthria/dysphagia/oculomotor apraxia/seizures/chorea (variable)/ tremor/ataxia

    Treatment: Symptomatic

    Prognosis: Death usually within 10 years postonset

    Biochemical Defect: CAG trinucleotide repeat expansion in Huntington gene/onset earlier with increased CAG repeat number—juvenile cases > 60 repeats/pathophysiology of gene product unknown

    Testing: Caudate atrophy by neuroimaging/molecular genetic testing available—chromosome 4p16 (MIM# 143100)

30. Wilson Disease

    Genetics: Autosomal recessive

    Signs/Symptoms: Onset > 5 years/Kayser-Fleischer rings in 90% of patients with neurologic symptoms (visualization may require slit lamp)/insidious, slowly progressive dementia—school problems and psychiatric disturbance/rigidity/mask-like facies/dysarthria/tremor/dystonia/choreoathetosis/dysphagia/hepatic dysfunction/hemolytic anemia

    Treatment: Dietary copper restriction/copper chelation therapy/liver transplantation

    Prognosis: Good with early treatment

    Biochemical Defect: Deficiency of ATPB7 copper-transporting ATPase with resultant decreased copper transport from hepatocytes into bile

    Testing: Low serum ceruloplasmin and copper levels/increased urinary copper excretion/increased copper on liver biopsy/molecular genetic testing available—chromosome 13q14-q21 (MIM# 277900)

31. Lesch-Nyhan Syndrome

    Genetics: X-linked recessive

    Signs/Symptoms: Onset 3 to 6 months/hypotonia evolves to spasticity/dystonia/rigidity/choreoathetosis/self-mutilation at > 2 years—lips, cheeks, fingers/head banging/subtle progressive dementia/aggressive behavior/abusive language/spitting/dysarthria/dysphagia/vomiting/gout/renal stones

    Treatment: Symptomatic/allopurinol for gout and renal stones

    Prognosis: Death in second to third decade

    Biochemical Defect: Hypoxanthine-guanine phosphoribosyltransferase

    Testing: Screen for elevated uric acid in blood and urine/enzyme assay in erythrocytes or fibroblasts/molecular genetic testing available—chromosome Xq26-q27 (MIM# 300322)

32. Rett Syndrome

    Genetics: X-linked dominant—females predominantly affected

    Signs/Symptoms: Onset 6 to 18 months/autistic regression—rapid loss of reciprocal interaction/compulsive behaviors with loss of purposeful hand movements—stereotypies, such as hand wringing/acquired microcephaly/bruxism/paroxysmal apnea or hyperpnea/vasomotor instability/gait apraxia/hypotonia evolves to spasticity/ataxia/tremor/dystonia/seizures/scoliosis/growth retardation/cognitive decline stabilizes in mid-to-late childhood

    Treatment: Symptomatic

    Prognosis: Death in adult life

    Biochemical Defect: Diminished MECP2 transcriptional repressor activity

    Testing: Molecular genetic testing available—chromosome Xq28 (MIM# 312750)

33. GM_1 Gangliosidosis Type II

    Genetics: Autosomal recessive

Signs/Symptoms: Onset 12 to 18 months/gait abnormalities/ataxia/spasticity/mild developmental delay followed by rapidly progressive dementia/strabismus/seizures/dysphagia/no neuropathy/no dysmorphism/no visceromegaly

Late-onset forms: Childhood through adult/slowly progressive/spasticity/dystonia

Treatment: Symptomatic

Prognosis: Death < 10 years

Biochemical Defect: β-galactosidase

Testing: Enzyme assay in leukocytes or fibroblasts/molecular genetic testing available—chromosome 3p21 (MIM# 230600)

34. Mucolipidosis IV

Genetics: Autosomal recessive—increased incidence in Ashkenazi Jews

Signs/Symptoms: Onset < 6 months/corneal clouding/retinal pigmentary degeneration/severe static delay in early development/hypotonia/short stature/microcephaly/no facial dysmorphism/no dysostosis/no visceromegaly

Treatment: Symptomatic

Prognosis: Protracted course with death in second to third decade

Biochemical Defect: Mucolipin-1

Testing: Low serum gastrin level/lysosomal inclusions by skin or conjunctival biopsy/molecular genetic testing available—chromosome 19p13 (MIM# 252650)

35. Neuronal Ceroid Lipofuscinoses (NCL)

Disorder: Infantile NCL (Santavuori—Haltia)

Genetics: Autosomal recessive

Signs/Symptoms: Onset 6 to 24 months/rapidly progressive dementia and motor deterioration, myoclonic seizures, and vision loss with retinal pigmentary degeneration/followed by optic atrophy and acquired microcephaly

Treatment: Symptomatic

Prognosis: Vegetative 2 years postonset/death < 10 years

Biochemical Defect: Palmitoyl-protein thioesterase 1

Testing: Skin, conjunctival or rectal biopsy for electron microscopy + for granular osmophilic inclusions/enzyme assay in leukocytes or fibroblasts/molecular genetic testing available—*CLN1* gene on chromosome 1p32 (MIM# 256730)

Disorder: Late infantile NCL (Jansky-Bielschowsky)

Genetics: Autosomal recessive

Signs/Symptoms: Onset 2 to 4 years/seizures early—mixed with prominent myoclonus/retinal pigmentary degeneration (may precede vision loss)/rapid dementia/spasticity/ataxia/late-onset visual failure leading to optic atrophy

Variant Forms: Finnish—*CLN5* gene chromosome 13q21-q32 (MIM# 256731)

Gypsy/Indian–CLN6 gene chromosome 15q21-q23 (MIM# 601780)

Turkish–CLN8 gene chromosome 8pter-p22 (MIM# 600143)

Treatment: Symptomatic

Prognosis: Death at 10 years to mid-adult life

Biochemical Defect: Tripeptidyl-peptidase 1 (80%-*CLN2* gene)

Palmitoyl-protein thioesterase (8%-*CLN1* gene)

Variant forms (12%)

Testing: Skin, conjunctival or rectal biopsy for electron microscopy + for curvilinear bodies/enzyme assay in leukocytes and fibroblasts/molecular genetic testing available—*CLN2* gene on chromosome 11p15 (MIM# 204500)

Disorder: Juvenile NCL (Batten-Vogt-Spielmeyer)

Genetics: Autosomal recessive

Signs/Symptoms: Onset 4 to 13 years/early vision loss with retinal pigmentary degeneration (later optic atrophy)/slowly progressive dementia/dysarthria–palilalia/psychiatric symptoms/mixed epilepsy/Parkinsonian rigidity/spasticity late in course

Treatment: Symptomatic

Prognosis: Death in twenties to thirties

Biochemical Defect: Battenin—lysosomal membrane protein of unknown function (72%-*CLN3* gene)

Palmitoyl-protein thioesterase (21%-*CLN1* gene)

Tripeptidyl peptidase 1 (7%-*CLN2* gene)

Testing: Skin, conjunctival or rectal biopsy for electron microscopy + for fingerprint bodies (*CLN3*)/no enzyme assay for Battenin/molecular genetic testing available—*CLN3* gene on chromosome 16p12 (MIM# 204200)

36. GM_2 Gangliosidosis (Tay-Sachs disease)

Genetics: Autosomal recessive—increased incidence in Ashkenazi Jews

Signs/Symptoms: Onset 3 to 6 months/exaggerated startle response—hyperacusis/irritability/weakness/hypotonia evolving to spasticity/blindness/cherry red spot/ nystagmus/seizures/macrocrania > 1 year of age

Juvenile and adult forms reported: Severity inversely related to residual enzyme activity/dementia may be insidious and late onset/psychiatric symptoms/vision loss late/cherry red spot variable/optic atrophy/retinal pigmentary degeneration/spinocerebellar syndromes/extrapyramidal syndromes/motor neuron disease/progression over years to decades/variable phenotypes within families/no ethnic predilection

Treatment: Symptomatic

Prognosis: Death usually < 5 years

Biochemical Defect: Hexosaminidase A

Rare phenocopy with GM_2 activator protein deficiency (normal hexosaminidase A levels)

Testing: Enzyme assay in leukocytes or fibroblasts/molecular genetic testing available—chromosome 15q23-q24 (MIM# 272800)

37. Sialidosis Type I (Cherry Red Spot—Myoclonus Syndrome)

Genetics: Autosomal recessive

Signs/Symptoms: Onset—late childhood to teen years/cherry red spot/vision loss/multifocal myoclonus/slowly progressive dementia/ataxia/epilepsy/spasticity/dysarthria/optic atrophy—late/no visceromegaly/no dysmorphism

Treatment: Symptomatic

Prognosis: Death in mid-to-late adult life

Biochemical Defect: α-neuraminidase

Testing: Screen with urine for increased sialyloligosaccharides /enzyme assay in leukocytes or cultured fibroblasts/molecular genetic testing available—chromosome 6p21 (MIM# 256550)

38. Infantile Neuroaxonal Dystrophy

Disorder: Infantile Neuroaxonal Dystrophy I (Seitelberger Disease)

Genetics: Autosomal recessive

Signs/Symptoms: Onset 6 to 24 months/optic atrophy—blindness/rapidly progressive dementia and motor regression/hypotonia evolves to spasticity with depressed reflexes due to neuropathy (sensorimotor)/involuntary movements/facial dysmorphism

Treatment: Symptomatic

Prognosis: Death < 10 years

Biochemical Defect: Phospholipase A2 (some cases)

Testing: Suspect on clinical grounds with supportive electromyographic studies/axonal spheroids by nerve biopsy/molecular genetic testing available on a research basis—chromosome 22q13 (MIM# 256600)

Disorder: Schindler Disease Type I

Genetics: Autosomal recessive

Signs/Symptoms: Onset 6 to 24/optic atrophy—blindness/rapidly progressive dementia and motor regression/myoclonic epilepsy/hypotonia evolves to spasticity

Treatment: Symptomatic

Prognosis: Vegetative 3 years postonset

Biochemical Defect: α-N-acetylgalactosaminidase

Testing: Axonal spheroids in nerve or brain biopsy/enzyme assay in leukocytes or fibroblasts/molecular genetic testing available—chromosome 22q11 (MIM# 609241)

Suggested Readings

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Practitioner and Patient Resources

Online Mendelian Inheritance in Man (OMIM)
McKusick-Nathans Institute for Genetic Medicine
Johns Hopkins University
Baltimore, MD
National Center for Biotechnology Information—National Library of Medicine
Bethesda, MD
<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>
Continuously updated, literature-based reviews regarding the genotype and phenotype of heritable disorders. For new information regarding the degenerative disorders summarized in this chapter, enter the MIM# of the disorder in the search window of the welcome page.

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<http://www.genetests.org>
In addition to outstanding reviews of selected degenerative disorders in the *GeneReviews* section, this Website provides updated information regarding clinical services and the performance of molecular genetic testing for heritable disorders.

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CHAPTER 52

MITOCHONDRIAL CYTOPATHIES

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The term "mitochondrial cytopathy" refers to a diverse group of inherited or acquired disorders. Deficient energy production caused from defects in the mitochondrial structure or the enzymes contained within this organelle are the basis for the clinical features of these illnesses

Mitochondria are subcellular organelles, contained in all human cells except mature erythrocytes, whose main role is to generate adenosine triphosphate (ATP) by phosphorylating adenosine diphosphate (ADP). The individual mitochondrion is a bilayer structure and can be thought of as containing four compartments: (1) an outer mitochondrial membrane, (2) a heavily folded inner mitochondrial membrane, (3) an intermembrane space that exists between these two membranes, and (4) the matrix, which is contained within the inner membrane. Numerous transport channels are present on the outer mitochondrial membrane. Most of the electron transport chain is embedded within the inner membrane. Contact points exist where the inner and outer mitochondrial membrane touch, and these points contain the voltage-dependent anion channel and the adenine nucleotide translocase that allows ATP to exit the mitochondria in exchange for ADP. The inner membrane space holds the electrochemical gradient generated as hydrogen ions are pumped from the matrix while electrons are passed from one protein complex to another as part of electron transport chain (ETC) function. Hundreds of mitochondrial enzymes are located in the matrix. In addition to the matrix enzymes, normal metabolism also requires integrity of both membranes, normal transport channels and translocases, and the enzyme complexes comprising the respiratory chain (RC) located within the membranes themselves.

Bioenergetics

The terminal phase of energy generation, the process of oxidative phosphorylation, occurs in the five enzyme complexes referred to as the ETC or RC. Reduced nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide ($FADH_2$), generated mainly in the citric acid cycle and fatty acid β-oxidation, enter the ETC at complexes I and II, respectively. The reducing equivalents generated from the oxidation of NADH and $FADH_2$ are passed from one enzyme complex to the next via mobile electron transporters (coenzyme Q_{10} carries the electrons from complexes I and II to complex III, and cytochrome *c* carries the electrons from complex III to complex IV) as protons are translocated into the inner membrane space at the levels of complex I, III, and IV. Complex IV, also known as cytochrome-*c* oxidase, reduces molecular oxygen into water. Complex V phosphorylates ADP into ATP as protons move from the inner membrane space, through a channel in complex V, into the matrix. The energy stored in the third phosphate bond of ATP provides the bulk of the body's energy needs, including the energy to perform mechanical work, biochemical synthesis, and membrane pump function. ATP is able to exit the mitochondria through a channel known as adenine nucleotide translocase, where it is exchanged with ADP and orthophosphate (P_i). Inadequate production of ATP can result in failure of different organ systems (Table 52-1).

TABLE 52-1. Problems Associated with Mitochondrial Cytopathies

Organ System	Possible Problems
Brain	Developmental delays, mental retardation, dementia, seizures, myoclonus, neuropsychiatric disturbances, atypical cerebral palsy, hypotonia, ataxia, migraines, strokes and stroke-like episodes, apnea
Nerves	Weakness (which may be intermittent), neuropathic pain, absent reflexes, gastrointestinal problems (gastroesophageal reflux, constipation, pseudo-obstruction), fainting, absent or excessive sweating resulting in temperature regulation problems
Muscles	Weakness, hypotonia, cramping, muscle pain, myoglobinuria
Kidneys	Proximal renal tubular wasting resulting in loss of protein, magnesium, phosphorous, calcium, and other electrolytes
Heart	Cardiac conduction defects, cardiomyopathy
Intestines	Vomiting, diarrhea, failure to thrive, pseudo-obstruction
Liver	Hypoglycemia, nonalcoholic cirrhosis, liver failure
Eyes	Retinitis pigmentosa, optic atrophy, ophthalmoplegia
Ears	Sensorineural hearing loss
Bone marrow	Sideroblastic anemia, myelodysplasia
Pancreas	Diabetes and exocrine pancreatic failure
Systemic	Failure to gain weight, short stature, fatigue, respiratory problems (including intermittent air hunger, endocrine failure)

Molecular Genetics

There is recent improved understanding regarding the disease states caused by disorders of the control of mitochondrial replication, the interactions of the gene products of the two genomes (mitochondrial deoxyribonucleic acid [mtDNA] and nuclear DNA), mitochondrial toxins, and the structure of the mitochondrial membranes themselves, which include the embedded channels and translocases. A unique feature of mitochondria is that they contain their own DNA, mtDNA, and most of the data available about the pathophysiology of mitochondrial disorders are based on the described mtDNA mutations. This circular gene contains 16,569 base pairs. Aside from a 1 kbp region that contains regulation and initiation sequences, the entire gene is composed of coding regions, without introns. Each mitochondrion contains 2 to 10 copies of mtDNA. The mtDNA has a different genetic code and uses different ribosomal ribonucleic acid (rRNA) and transfer ribonucleic acid (tRNA) from that contained in the cell nucleus. The mtDNA encodes for its unique 2 rRNAs and 22 tRNAs, as well as for 7 of the 48 subunits of complex I, 1 of the 9 or 10 subunits of complex III, 3 of the 13 subunits of complex 4, and 2 of the 12 subunits of complex V. It is estimated that there are about 850 proteins required for mitochondrial support and function, therefore, most of the mitochondrial structure and the enzymes contained within are encoded by the nuclear chromosomes, for which the proteins must be transported into the mitochondria through various mechanisms. A rapid increase in the number of mitochondrial diseases linked to specific nuclear DNA mutations are being reported in the last few years and it is believed that the vast majority of mutations have yet to be discovered.

During the process of fertilization, the sperm contributes only nuclear DNA; therefore, the mitochondria contained in the fertilized egg, and thus the mtDNA, are solely maternal in origin. During mitosis, the mitochondria are randomly distributed to daughter cells. Variable ratios of normal to mutant mtDNA are found in each cell, a process known as heteroplasmy, a feature rather unique to mtDNA disorders. Likewise, some tissues may have higher or lower percentages of mutant mtDNA compared with other tissues. The percentage of mutant mtDNA in any cell or tissue can be quantified and results in variable degrees of pathology. Because of heteroplasmy, different tissues are affected variably in the same person, despite all tissues having the same genetic defect. Likewise, siblings with the exact mtDNA mutation may be variably affected, both in terms of organ system involvement as well as overall severity of the illness. It is essential to note that not all mitochondrial diseases are a result of mutations in mtDNA. In fact, most are probably due to nuclear DNA mutations or combinations of both mtDNA and nuclear mutations. In addition, not all mutations in mtDNA result in a pathologic state, either because the mutation does not result in a critical malfunction of the encoded protein, or because the mutational load does not affect the energy efficiency of the cell, tissue, or organ. Because there are 2 to 10 copies of mtDNA per mitochondria (with variable degrees of heteroplasmy) and hundreds of mitochondria per cell, the metabolic integrity of any cell is determined by the collective function of the mitochondria in that cell. In other words, the health of the population of mitochondria within a cell determines the overall health of that cell. The clinical correlation between genotype and phenotype is not entirely understood. For many well-described mutations, a number of clinical presentations exist, depending on the degree of heteroplasmy and distribution of the mutant mitochondria. In addition, a specific phenotype may have a number of potential different genetic mutations.

The most important nuclear-encoded gene that is linked to known mitochondrial diseases is *POLG1*, located at 15q25, which encodes for DNA polymerase γ, the enzyme required for mtDNA synthesis (replication). Although a mitochondrial link between Alpers syndrome and associated disorders had been suspected for years, it was not until 1999 that there was a more global acceptance of this view when several patients with mtDNA depletion were

described. By 2001 there were seven described mutations in *POLG1* linked to Alpers poliodystrophy (also known as Alpers-Huttenlocher syndrome or Alpers hepatocerebral syndrome). In the ensuing five years there has been nothing short of an explosion in the reported pathologic mutations in this gene. By 2006 there were over 80 mutations that are linked to human disease in addition to Alpers poliodystrophy, and these include autosomal dominant chronic progressive opthalmoplegia (CPEO), autosomal recessive CPEO, sporadic CPEO, a variety of ataxia-neuropathy syndromes and a CAG trinucleotide repeat sequence linked to immobile sperm/male infertility. It is thought persons with mutations in this gene are highly susceptible to that the fatal liver toxicity caused by valproic acid and disodium valproate. In addition to mutations in *POLG1*, the genes that regulate the mitochondrial pools of deoxynucleotides cause human disease. These include thymidine phosphorylase (linked to mitochondrial neurogastrointestinal encephalomyopathy or MNGIE), thymidine kinase (*TK2* causing the myopathic form of mtDNA depletion syndrome, deoxyguanosine kinase (*DGUOK* causing the hepatocerebral form of mtDNA depletion syndrome) and *MPV17* (a gene encoding for an inner mitochondrial membrane protein linked to hepatic mtDNA depletion). A nuclear-encoded mtDNA helicase, Twinkle, causes multiple mtDNA deletions that result in a dominant adult-onset PEO. There are numerous genes responsible for assembly proteins. The *SURF1* gene (SURF1 protein) is responsible for complex IV assembly and mutations are associated with Leigh syndrome. SCO1 and SCO2 are chaperon proteins that transport copper into the inner mitochondrial membrane and assist in the assembly of complex IV. Mutations in the *SCO1* gene have been associated with neonatal encephalopathy and hepatic failure, while *SCO2* mutations cause neonatal encephalopathy and cardiomyopathy. The *BCLS1* gene codes for the protein that incorporates iron into complex III and mutations in this gene cause both Bjørnstad syndrome (pili corti and sensorineural deafness) and GRACILE syndrome (intrauterine Growth retardation, Aminoaciduria, Cholestasis, Iron overload, Lactic acidosis, and Early death). At this time, a number of commercial and university based laboratories perform mtDNA analysis and ETC enzymatic analysis. However, it is important to note that mitochondrial dysfunction can result from a number of different mechanisms and is not limited to mtDNA mutations or ETC function. Disturbed mitochondrial function can result from defects in transport of small and large molecules into the mitochondria, substrate utilization, citric acid cycle defects, β-oxidation defects, carnitine metabolism and handling, and the integrity of the outer and inner mitochondrial membranes. Therefore, inheritance patterns can constitute mitochondrial inheritance but also conventional Mendelian inheritance. Trinucleotide repeat patterns may also apply to some of these disorders.

Clinical Presentation

During infancy and early childhood, mitochondrial diseases typically present with altered levels of consciousness, often associated with global developmental delays, failure to thrive, recurrent episodes of vomiting, and poor immune function. Inborn errors that present during the first few weeks of life tend to have a more malignant course than those presenting later in life. Although infection is the most common cause of coma in a neonate, an evaluation for an inborn error of metabolism should always be considered in a neonate with an altered mental status. Because a child with an inborn error of metabolism commonly presents with bacterial sepsis, consideration of an inborn error should not be excluded solely because of a proven infection. Neonates can also present with combinations of hypertrophic cardiomyopathy, hypotonia, and liver failure. In infancy, the presentation can also include failure to thrive, recurrent vomiting and diarrhea, hypotonia, developmental delays and developmental regression, seizures, and renal tubular acidosis. Neuromuscular presentations, with or without central nervous system (CNS) involvement, generally are seen in toddlers and older children. The variety of clinical signs and symptoms are listed in Table 52-1, and the well-described clinical disorders, along with the known associated mutations, are described in Table 52-2.

Several dozen common reported disorders (and hundreds of potential disorders) are labeled inborn errors of energy metabolism, and these may affect normal CNS function through a variety of mechanisms. Disorders of ETC activity can deprive the brain of necessary energy (ATP) to ensure proper functioning of Na^+, K^+ adenosinetriphosphatase (ATPase). In addition to the disorders that result in deficient oxidative phosphorylation, numerous disorders proximal to the ETC result from deficient mitochondrial and cytoplasmic enzyme function. These include disorders of fatty acid oxidation, the citric acid cycle, the urea acid cycle, amino acid metabolism, and organic acid metabolism. Disorders of amino acid synthesis or degradation can cause a toxic buildup of neurotransmitters, as seen in nonketotic hyperglycinemia. Furthermore, because some of these disorders are pathologically active before birth, they can lead to an embryopathy that can result in an irreversible encephalopathic state. The brain malformation seen in pyruvate dehydrogenase (PDH) deficiency, which includes dysgenesis of the corpus callosum and optic nerve hypoplasia, is one such example.

TABLE 52-2. Common Phenotypes

Name	Key Features	Other Features	Mutations Associated with Phenotype (numeric designation indicates position of mutation in mtDNA)*
Lebers hereditary optic neuropathy (LHON)	Visual loss beginning in young adulthood	Wolff-Parkinson-White multiple sclerosis-like syndrome	3394, 3460, 4160, 4917, 7444, 11778, 13708, 14484, 15257
Mitochondrial encephalomyopathy, lactic acidosis and stroke-like syndrome (MELAS)	Varying degrees of cognitive impairment and dementia, lactic acidosis, strokes, and transient ischemic attacks	Hearing loss	3243, 3271
Myoclonic epilepsy and ragged-red fibers (MERRF)	Progressive myoclonic epilepsy, clumps of diseased mitochondria accumulate in the subsarcolemmal region of the muscle fiber and appear as "ragged-red fibers" when muscle is stained with modified Gomoric trichrome stain	Short stature	8344, 8356
Leigh disease, subacute sclerosing encephalopathy	After normal development up to some point (the disease usually begins late in the first year of life but the onset may occur in adulthood), a rapid decline in function occurs and is marked by seizures, altered states of consciousness, dementia, ventilatory failure		8993, 8344; pyruvate carboxylase deficiency, pyruvate dehydrogenase deficiency, complex I deficiency, complex IV (cox) deficiency, SURF-1 mutation SCO mutation
Neuropathy, ataxia, retinitis pigmentosa, and ptosis (NARP)	Progressive symptoms as described in the acronym, along with dementia		8993 The same mutation associated with the infantile form of Leigh disease, when heteroplasmy 70 to 90% will result in the NARP phenotype
Kearns-Sayre syndrome (KSS)	External ophthalmoplegia, cardiac conduction defects and sensorineural hearing loss		5 kB deletion or duplication of mtDNA, A3243G POLGI Mutatio Ins
Myoneurogenic gastrointestinal encephalopathy (MNGIE)	Gastrointestinal pseudo-obstruction, neuropathy		Thymidine phosphorylase deficiency, 10006, 12246, 12308

*Numeric designation indicates position of mutation in mtDNA.

Testing

It is difficult to know which patient should be tested for a mitochondrial disorder and how far to push the investigation if screening tests are not informative. The age of onset can vary, and the spectrum of presenting signs and symptoms is vast, with similar findings occurring in other illnesses. Common conditions that can mimic a mitochondrial cytopathy include, but are not limited to, primary endocrine diseases (diabetes, hypo- or hyperthyroidism, adrenal insufficiency), B_{12} deficiency, homocystinuria and associated disorders, primary muscle disease (polymyositis, dystrophinassociated glycoprotein muscular dystrophies), "failure to thrive," autoimmune disorders, glycogen storage disorders, depression, and related psychosomatic disorders. Symptoms in children who are victims of Munchausen syndrome by proxy often overlap with those seen in these disorders. It is crucial to note that parents of children ultimately found to have a mitochondrial disorder have been falsely accused of Munchausen syndrome by proxy. In older children and adults, other neurodegenerative disorders, such as the hereditary ataxias, multiple sclerosis, motor neuron disease, Huntington's disease, or combined systems degeneration, can mimic a mitochondrial disorder. Sometimes the distinction between a primary mitochondrial disorder and secondary mitochondrial failure is not so clear, as in Friedreich's ataxia (FA). In FA, the expansion of a nuclear-encoded trinucleotide repeat sequence results in the failure of frataxin, a mitochondrial-targeted protein. Over time, toxic levels of iron injure the mitochondria.

To rule out other diagnoses, take a careful history, perform a physical examination, and order appropriate laboratory testing. There is no accepted method of screening for mitochondrial disorders. Helpful laboratory tests include measures of blood glucose, lactate, ammonia, electrolytes, urine pH, and urine organic acids, a complete blood count, analysis of amino acids, and analysis of carnitine that includes the free carnitine level, a total carnitine level, and a quantitative measure of all acyl carnitine esters. Measuring cerebrospinal fluid (CSF) lactate also can be helpful in some instances. Magnetic resonance spectroscopy can provide a qualitative measure of lactate in many areas throughout the brain and CSF. Although a low CSF glucose level is seen in patients with

bacterial meningitis, it also can occur in patients who have glucose transport defect, a rare but treatable condition characterized by the lack of glucose transport across the blood-brain barrier. A low blood urea nitrogen (BUN), especially in the setting of dehydration, should automatically trigger consideration of an organic acid disorder or urea acid cycle defect, and an ammonia level should be obtained. Ammonia levels are physiologically elevated in the first few days of life but return to normal within 5 to 7 days of life. Neutropenia, anemia, and thrombocytopenia are often seen in the organic acidurias and other inborn errors. Fasting hypoglycemia is seen in glycogen storage diseases, disorders of fatty acid metabolism, disorders of gluconeogenesis, and ETC disorders. The combination of hypoglycemia without elevated urinary or blood ketones points to a fatty acid oxidation disorder. Galactosemia can present with *Escherichia coli* sepsis or meningitis, along with hypothermia and an elevated direct bilirubin level.

Lactate will accumulate in numerous metabolic disorders, as well as during anoxia, poisoning, and sepsis. Lactic acidosis is, therefore, frequently observed in the setting of altered level of consciousness, although an elevated lactic acid itself is not the cause for the abnormal sensorium. In most laboratories, a lactate level above 2.2 mM (20 mg/dL) is considered abnormal, but healthy infants will have higher lactic acid levels than older children.

A number of technical factors are crucial when obtaining blood and urine for metabolic studies. The blood obtained for lactate and pyruvate determination must be free-flowing. A struggling child or a tourniquet applied too tightly or for > 30 seconds can result in a falsely elevated lactate level. When obtaining blood pyruvate determination, it must be instantly (within seconds) denatured in an 8% perchloric acid solution. If this is not done, the red blood cells will consume glucose and produce pyruvate, resulting in a false elevation in the pyruvate level. Cooling the blood will not prevent the pyruvate concentration from increasing after the blood has been removed from the body. An elevated pyruvate level in the presence of a normal lactate is meaningless and occurs only because of technical difficulties.

The ratio of lactate to pyruvate reflects the redox state of the cells. An elevated lactate with the ratio of lactate to pyruvate preserved at 10–20:1 suggests a defect in PDH. An elevated lactate and an elevated lactate-to-pyruvate ratio (above 20:1) suggests a defect in ETC function or, less commonly, a pyruvate carboxylase deficiency. Both carbon monoxide and cyanide inhibit cytochrome-*c* oxidase and can cause lactic acidosis. Electron transport activity can be inhibited by sepsis or, more exactly, by the cytokine effects found in the setting of sepsis. Impaired ETC function along with the hypotension that can occur during sepsis can lead to lactic acidosis.

It is crucial to note that a normal blood lactic acid level does not rule out the possibility of a mitochondrial disease, especially in an older child. Furthermore, the presence of renal tubular acidosis may result in normal blood lactate levels because of increased excretion of lactate in the urine. There are patients with persistently elevated CSF lactate with normal plasma levels. The observation of persistent lactic acidosis (> 2.2 mM) along with elevation in the lactate-to-pyruvate ratio is highly suggestive of a respiratory chain disorder. Table 52-3 provides a guide for laboratory diagnosis of mitochondrial disorders.

Finally, lactic acidosis occurs in glycogen storage diseases as well as in Lesch-Nyhan syndrome, Rett syndrome, Prader-Willi syndrome, and Angelman syndrome. Therefore, it is more efficient to test for a specific syndrome if a child fits into the clinical spectrum of these disorders.

Treatment

There are no proven therapies for mitochondrial cytopathies. Because of the variable and unpredictable course of these diseases, even in family members with the same genotype and phenotype, appropriate randomized studies are extremely difficult to conduct. Therefore, there are few data from phase 3 studies that can be used to prove any treatment effective, although case reports and small studies suggest that trials of given therapies may be effective in any one patient.

Treatment of symptoms is the standard of care, and trial and error is often the only guide for the clinician and family. For example, antiepileptic drugs are used to treat seizures, regardless of the mitochondrial etiology. Certain medications are typically avoided in those with known mitochondrial diseases because of their methods of action, although there may not be overwhelming clinical evidence these medications are dangerous. Finally, a therapeutic trial of vitamin and cofactor supplements is generally recommended, but cannot be advised or supported by class I or class II data. However, there remains controversy as to the legitimacy of requiring evidence-based medicine for support of treatment on such rare diseases, especially if the proposed treatment has an extremely low risk of side-effects in the setting of a potentially devastating disease. Therefore, it is reasonable to state that such vitamin and cofactor therapy is reasonable, but not a mandatory treatment option, and certainly should not be considered as a standard of care. A comprehensive review of this subject is provided in the Suggested Readings.

The clinical benefits for cofactor and vitamin therapy can include improved strength and endurance, although

TABLE 52-3. Laboratory Evaluation of Mitochondrial Disorders

Primary Evaluation		
Test	**Tissue***	**Comment**
Glucose	B, CSF	Hypoglycemia is seen in numerous metabolic disorders that affect gluconeogenesis, including defects in pyruvate carboxylase, phosphoenopyruvate carboxykinase, 1,6 diphosphofructase, glycogen storage diseases, ETC defects, fatty acid oxidation defects, organic acidurias. Hyperinsulin states should also be excluded. Low cerebrospinal fluid glucose in the absence of infection should be an indication of a glucose transport defect.
Electrolytes	B	Calculate anion gap
Blood counts	B	Anemia, thrombocytopenia, and neutropenia are seen in a variety of metabolic diseases, especially the organic acidurias. Primary and secondary disorders of folate and B_{12} metabolism should be considered.
Lactate	B	Tourniquet must be released before blood is sampled (see text)
Creatine kinase	B	Mild elevation common in myopathic forms
Urine analysis	U	High pH may suggest renal tubular acidosis
Ammonia	B	Fasting sample most useful; elevated ammonia (up to 150 μM) is normal in the first few days of life; elevated in urea acid cycle defects and organic acidurias.
Organic acids	U, CSF	Samples must be kept refrigerated or frozen. Urine collections may be random or timed, and may be collected after a fasting period or glucose load, depending on the clinical situation. Correct interpretation requires knowledge of the timing and composition of last meal and the age of the patient. The presence of abnormal amounts of lactate, pyruvate, citric acid cycle intermediates, and 3-methylglutaconic acid suggests mitochondrial dysfunction. Dicarboxylic acids are seen in disorders of fatty acid oxidation and glutaric aciduria type II. Specific disorders of organic acid and amino acid metabolism can be diagnosed by a typical pattern of abnormal organic acid analysis. Note that 3-methylglutaconic acid can be seen in patients on progesterone, corticosteroids, or during extreme stress, and some organic acids (hippurate and benzoate) are found in preservatives and gelatin-containing products.
Ketones	B, U	Often present in fed individuals with respiratory chain dysfunction. Elevation in the beta-hydroxybuterate/acetoacetate ratio is highly suggestive of a respiratory chain dysfunction. A fatty acid oxidation defect should be considered if ketones are absent during fasting, starvation, or an illness that results in vomiting, diarrhea, and dehydration.
Mitochondrial DNA Southern blot	B, M	If a patient fits into a specific, well-described mitochondrial phenotype, such as CPEO, KSS, or MELAS, Southern blot testing may lead to a rapid diagnosis.
Nuclear DNA Mutations	B	Assembly Genes: *SCO1, SCO2, SURF1, COX10, BCLS1* mtDNA Depletion: *POLG1, MPV17, dGUOK, TK2* ADP-ATP Translocase:*ANT1* DNA Helicase: *TWINKLE* MINGLE: *thymidine phosphorylase* (low thymidine level also diagnostic)
Bone marrow biopsy	—	Perform only if indicated due to anemia. Sideroblastic anemia is part of Pearson syndrome
Brain MRI	—	Bilateral symmetric lesions of basal ganglia and brainstem, leukodystrophy, multifocal areas of hyperintense signal
Ophthalmology consult	—	Assess for retinitis pigmentosa or optic atrophy
Cardiac evaluation	—	Routine electrocardiogram and echocardiogram (see text)
Secondary Laboratory Evaluation		
Test	**Tissue***	**Comment**
Lactate	B, CSF	See above
Pyruvate	B	Proper determination of pyruvate requires the specimen be instantly deproteinized. Pyruvate not useful if lactate is normal. Disregard results if not properly corrected.
L/P ratio	B	The ratio of lactate to pyruvate can be very helpful in determining if lactic acidosis is due to an OXPHOS disorder (L/P >20) or pyruvate dehydrogenase deficiency (L/P ~ 10)
Amino acids	B, U, CSF	Urine collections may be random or timed and may be collected after a meal or after fasting, depending on the clinical situation. "Generalized aminoaciduria" may indicate the presence of proximal renal tubular dysfunction due to mitochondrial cytopathy, as well as other medical conditions. Alanine is the amino acid precursor to pyruvate; therefore, an elevated alanine can be helpful in the diagnosis of an OXPHOS disorder. Because alanine can be elevated after a meal, one technique of compensating for dietary fluctuations is to calculate the ratio of alanine to lysine (which corresponds closely with dietary intake). An elevated alanine along with an alanine:lysine ratio > 3 suggests true hyperalaninemia. Many specific amino acid disorders can be diagnosed with a specific amino acid profile.
Organic acids	U, CSF	Often worth repeating, especially during an acute illness, as abnormal organic acids profiles are not present at all times.

Continued on next page

Carnitine analysis	B, U, M	Most laboratories determine the free carnitine and total carnitine. Fractionation into specific acyl carnitines may be helpful in some situations and can help determine disorders of long- and medium-chain acyl CoA dehydrogenase deficiency and GA II. Urine collections may be random or timed and may be collected after a fasting period or carnitine load, depending on the clinical situation. Serum carnitine deficiency is almost always a secondary phenomena due to a disorder of fatty acid oxidation or oxidative phosphorylation. Elevated urinary carnitines, especially in the setting of serum carnitine deficiency, is an indication of a metabolic disorder.
Ketones	B, U	Determining the ratio of β-hydroxybutyrate and acetoacetate may be helpful and offers a similar estimate of the redox state as does the lactate: pyruvate ratio. This test is most valuable if collected during an acute illness or after a fast.
Acyl glycines	U	Useful in detection of disorders of β-oxidation and electron transfer flavoprotein (glutaric aciduria type II)
Skin biopsy	—	Electron microscopy may reveal structural defects in mitochondrial structure. A fibroblast culture can be established with the skin obtained from a biopsy. This can be sent for testing ETC activity, β-oxidation disorders, as well as for various other specific enzyme-deficient disorders.

Tertiary Laboratory Testing

Test	Comment
Repeat testing	Repeating some of the above-listed tests, sometimes under different conditions (such as during an illness), may be helpful.
Provocative metabolic testing	Under monitored conditions, usually in the hospital, repeating some of the above tests after a glucose load, fructose load, protein load, and fasting may be helpful. Offered in very few centers.
ETC enzymology	This is the most commonly performed test for mitochondrial function. It can be performed on homogenates of whole tissue (muscle, liver), skin fibroblasts, or freshly isolated disrupted mitochondria. Provides indication of the activity of the catalytic component of ETC complexes I, II, III, and IV. It provides no information about nonenzymatic components of the ETC complexes, membrane integrity, or substrate transport defects. Improperly prepared tissue, especially in the case of tissue homogenate, is subject to false-positive results.
OXPHOS polarography	Performed only on freshly isolated intact mitochondria. Provides functional estimates of the integrity and efficiency of oxidative phosphorylation, fatty acid oxidation, citric acid cycle function, inner and outer mitochondrial membrane function, substrate transport, and respiratory control. Offered in very few centers. New and smaller polargraphs may allow this testing to be performed on very small samples allowing more centers to offer this testing.
Specific enzyme function	Performed on skin fibroblasts, lymphocytes, and other tissues, depending on the laboratory and specific enzymatic test.
Light microscopy	The presence of ragged red fibers, ragged blue fibers, numerous COX-negative fibers is highly suggestive of a mitochondrial disorder. Abnormal lipid or glycogen accumulation is also indicative of a metabolic disorder.
Electron microscopy	The presence of pleomorphic mitochondria, paracrystalline inclusions, and mitochondrial proliferation is highly suggestive of a mitochondrial disorder. Abnormal lipid or glycogen accumulation is also indicative of a metabolic disorder.

B = blood; CPEO = chronic progressive external ophthalmoplegia; CSF = cerebrospinal fluid; ETC = electron transport chain; GA = glutaricaciduria; KSS = Kearns-Sayne syndrome; M = muscle; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome; MRI = magnetic resonance imaging; OXPHOS = oxidative phosphorylation; U = urine.

patients report a variety of benefits. It is impossible to eliminate a placebo effect, but most patients and their families decide which supplements to continue and which to discontinue on the basis of their own perceptions of effectiveness. For any of the cofactors, a trial course is reasonable. However, it is not possible to suggest these therapies be mandatory given the lack of clinical studies available. Coenzyme Q_{10} can be given at dosages ranging from 5 to 15 mg/kg/d in two to three divided doses. We also usually give patients a trial of levocarnitine at dosages of 30 mg/kg/d in two to three divided doses, even if there is not a systemic carnitine deficiency. Riboflavin (vitamin B_2) at dosages of 100 to 400 mg/d has been shown to be beneficial in some patients and is also used to treat associated migraine. The use of creatine has been shown to improve strength in patients with mitochondrial myopathies, although its long-term use has not been studied. Because of the potential for renal toxicity, long-term use of creatine should be only undertaken with caution. The use of antioxidants (α-lipoic acid, vitamin E, vitamin C, β-carotene, selenium, and *N*-acetylcysteine) to lessen free radical damage to the mitochondrial membrane has a scientific rationale, but again proof of effectiveness does not exist. The other B vitamins have been used, with reports of effectiveness in small numbers of patients, likely those with a rare but specific vitamin-responsive syndrome.

Medications that are toxic to the mitochondria are of increasing interest. Because bacteria and mitochondria share a common genetic anthropology, including similarities in their replication mechanisms and structure of their rRNA, some antibiotics should be avoided. The aminoglycosides and chloramphenicol are well-known examples: they have been associated with deafness and liver failure, respectively. The penicillins and cephalosporin drugs are

safe, given their mechanism of action. However, there is little research on other antibiotics, so symptoms should be monitored closely, especially if there will be prolonged use of drugs that interfere with bacterial DNA replication, transcription, or translation. Regardless, appropriate antibiotics should not be withheld in situations where there are no alternatives.

The reverse transcriptase inhibitors used to treat infections with the human immunodeficiency virus are well-known mitochondrial toxins. Valproate has been associated with liver failure in patients with mitochondrial disease; therefore, we avoid using this medication. However, valproate has been used safely, and experts disagree about its use in mitochondrial diseases. Some general anesthetics, such as propofol and the barbiturates, inhibit mitochondrial respiration in experimental models. Propofol is delivered in a lipid solute, so long-term administration of this drug (for example, for treatment of status epilepticus), can cause potential problems for patients with fatty acid oxidation disorders. Propofol has been used safely for short surgical procedures in mitochondrial patients. For practical purposes, volatile anesthetics appear to be tolerated in most patients unless other contraindications exist.

There is great interest regarding the emergency management of a child in crisis with a mitochondrial cytopathy. Unfortunately, this has not been studied in any systematic fashion. Except for children with PDH deficiency, a glucose containing balanced salt solution (usually 5 to 10%) should be administered to ensure normoglycemia and reverse any catabolic state that may be occurring. Lactate-containing solutions should be avoided. In the case of PDH deficiency, glucose is rapidly converted into pyruvate, and then lactate, without any further ability to be metabolized, and these patients should be rehydrated with a balanced electrolyte solution and given parenteral fats for caloric support until their diet can be restarted. In patients with known metabolic disorders, we often add levocarnitine (100 mg/kg/d in three or four divided doses) to the intravenous solution.

In critical situations, when lactic acid and ammonia levels are extremely elevated, the use of continuous infusion insulin (0.1 U/kg/h), using very frequent glucose monitoring, may help reverse catabolism, decrease circulating toxic free fatty acids, and lower lactic acid and ammonia levels. The use of sodium benzoate, phenylbutyrate, and sodium phenylacetate can bind conjugate ammonia in the case of severe hyperammonemia. Enteral use of lactulose also can help lower ammonia levels. Dialysis is required in extreme situations. Referral to a metabolic center is often required.

Dietary management for mitochondrial disorders remains largely trial and error. A low-carbohydrate, high fat diet is helpful for some patients with complex I deficiency, although others do better on a high-carbohydrate, low-fat diet. Approximately one in four patients with electron transport chain defects demonstrate secondary defects in fatty acid metabolism as determined by fibroblast enzyme testing, and may benefit from a diet with frequent feedings and having a low fat content. Patients with PDH deficiency should be treated with a ketogenic diet. Despite the urge to treat patients who are failing to thrive due to mitochondrial disorders with a high-calorie diet, this should be avoided because it is not effective and results in the generation of toxic metabolites from the inability to metabolize food. The use of frequent, small-volume feedings is generally well tolerated. Using less calorie-dense nutrition spread over the day and night may result in the ability to give a high enough volume, with the final result being a higher calorie intake over the 24 hour day For children with primary and secondary gluconeogenetic defects, avoidance of fasting, including overnight fasting, is recommended.

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Practitioner and Patient Resources

United Mitochondrial Disease Foundation
http://www.umdf.org
The United Mitochondrial Disease Foundation's mission is to promote research for cures and treatments of mitochondrial disorders and to provide support to affected individuals and families.

Mitomap
http://www.mitomap.org/
www.genetests.org
www.horizonmedicine.com
www.bcm.edu/geneticlabs/

Chapter 53

Mental Retardation

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Mental retardation is one of the most frequently diagnosed disabling conditions in our society. Identifying the cause of mental retardation is central to understanding the nature of the problem, providing answers to questions regarding genetic risks, directing specific therapies, and achieving meaningful inclusion of individuals with this disability into society.

Intuitively, it is understood that individuals with mental retardation have "something different" about the structure and organization of the brain. In the past, defining what that "something" might be was a high-cost, low-yield endeavor. Continued technologic advances greatly enhance our ability to identify specific etiologic factors; nevertheless, the patient with mental retardation continues to represent a diagnostic and management challenge for the physician and the family.

Background

Although several classification systems are used to categorize individuals with mental retardation, the two most widely accepted definitions are those adopted by the American Association on Mental Retardation (AAMR) and the American Psychiatric Association (APA) (*Diagnostic and Statistical Manual of Mental Disorders* [DSM-IV]). In both classification systems, mental retardation is defined as significantly subaverage intellectual function with limitations of adaptive behavior manifesting during the developmental period. The determination of subaverage intellectual function requires an intelligence quotient (IQ) score of 2 or more standard deviations below the mean (about 70 to 75 or below), on the basis of scores obtained on one of the standardized, individually administered measures of intellectual function. *Concurrent deficits in adaptive function* refer to impairments in the individual's ability to meet age-appropriate standards of personal independence and social responsibility. These are defined by limitations in at least two of the following adaptive skill areas: communication, self-care, home living, social and interpersonal skills, use of community resources, self-direction, functional academic skills, health and safety, leisure, and work. In addition, onset during the developmental period requires manifestation of the above criteria before age 18 years.

Although the essential features of the AAMR and DSMIV definitions of mental retardation are similar, the assignment of levels of severity or disability differs between the two diagnostic schemes. The DSM-IV subdivides individuals with mental retardation into degrees of severity on the basis of their level of impairment in intellectual function (ie, mild, moderate, severe, or profound) (Table 53-1). The AAMR focuses on the abilities of individuals to function in an inclusive environment and defines the degree of severity on the basis of the patterns and intensity of supports needed (ie, intermittent, limited, extensive, or pervasive). The term *developmental delay* may be more appropriate than *mental retardation* when a standardized intellectual measure is not used or when a child is too young for a standardized assessment to be valid. Unfortunately, this less precise term is often used to avoid the more appropriate but emotionally charged term "mental retardation." This euphemism can be a barrier to parental understanding and adjustment if they mistakenly assume the physician means the child will "catch up" when the term "delayed" is used. Children may seem to catch up in the context of an erroneous assessment of their developmental level, usually in the setting of an intercurrent illness that, when resolved, allows the child to thrive. When accurately assessed, however,

TABLE 53-1. Classification of Severity of Mental Retardation*

Etiologic Classification	DSM-IV Clinical Classification	SD	IQ	Educational Classification	Functional Support Required
Mild	Mild	2–3	55–70	EMH	Supervision as necessary
	Moderate	3–4	40–55	TMH	Supervised independent activity
Severe	Severe	4–5	25–40	Severely/Profoundly Handicapped	ADLs supervised
	Profound	> 5	< 25		All ADLs provided

* From the standpoint of etiology, two classes (mild and severe) are the most useful. From the standpoint of predicting the educational and support system required, the clinical classification is the most useful.

ADL = activity of daily living; EMH = educationally mentally handicapped; IQ = intelligence quotient; SD = standard deviation; TMH = trainable mentally handicapped.

children with significant delays in the acquisition of developmental milestones rarely catch up to their age-matched peers. The use of euphemisms when the physician knows the family is misreading his or her intent is often mistakenly felt to be a kindness to the parents. Such misunderstanding is not only counterproductive to the process of coping with a diagnosis of mental retardation and the psychosocial adjustment necessary for the family, it also, more often than not, leads to a degree of distrust of the physician. Recent evidence indicates that the best way to inform patients and their families about a disability is for the physician to explain the situation in an honest and straightforward but caring manner. Terms should be stated in a precise way and the definitions explained in a frank and open discussion. In addition, the physician should keep in mind that such a dialogue may require more than one visit and may also require more time than the standard clinic appointment.

When discussing etiology, it is convenient to divide mental retardation into mild and severe categories (IQ 50–70 and < 50, respectively). Mild mental retardation differs significantly from more severe forms in terms of its presentation, prevalence, etiology, associated features, management, and prognosis. Specifically, mild mental retardation occurs in roughly 30 individuals per 1,000 population, while severe mental retardation occurs in 3 to 4 per 1,000 population. Despite being 10 times as frequent, the etiology of mild mental retardation is less often defined than that of severe mental retardation. The etiology of severe mental retardation can be identified in about 80% of the patients (Tables 53-2 and 53-3). The major identifiable causes of severe mental retardation differ somewhat from the causes of mild mental retardation in that major chromosomal anomalies are less common in mild mental retardation, whereas polygenic inheritance and socioeconomic, geographic, racial, and gender factors are more important in patients with a mild form than in those with a severe form of mental retardation.

Among individuals with more severe forms of mental retardation, there is a high prevalence of associated impairments that further limit the individual's adaptive abilities and affect outcome. Seizure disorders develop in more than 20% of children with mental retardation and increase with greater severity of mental retardation. Sensory impairments, particularly visual deficits, are found in more than 50% of children with severe mental retardation and 25% of those with mild mental retardation. Other associated disorders include cerebral palsy, feeding problems, failure to thrive, and speech and language impairments.

The prevalence of psychiatric disorders and behavioral problems is also higher in children and adults with mental retardation than in the general population. In addition to having more behavioral difficulties in general, some behavioral problems, such as aggression and noncompliance, occur more often in individuals with mental retardation. Furthermore, there are other specific disorders, such as pica, rumination, self-injury, and stereotypy, that are more specific to children and adults with mental retardation and rarely seen in the general population. The management of such patients with dual diagnoses is complex and usually requires an interdisciplinary approach.

Evaluation

Patients with mental retardation may present with a wide variety of complaints, but generally only those patients

TABLE 53-2. Identifiable Causes of Severe Mental Retardation

Etiology	Percentage	Examples
Chromosomal abnormalities	30%	Down (20%), FraX (6%), all others (4%)
Injury to developing brain	15–20%	Teratogens, Prenatal injury, Perinatal injury, Postnatal injury
Central nervous system malformations	10–15%	Induction defects, Migration defects, Hydrocephalus
Multiple congenital anomaly syndromes	4–5%	Noonan syndrome, Rubinstein Taybi syndrome, Sotos syndrome
Endocrine and metabolic causes	3–5%	Mucopolysacharride storage disorders, Lesch Nyhan syndrome

TABLE 53-3. Identifiable Causes of Mild Mental Retardation

Etiology	Percentage	Examples
Chromosomal	4–8%	Misc. deletions, duplications and rearrangements
Injury	15–20%	Fetal exposure to ETOH, Maternal Diabetes
Malformations	10%	Agenesis of CC, Subtle cerebral dysgenesis
Multiple congenital anomalies	?	Shprintzen syndrome (velocardiofacial syndrome)
Endocrine and Metabolic	?	Congenital hypothyroidism, Galactosemia
Polygenic conditions	50%	Familial mental retardation

with more severe impairments or those with obvious dysmorphic features will present in the first year of life. For example, severe and profound mental retardation frequently presents in the first months of life as delayed motor development, whereas moderate mental retardation may present as a language delay in a toddler with normal motor development. Furthermore, mild mental retardation may not be diagnosed until a child enters school and demonstrates poor educational performance and social development in comparison to normal peers.

The etiology and course of mental retardation are highly individual and are influenced by various psychological, medical, environmental, and cultural factors. A comprehensive, mulitmodal evaluation is necessary before interventions can be planned and implemented. The primary-care provider is frequently the first professional to make the diagnosis of mental retardation and often assumes the responsibility for facilitating and coordinating the evaluation.

Intellectual Assessment

Developmental assessment should be part of every well-child examination.Most physicians will apply one or more standardized screening tests to evaluate the developmental progress of their patients. Most screening tests assess gross motor, fine motor, social, and language skills. For the young child, the level of acquisition of developmental skills is usually expressed as a developmental age or the age at which the average child would be expected to accomplish the task in question. The developmental age is compared with the chronologic age in a ratio generally referred to as the developmental quotient (developmental age/chronological age × 100), which gives a measure of the patient's development expressed as a percentage of the average developmental level. If the developmental quotient of the patient is 75% or less, that patient warrants further investigation, both from the standpoint of the medical examination and the psychometric evaluation.

A comprehensive evaluation of an individual with suspected mental retardation includes the administration of an individualized, standardized IQ test. Although there are a number of IQ tests available, the Bayley Scales of Infant Development (BSID): Second Edition, the Stanford-Binet: Fourth Edition (SB:FE) Intelligence Scale, and the Wechsler Scales are the most frequently used. Important considerations when conducting an intellectual evaluation include ethnic, cultural, and language background as well as the presence of any associated impairments (eg, sensory or motor impairments). These conditions may invalidate certain intelligence tests, result in falsely low scores on standardized intellectual assessments, or require the use of specially modified assessment instruments. The BSID provide a mental development index (similar to IQ) as well as a psychomotor development index and are used in children under 42 months of age. The SB:FE is composed of 15 subtests that evaluate 4 areas of intellectual function (verbal reasoning, abstract and visual reasoning, quantitative reasoning, and short-term memory) and yield a composite standard age score roughly equivalent to a Full-Scale IQ score with a mean of 100. The SB:FE is standardized for individuals aged 2 years through 23 years. The Wechsler Scales are the most widely used set of IQ assessment devices in individuals older than 3 years of age. The Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) is used for children aged 3 to 7 years and yields the traditional Full-Scale IQ, Verbal IQ, and Performance IQ. The Wechsler Intelligence Scale for Children-III (WISC-III) is composed of 13 subtests and is used for children 6 through 16 years of age. The WISC-III yields scaled scores for each subtest as well as Full-Scale, Verbal, and Performance IQ scores. Scores derived from a factor analysis of the subtest scores are given for four additional scales, including verbal comprehension, perceptual organization, freedom from distractibility, and processing speed. The Wechsler Adult Intelligence Scale-Revised (WAIS-R) is designed for adults aged 16 through 74 years. The scale includes 11 subtests, from which a Full-Scale IQ, Verbal IQ, and Performance IQ are derived.

Adaptive Evaluation

In addition to an intellectual evaluation, measurement of an individual's adaptive skills is necessary to make a diagnosis of mental retardation. Furthermore, identifying an individual's behavioral strengths and weaknesses can play an important role in the ongoing habilitation process. Most adaptive behavior rating scales require detailed

information regarding an individual's behavior to be provided by an informant, such as a parent, teacher, or other caretaker.

The Vineland Adaptive Behavior Scale (VABS) is the most commonly used test of adaptive behavior. The VABS yields standard scores for four domains (ie, communication, daily living skills, socialization, and motor skills) and a total adaptive behavior composite score. Alternate adaptive behavior rating scales include the American Association on Mental Deficiency's Adaptive Behavior Scale (ABS), the Inventory for Client and Agency Planning (ICAP), and the Woodcock-Johnson Scales of Independent Behavior.

Audiometric Testing

A complete audiologic evaluation is indicated in the initial work-up of every child who presents with developmental delay, particularly those with language delay. This is done to rule out a hearing impairment as the etiology or an important contributing factor in the delay. Moreover, the frequent association of sensory impairments with mental retardation is another reason to include audiologic testing in the comprehensive evaluation process. In addition, audiometric and vestibular testing should be considered in younger children with developmental delays associated with hypotonia. A child with hearing loss and vestibular abnormalities will present with speech and language delays and hypotonia (and the associated motor delays). Clearly, this scenario could be confused with mental retardation.

Vision Testing

A complete ophthalmologic examination should be performed to evaluate the individual's visual abilities and rule out problems such as strabismus,myopia, and cataracts.

Psychiatric and Behavioral Assessment

A number of psychiatric, medical, and biological etiologies are proposed for the occurrence of behavioral problems in the population of individuals with mental retardation. Although often difficult to diagnose, the full range of psychiatric disorders is seen in both children and adults with mental retardation. Unrecognized medical conditions (eg, dental problems, occult infections, pain, sleep disorders, gastrointestinal disorders, and musculoskeletal problems) as well as the side effects of medications may also manifest as behavioral symptoms. In addition, a number of syndromes or disorders have been associated with specific behavioral problems, such as stereotypic hand wringing (in Rett syndrome) and self-injury (in Lesch-Nyhan syndrome and de Lange's syndrome). Alternatively, many behavioral problems can be viewed as constellations of behavioral excesses and skills deficits that serve a functional purpose for the individual. The four major behavioral etiologies include positive reinforcement (eg, the child or adult learns that the problem behavior results in increased attention), negative reinforcement (the child learns that the problem behavior stops an aversive event), self-stimulation (the behavior increases or decreases stimulation), and communication (the child uses the behavior to communicate needs to others). A comprehensive assessment is necessary to determine the most appropriate treatment for a specific behavior problem. This assessment may include medical and psychiatric evaluations; interviews with the parents, child, or adult with mental retardation and other caretakers; the use of behavioral checklists and rating scales; behavioral observations; and an informal or formal functional analysis.

Medical Diagnosis: Search for an Etiology

History and Physical Examination

As soon as a child has been confirmed as having a significantly low development quotient (DQ) or IQ, a search for a diagnosis (etiology) should commence. This search is important for several reasons. Most families sincerely want an answer to the question "Why?" If an underlying etiology can be identified, then additional questions about prognosis and recurrence risks can be answered. Before initiating any series of evaluations, the family should be informed of what is involved, including cost, time expenditure, and diagnostic yield. We discourage a "shotgun" approach to these investigations. In particular, the laboratory and neuroimaging studies to be performed should be carefully planned and requested with specific etiologies in mind (rather than ordering a "mental retardation panel"). As in most diagnostic exercises, the patient with mental retardation should have a careful history and physical examination first. Then, selected laboratory and imaging studies should be requested. In the text that follows, we highlight the components of the medical evaluation that are specific to a child with mental retardation.

Pregnancy History

Given that the vast majority of children with mental retardation have an etiology of prenatal onset, careful scrutiny of the pregnancy history is important. The mother should be questioned about any potential teratogen exposures during the pregnancy. Often, this is not done or is done indirectly because of the practitioner's concern over offending the parent. Regardless, although the questions

may be uncomfortable, they should be asked. Alcohol is the most important teratogen to inquire about. The spectrum of ethanol-related birth defects represents the most common preventable form of mental retardation in children in developed countries. The prevalence of alcohol-related mental retardation is in the same order of magnitude as that of Down syndrome, ranging from 1 in 28 to 1 in 750. It is estimated that 8% of all cases of mild mental retardation are a result of prenatal exposure to alcohol. Aside from those children with classic features of fetal alcohol syndrome, it may be difficult, if not impossible, to identify alcohol-related birth defects, because none are specific to this exposure. Until a more specific objective methodology is developed to identify children with subtle alcoholrelated birth defects, the physician is often left with just a clinical suspicion.

Other important teratogens to inquire about include prescription medications (eg, antiepileptic drugs, isotretinoic acid), over-the-counter medications, and herbal and other "health" supplements. The clinician should also ask questions about maternal health status during pregnancy, as medical conditions such as diabetes, infections, hyperthermia (with or without infection), and phenylketonuria (PKU) can significantly affect development of the fetal brain. For example, maternal PKU is rare, with estimates of between 1 in 25,000 and 1 in 30,000 women in their reproductive years having unrecognized maternal hyperphenylalaninemia. However, it is recommended that all women who have given birth to a child with idiopathic mental retardation and microcephaly without a known etiology should have a serum screening test for hyperphenylalaninemia because of the exceptionally high (approaching 100%) recurrence risk if it is not identified and treated.

Family History

A detailed family history of any patient with mental retardation should be obtained. The history should include information about relatives with mental retardation, developmental delays, or other neurodevelopmental or neurobehavioral conditions. If possible, parental IQs should be documented. If not possible, practical estimates of parental intellect (eg, school performance, occupation) may be helpful. Insights into a genetic etiology of the mental retardation should be sought with questions about relatives with multiple miscarriages, infertility, or unexplained infant deaths. Additionally, other important issues, such as consanguinity, should be raised.

Physical Examination

A thorough physical examination may provide clues to the underlying etiology of the mental retardation. Growth parameters, particularly head circumference, should be accurately obtained, plotted, and compared with any available previous measurements. Minor craniofacial dysmorphisms often signal underlying cerebral dysgenesis. Any major congenital anomaly should be noted, and screening for malformations not detectable by exam should be considered (eg, cardiac or renal ultrasonography). Because of the known embryologic association between the neural ectoderm and the skin, careful attention should be paid to the cutaneous exam. A Wood's lamp inspection is often helpful in detecting more subtle pigmentary changes. Both hyper- and hypopigmented lesions, as well as angiomatous malformations, are significant.

Laboratory Studies

Chromosomal Testing

Tremendous advancements in cytogenetic techniques have been made in the 40 years since the report of a chromosomal origin of Down syndrome. These have allowed the identification of a large number of specific syndromes associated with chromosomal abnormalities, most of which have developmental delay and mental retardation as consistent features. Improved banding techniques are now able to "stretch" the chromosome to the point that prometaphase analysis has resulted in increased resolution to approximately the 850-band level. This resolution translates to an area of the genome of 40 to 50 functioning genes per band. As such, it is recommended that (1) all patients with idiopathic mental retardation have prometaphase chromosomes performed ("standard" banding techniques are inadequate for identifying small chromosomal changes) and (2) any patient with idiopathic mental retardation who has had chromosome studies done that are more than 5 years old should have the test repeated. In our experience, it is common to find small chromosome rearrangements that were not previously noted, given the technology now available.

Mosaicism

As noted above, pigmentary changes and neurologic abnormalities are strongly associated. This association can often be explained by chromosomal and genetic mosaicism. Many patients with pigmentary anomalies and mental retardation will have normal lymphocyte (blood) karyotypes, but mosaicism can be demonstrated by sampling other tissues, such as skin fibroblasts. Mosaicism for various chromosomal aneuploidies has been described in patients with abnormal pigmentation and mental retardation. Most often, these changes occur along Blaschko's lines. It is recommended that cytogenetic studies be performed first on peripheral blood of patients with mental retardation and skin pigmentary abnormalities. If, however, the karyotype fails to

demonstrate any chromosomal abnormality, a sampling of a different tissue (preferably skin) in these patients is warranted. It does not matter whether skin is taken from normal or abnormally pigmented cells or from a particular side of the body.

Fragile X Syndrome

Fragile X syndrome is the most common inherited cause of mental retardation in boys. Those with "full" fragile X syndrome often have a recognizable phenotype in addition to mental retardation. Clinical features suggestive of fragile X syndrome include macro-orchidism (onset before or after puberty), large or prominent ears, long and narrow face or jaw, hyperextensible finger joints, hypotonia, and autism or autistic-like behavior. Girls with the fragile X mutation may have frank mental retardation or more subtle neurobehavioral problems, depending on the size of the trinucleotide expansion and the degree of lyonization. A positive family history of mental retardation is usually present in people with fragile X syndrome.

With the identification of an expanded trinucleotide repeat in the *FMR1* gene at Xq27, the standard diagnostic test for fragile X syndrome is now the quantification of the size of the trinucleotide repeat by deoxyribonucleic acid (DNA) techniques, such as polymerase chain reaction and Southern blot. The use of methylation studies is often helpful in determining prognosis, and is used by most laboratories doing clinical DNA studies for fragile X syndrome. It is debated whether all patients with mental retardation should have testing for fragile X syndrome. The use of various selection criteria has been suggested. However, if no selection criteria are used and all patients with idiopathic mental retardation are tested for fragile X syndrome, the reported positive detection rate is in the range of 1 to 10%. It is our opinion that even a few-percent yield is acceptable, given the significance of the information provided by a positive test for fragile X syndrome with regard to clinical outcome, therapies, and the important family implications.

In a patient with Fragile X syndrome as the cause of their mental retardation, further studies are usually indicated. At risk family members should be identified and offered testing. Methylation studies and X-chromosome inactivation studies may yield important information for clinical predictions/correlates on selected persons in the kindred.

Continued advances in the understanding of the pathophysiologic mechanisms involved in Fragile X have translated into new clinical testing options and issues. For select families, there may be 'typical' mutation in the Fragile X gene rather than an expansion of the trinucleotide repeat. Diagnosis of this situation requires gene sequencing of the FMR gene—and this is now a clinically available test. In addition, clinicians should be aware of the other pathogenic mechanisms involved in the premutation carriers of Fragile X, such as the recently described Fragile X-associated Tremor/Ataxia Syndrome (FXTAS). When evaluating boys for an etiologic cause of their mental retardation, the family history should also include information about neurologic disorders in the 'upstream' members of the pedigree.

Fluorescent In Situ Hybridization

The advent of fluorescent in situ hybridization (FISH) techniques has greatly expanded the ability to identify chromosomal anomalies. FISH studies make it possible to localize specific DNA sequences by fluorescent labeling in metaphase or prometaphase chromosomes, thereby providing numerous new markers. They have been adapted to clinical cytogenetics by the use of a cocktail of single copy probes derived from a specific chromosomal subregion. The use of FISH in the evaluation of children with mental retardation has many applications: (1) in situ hybridization with alphoid sequences (centromeric specific probes) enables rapid screening for autosomal aneuploidies, identification of the chromosomal origin of the centromeres in marker and ring chromosomes, and characterization of the monocentric, dicentric, and isodicentric nature of specific chromosomal abnormalities; (2) FISH may be applied in cases that are particularly difficult, using standard cytogenetic techniques, such as small insertions or deletions, ring chromosomes, small marker chromosomes, and abnormalities of, or around, the centromere; and (3) the list of multiple anomaly syndromes known to be due to contiguous gene deletions that can be confirmed by FISH studies is rapidly expanding. It is important to note that one cannot simply request a "FISH study"; rather, the cytogenetic laboratory needs to be informed of which particular condition is suspected. Thus, specific clinical features are important in directing the request for FISH studies (Table 53-4).

Telomeric Probes

Cryptic chromosomal rearrangements involving the telomeric portions of human chromosomes have been described as being responsible for a significant proportion of cases of unexplained mental retardation and other congenital anomalies. Specific subtelomeric FISH probes have been developed for each of the 42 telomeric regions in the human genome. The use of subtelomeric probes for the detection of subtle chromosome abnormalities that are not detectable by classic cytogenetics is a powerful tool; however, it is expensive and time consuming, considering currently available approaches. Current information suggests this test will be positive (abnormal) in 7 to 8% of patients with severe (IQ < 50) mental retardation. The yield is much lower, on the order of 0.5%, in

TABLE 53-4. Some of the More Common Contiguous Gene Syndromes Diagnosable by FISH Studies

Syndrome	Notable Features	FISH probe
1p deletion syndrome	Mental retardation, malformed ears, short neck, bulbous nose, congenital heart defects, digital abnormalities, and small deep set eyes	1p36
Angelman	Seizures, unusual broad-based gait, inappropriate laughter, no acquisition of speech, hypopigmentation, distinct facies (prognathism, prominent malar eminences)	15q11–13
Miller-Dieker	Type I lissencephaly, microcephaly, seizures, minor facial changes	17p13.3
Prader-Willi	Hypotonia, failure to thrive (infancy), obesity (childhood onset) hypogonadism, small hands/feet, short stature, hypopigmentation, almond-shaped eyes	15q11–13
Smith-Magenis	Coarse facies, autistiform/self injurious behavior	17p11.2
Velocardiofacial/ DiGeorge spectrum	Palatal anomalies, conotruncal heart defects, learning disabilities, hypocalcemia (hypoparathyroidism), immune deficiency (thymic hypoplasia)	22q11.2
Williams	Infantile hypercalcemia, distinct facies, "elfin-like," hoarse voice, supravalvular aortic stenosis, verbal loquaciousness	7q11.23
Wolf-Hirschhorn	"Trojan-helmet" configuration to nose, microcephaly, palatal and cardiac anomalies	4p16.3
Sotos syndrome	Overgrowth, advanced bone age, macrocrania, hypotonia, behavioral changes,	5q35

patients with IQs from 50 to 70. This actually makes subtelomeric deletions the most common identifiable cause of severe mental retardation. Thus, this test is absolutely indicated for these patients. It is less clear whether these studies are indicated for those with mild mental retardation. It is reasonable to consider these studies as a second-tier test for this group. Other comorbid features (eg, congenital anomalies) would increase the indication for these tests.

The most recent application of FISH technology has been the advent of array comparative genomic hybridization (aCGH). This testing modality couples the technology of FISH with chip-based microarray. In brief, this allows the performance of hundreds to thousands of individual FISH tests in a rapid laser-read, computer-interpreted format. The specific microarray chip can be customized to any desirable combination of know DNA probes. Most commercially available chips include the individual disorder FISH probes and the subtelomeric FISH panel. Besides these probes, the chips are customized by adding a few hundred to several thousand additional probes. The larger chips in current use may have 2500–3000 probes and cover most of the genome in intervals as small as 1 mega base (Mb). Array CGH technology is continuing to evolve. As of the time of this writing, it is very cost effective (as inexpensive as doing 3 individual FISH tests) and has quite a high yield. The currently reported detection in a cohort of patients with mental retardation (IQ < 70) is approximately 8%. This 8% represents only the abnormal cases who had previously normal cytogenetic studies. This then represents an additional 8% above the cytogenetic yield with submicroscopic deletions and duplications which are not detectable by classic cytogenetics but which have clinical relevance. Approximately half of abnormalities identified represent changes in the subtelomeric regions and the other half previously undescribed chromosomal aneuploidies.

Molecular Studies

The number of clinically available molecular studies is continually increasing. It is extremely difficult to keep up with which studies are available and which laboratories are offering them, as well as which are offered in a research setting. In fact, it is practically necessary to use Internet-based databases to keep up with such information. The molecular diagnosis of fragile X syndrome has been discussed above. In general, few other molecular diagnostic studies are indicated without clinical or laboratory indicators other than mental retardation alone. However, as molecular studies are developed and applied to a broader range of phenotypes, atypical presentations of classically defined disorders are being discovered. For example, the recent discovery of the gene responsible for Rett syndrome has led to the development of a clinical molecular testing panel for confirmation of the diagnosis. Soon after this test was made available, many individuals were reported with mutations in the "Rett gene" that did not have classic features of the syndrome. In fact, many had a phenotype that could only be described as solely mental retardation with perhaps subtle autistiform behaviors. This then raises the question "Should all patients with idiopathic mental retardation be tested for the Rett syndrome gene?" Just in the past 3 years, this answer has changed. Current recommendations are to consider *MECP2* testing in all girls with unexplained mental retardation. The diagnostic yield is probably too low to make the same recommendations for boys. However, as noted above, other comorbid features would be appropriate indicators to do these studies. *MECP2* studies should be considered in all patients with mental retardation occurring in conjunction with microcephaly, seizures, spasticity, or stereotypic behaviors. Whether the diagnostic yield for this test is sufficient enough to do in individuals with isolated mental retardation is yet to be clearly defined.

The same concept of an 'expanded phenotype' as described above for MECP-2 mutations holds true for many other genes that affect neurodevelopment. Population studies in X-linked mental retardation have identified several genes on the X-chromosome that cause mental retardation. Genetic changes in some of these genes appear to only cause non-syndromic mental retardation. In many of the other identified genes, the phenotype may be that of a syndromic or non-syndromic mental retardation depending on the particular mutation. Commercially available gene sequencing panels of X-linked mental retardation (XLMR) genes are available. Examples of the genes tested in a representative panel might include full sequencing of the genes ARX, DLG3, FACL4, FTSJ1, JARID1C, PQBP1, TM4SF2, and ZNF41. In our experience, performing this panel on patients with unexplained mental retardation (after completing the standard evaluations) is a reasonably high yield endeavor. Still, this is also an evolving technology. Several important questions as to the overall diagnostic yield in large unselected populations and specific selection criteria are yet to be answered. In addition, acceptance by third party and other payers lags significantly behind.

Endocrine or Metabolic Studies

The incidence of inborn errors of metabolism in the population of patients with mental retardation is estimated at 3 to 7%. As the field of biochemical and metabolic genetics continues to expand, it seems that more metabolic disorders are being delineated daily. The central clinical issue, however, is when to perform metabolic screening in patients with idiopathic mental retardation. We feel that metabolic tests generally confirm clinical impressions rather than yield unexpected diagnoses. It is rare to discover an inborn error of metabolism on a metabolic survey in those cases where the clinical picture did not already suggest such a condition. An underlying metabolic etiology for mental retardation in a given patient may be suggested by routine laboratory studies or specific signs and symptoms. It is not uncommon for children with mental retardation to have already had routine laboratory studies done as part of health care maintenance. Table 53-5 lists some of the common laboratory findings and the metabolic condition suggested by those findings. Important laboratory findings indicative of a metabolic disorder include hypoglycemia, hyperammonemia, lactic acidosis, and low serum cholesterol. Clinical symptoms that may suggest a metabolic disorder include seizures, neuroregression, acquired vision or hearing loss, episodic illness or vomiting, dietary avoidances, and dysostosis multiplex. In only those cases where a metabolic disorder is suggested on a clinical or laboratory basis, metabolic screening is effective in directing further definitive metabolic studies. In such situations, an effective first-round screening would include urine neurometabolic screening (for amino acids, organic acids, complex and simple sugars, and mucopolysaccharides), serum lactate, ammonia, and very-long-chain fatty acids and acyl carnitine profiles. In the absence of symptoms or laboratory abnormalities, metabolic screening has a very low yield and, in our opinion, is not routinely indicated.

TABLE 53-5. Laboratory Findings Suggestive of a Metabolic Disorder

Laboratory Finding	Possible Metabolic Condition
Low cholesterol	Smith-Lemli-Opitz
Acidosis	Lactic acidosis, organic acidemias
Hyperuricemia	Lesch-Nyhan/variants
Hyperammonemia	Urea cycle defects
Hypoglycemia	Fatty acid disorders, carbohydrate disorders
Anemia	Thalassemia–MR syndrome, disorders of intermediary metabolism
Increased transaminases	Multiple disorders

Much attention has been given to the relatively newly described congenital disorders of protein glycosylation (ie, carbohydrate-deficient glycoprotein [CDG] abnormalities). Testing for CDG should be performed in children with mental retardation and other specific indicators. Such indicators would include failure to thrive, ataxia or cerebellar disease, pigmentary retinal changes, inverted nipples, seizures, hyporeflexia, or organomegaly. Recommended testing would be studies to evaluate transferrin glycosylation, antithrombin III activity, and thyroid binding globulin levels. Serum lead levels should only be considered for children identified as having significant risk factors for lead exposure. Thyroid function studies are not indicated if the child had a normal newborn screen and no clinical evidence of thyroid disease.

Recently described disorders of nucleotide metabolism may represent an exception to the above recommendations. Screening for these disorders can be complicated. There is insufficient information regarding the frequency of these disorders to allow definitive statements about yield of screening; however, a serum and urine uric acid level may be a reasonable screening test in individuals with idiopathic mental retardation, even in the absence of other factors such as abnormal head size, abnormal neurologic examination, or dysmorphic features.

Radiology and Imaging

Neuroimaging is a standard component of the evaluation of a patient with mental retardation (Schaefer and Bodensteiner, 1998). Although there has been some debate as to the cost-effectiveness of routine neuroimaging in patients with mental retardation, we believe that invaluable

information that would otherwise be unavailable is gathered by imaging the brain. Some have advocated only imaging a select group of patients with mental retardation (eg, those with micro- or macrocephaly). We have found that the yield is sufficiently high, even in an unselected population, to justify the investigation. Without question, the imaging modality of choice is magnetic resonance imaging (MRI). In the name of cost saving, computed tomography studies are sometimes done. However, this modality is inadequate for imaging the soft tissue of the central nervous system (CNS), and the patient ultimatly requires an MRI anyway. As such, we recommend performing a brain MRI on all patients with mental retardation.

It is not surprising that malformations of the brain are associated with mental retardation. Neuropathologic studies in patients with mental retardation have suggested that a large percentage of patients with severe mental retardation have some degree of brain malformation (cerebral dysgenesis). Reported estimates range from 34 to 98%, with the larger, more in-depth studies suggesting numbers at the higher end of this range. There is a wide range of the incidence of cerebral dysgenesis identifiable from premortem clinical evaluation of patients with severe mental retardation. The diagnostic yield continues to improve with advances in neuroimaging techniques. Currently, brain MRI studies (with the use of quantitative tools, if necessary) may demonstrate CNS anomalies in up to 50 to 60% of patients with mental retardation. It is important to note, however, that many of these anomalies are subtle. It is recommended that clinicians review the scans for themselves and not rely solely on the radiographic report. The scans should be reviewed in light of the possibility of subtle changes, such as differences in the relative size of specific structures, gray–white matter proportions, and the sizes of fluid spaces (Schaefer and Bodensteiner, 1999).

Electrophysiology

An electroencephalogram (EEG) is not an indicated diagnostic test for idiopathic mental retardation. This study should be reserved for those children in whom the history and physical examination suggest seizures.

Other Diagnostic Studies

An emerging body of literature is demonstrating that "behavioral phenotypes" (in contrast to physical dysmorphic features) may provide important clues for directing the diagnostic work-up. For example, many individuals with mental retardation display autistic-like behaviors. Caution has to be applied here because as IQ decreases, socialization and communication are progressively impaired. However, the presence of truly autistic behaviors in a patient with idiopathic mental retardation should "slant" the diagnostic work-up. In contrast to the recommendations noted above, all patients with mental retardation and autistic behaviors should have *MECP2* testing, screening for nucleotide metabolic disorders, chromosome 15 methylation studies, FISH screening for centromeric duplications of chromosome 15, FISH screening of chromosome 17 (for Smith-Magenis syndrome), and an EEG.

Treatment and Intervention

The evolution of our philosophy with respect to the treatment and care of individuals with mental retardation—regarding educational, health, and social services, a number of legislative and court decisions, and the recent emphasis on "deinstitutionalization" and educational programming—has allowed more of them to remain in the community. Now, more than ever before, individuals with mental retardation reside with their families or in supervised living and vocational settings and receive support from community resources. Indeed, most individuals with mental retardation require only intermittent support and are able to achieve a degree of economic and social independence. However, in addition to needs for the same array of services provided for the general population (eg, dental services, and routine health care maintenance), many individuals with mental retardation have special needs and may require diverse supplemental services. These other services may include special education; behavioral intervention; access to social, recreational, and leisure activities (eg, Special Olympics); skills training; specialized psychiatric services; assisted living services; and work or vocational programs. The most effective interventions for individuals with mental retardation are multidisciplinary in nature and are aimed at improving their overall quality of life and integrating them into the mainstream of society.

General Health Supervision and Treatment of Special Medical Needs

In addition to conducting a comprehensive medical evaluation of the underlying developmental disability, problems that require specific medical interventions must also be identified and treated. It is important for the physician to realize that many patients with mental retardation have associated disabilities and impairments and require more than routine health care maintenance and acute illness interventions. For example, cardiac, orthopedic, endocrine, ophthalmologic, and hematologic complications must be considered in the medical management of a patient with Down syndrome. In addition to providing health care services, the physician must be prepared to consult with and collaborate with professionals from

interdisciplinary treatment teams. Indeed, the physician is often viewed as the team leader, coordinating the different evaluations and treatments and acting as a liaison to the patient, family, and other professionals.

Treatment of Associated Impairments

Associated impairments, including cerebral palsy, seizure disorders, sensory impairments, communication impairments, feeding problems, sleep problems, and psychological or behavioral disorders, are common and must be adequately identified and treated to achieve an optimal outcome. The prevalence of associated impairments increases with increasing severity of mental retardation. Treatments may include medical intervention, nursing services, occupational therapy, physical therapy, the use of adaptive equipment, speech-language therapy, nutritional counseling, audiology services, psychological intervention, recreation therapy, and social work services.

Educational Services

Educational services include those provided through public and private schools and vocational training programs. Since the 1950s, a number of important legislative and court decisions have had a direct impact on the education of children with mental retardation (Table 53-6). Furthermore, our philosophy of education has broadened to include the teaching of academic, social, and self-care skills that enhance the individual's quality of life and specifically address individual strengths and weaknesses. Increased emphasis has been placed on teaching ageappropriate skills and on teaching functional skills in their natural context. For individuals with mild mental retardation, the goal of education is to enhance adaptive abilities and vocational skills to facilitate their ability to live as independently as possible in an adult community.

Early intervention services are educational programs for infants and children under the age of 3 years with special needs. An Individualized Family Service Plan (IFSP) is a family focused plan developed for each child on the basis of a comprehensive, interdisciplinary assessment. An IFSP includes information regarding the child's developmental level; the family's concerns, priorities, and resources; the major goals for the child and family, including the criteria, procedures, and time lines for determining progress; the early intervention services to be provided; the name of the service coordinator responsible for implementing the plan; and the procedures for transition from early intervention to preschool services.

At age 3 years, children transition to school-based special education programs. Under the Individuals with Disabilities Education Act (IDEA), children aged 3 to 21 years are entitled to a free, individualized, appropriate education in the least restrictive environment. An array of placement options exists, ranging from the regular classroom (least restrictive) to institutional placement (most restrictive), including resource services, special class placement, and specialized schools. The Individualized Educational Plan (IEP) replaces the IFSP. The IEP is a written service plan for children aged 3 to 21 years that provides a statement of the child's current level of functioning, annual goals, short-term objectives, related services being provided, the percentage of time the student spends in general education, and the beginning and ending dates for special education services. A child's IEP is updated yearly.

IDEA also requires that when a student turns 14 years of age, schools begin formal planning for the transition from school to adult life. A statement of the transition services must be included in the IEPs of high school students, addressing their needs and goals in the areas of instruction, related services, community experiences, employment

TABLE 53-6. Landmark Federal Educational Legislation

The Education for All Handicapped Children Act PL 94-142 (1975)	Required that an evaluation, a free and appropriate public education in the least restrictive environment, a written Individualized Education Program (IEP), related services (eg, speech pathology, medical evaluations), parental participation, and due process be provided for all handicapped children, ages 5 to 18 years. The age range was extended to include children aged 3 to 21 years in 1977.
Education of Handicapped Children Act Amendments PL 99-457 (1986)	Mandates the development of services for preschool children aged 3 to 5 years that demonstrate or are at risk for developmental disabilities. Part H provided incentives for the provision of services to infants and toddlers with disabilities (birth through age 3 years) and their families through coordinated, interdisciplinary, interagency early intervention programs, including development of an IFSP.
Individuals with Disabilities Education Act (IDEA) PL 101-476 (1990)	Reauthorization and expansion of the Education of Handicapped Children's Act.
Individuals with Disabilities Education Act Amendments PL 102-119 (1991)	Mandates that early identification and intervention be initiated in the preschool years (age 3–5 yr) for children who have been identified as having disabilities and for children at risk for developmental disabilities.

planning and preparation, postsecondary-school living requirements, and, if appropriate, the acquisition of daily living and functional vocational skills. Schools must involve students, parents, and other community resources and agencies in the transition planning process.

Employment Services

Passage of the Americans with Disabilities Act (ADA, Public Law 101-336) in 1990 created comprehensive civil rights legislation to help integrate individuals with disabilities into every segment of society. It specifically prohibits discrimination and requires accessibility and accommodation.

It has had a direct impact on employment opportunities for individuals with mental retardation and other disabilities. Employment services available for adults with mental retardation include competitive employment, supported employment, volunteer work, day treatment programs, and sheltered workshops.

Supported employment opportunities have resulted in successful work adaptation in the community for many adults with mental retardation. Under supported employment programs, individuals are placed into a working environment and trained by a coach to do a specific job, bypassing the need for a "prerequisite" sheltered workshop experience. Individuals with more severe levels of mental retardation may perform basic or simple tasks in a closely supervised workshop setting.

Treatment of Problem Behaviors

The selection of a treatment should be individualized and based on the following factors: developmental level, chronologic age, the urgency with which reduction of the problem behavior is needed, the underlying function of the behavior, the availability of practical and effective treatments, the ability of the caregivers to implement the intervention, family and cultural contexts, and patient and parental preferences. To be successful, an intervention that reduces a problem behavior must replace that behavior with another, more appropriate behavior. The success of the intervention can be judged on the improvement in the quality of life it produces for the individual with mental retardation and the family.

Behavioral Interventions

Behavior modification strategies can be used to decrease an undesirable behavior, increase a desired behavior, or teach a new behavior and are typically chosen on the basis of the least restrictive but most-effective treatment available.

Antecedent Interventions

Antecedent treatments identify conditions that immediately precede and influence the occurrence of the problem behavior. A systematic manipulation of the environmental conditions that result in the behavior is then designed to change the frequency of the behavior.

Positive Reinforcement Interventions

Positive reinforcement uses a reinforcer (an item or activity the individual desires and will work to obtain) to increase the likelihood of a behavior recurring. To be successful, the reinforcer must immediately follow the occurrence of a specific behavior targeted for increase. Positive reinforcement procedures can also be used to decrease the frequency of a behavior by making reinforcement differentially contingent on the nonoccurrence of that behavior. There are a number of differential reinforcement procedures that can be used, including differential reinforcement of other behavior, which reinforces the absence of the problem behavior and the occurrence of any other behavior. In differential reinforcement of alternative behavior and differential reinforcement of incompatible behavior, replacement of the problem behavior with an appropriate alternative response or a behavior that is physically incompatible with the problem behavior is reinforced.

Negative Reinforcement Interventions

Negative reinforcement procedures increase the frequency of a response that is followed by the removal of a negative reinforcer. For example, temper tantrums (problem behavior) used by a child to escape a task demand (negative reinforcer) will increase in frequency if the child is successful in avoiding the task. However, if the child is made to comply with the task despite the temper tantrum, the temper tantrums will likely decrease and disappear.

Punishment

Punishment decreases the likelihood of a behavior recurring under similar conditions in the future through an action taken immediately after the behavior. Punishment procedures may involve (1) the presentation of an aversive or undesirable stimulus after the occurrence of the problem behavior (eg, verbal reprimands, facial screening, restraint), (2) the withdrawal of something the individual likes after the occurrence of the behavior (eg, time out and removal of attention), and (3) requiring the individual to engage in an undesirable, aversive behavior immediately after exhibiting the problem behavior (eg, forced-arm exercises after being aggressive).

Pharmacotherapy

Pharmacotherapy is commonly used in children and adults with mental retardation for the treatment of psychiatric disorders as well as behavior problems, including aggression, self-injury, agitation, property destruction,

and stereotypy. The use of psychotropic drugs in this population is influenced by a number of factors, with increasing drug use correlated with increasing age, decreasing intellectual impairment, and increasing number and severity of behavior and psychiatric problems. Medication is typically considered when behavioral interventions have been unsuccessful or when there is no apparent motivation for the behavior and it is presumed to be of organic origin. In general, medication in considered as one component in a broad treatment model, with the selection of the drug based on a comprehensive assessment and diagnosis of the problem behaviors. It is standard practice to combine psychopharmacologic treatment with behavioral and other interventions.

The theoretical rationales, indications, and management principles that guide drug therapy in the general population are, for the most part, consistent with psychotropic drug use in patients with mental retardation.

However, physicians must be aware that some psychotropic medications have differential effects in individuals with mental retardation. For example, stimulants, the drugs of choice for treating attention-deficit hyperactivity disorder, show decreasing efficacy as the severity of mental retardation increases. Although individuals with mild to moderate mental retardation may show improvement in hyperactivity and other problem behaviors with stimulant medication, stimulants may have no effect or may worsen the behavior of those with severe or profound mental retardation. Children with mental retardation are also at a significantly greater risk for the development of side effects (particularly motor tics and severe social withdrawal) from stimulant medications than are children in the general population.

Other Treatments

Some individuals with mental retardation have disorders that compromise their nutritional well-being (eg, phenylketonuria, galactosemia, and maple syrup urine disease) and require specific nutritional interventions. "Fad treatments" consisting of various nutritional, dietary, and hormonal approaches claiming to produce cognitive, behavioral, and emotional changes in individuals with mental retardation flourished in the 1970s and 1980s. Examples of these treatments include supplementation with multi- or megavitamins, minerals, folic acid, and vitamin B_6, as well as dietary manipulations with restrictions of food additives (eg, Kaiser Permanente diet), sugar, and caffeine or the use of serotonin-enhancing diets. However, there is virtually no sound scientific evidence in the literature demonstrating beneficial effects for most of these treatments. We recognize that in the field of mental retardation, with few proven treatments, there is often overwhelming enthusiasm for new treatments regardless of whether there is a good rationale for using them or whether they have been proved efficacious. When counseling a family about "new" or "fad" treatments, the physician must remain sensitive to the family's need to search beyond the realm of current and traditional medicine to find solutions to their seemingly incurable situations. Rather than immediately discouraging the use of all harmless but unproven treatments, a physician should openly discuss with the patient and caregivers what is known about the benefits of a specific treatment approach and any possible adverse effects.

Suggested Readings

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Practitioner and Patient Resources

The Arc of the United States
500 E Border St, Ste 300
Arlington, TX 76010
Phone: (817) 261-6003
TDD: (817) 722-0553
Fax: (817) 277-3491
E-mail: thearc@metronet.com
http://www.thearc.org
The Arc (formerly Association for Retarded Citizens of the United States) is the largest volunteer organization in the United States devoted solely to the welfare of disabled persons and their families. The Arc works on the national, state, and local levels to provide services, guidance, advocacy, free public educational opportunities, and resources to parents and other individuals, organizations, and communities concerned with solving the problems caused by retardation.

Beach Center on Families and Disability
Life Span Institute
1052 Dole Hall
The University of Kansas
Lawrence, KS 66045
Phone: (785) 864-7600
E-mail: beach@dole.Isi.ukans.edu
http://www.lsi.ku.edu/lsi/centers/
The Beach Center on Families and Disability is a research organization that was established in 1988. The Center's central theme is family empowerment through programs of research, training, and information dissemination. These goals are achieved by motivating families to take an active role in finding appropriate services, supporting families to obtain the resources and skills that they and their children need, and building a society that responds to the needs of the family and its children. Educational materials are produced and distributed by the organization, including booklets and brochures on family support issues, abuse and neglect, emotional health.

Council for Exceptional Children (CEC)
1110 North Glebe Road, Suite 300,
Arlington,VA 22201
Voice phone: (703) 620-3660
TTY: (866) 915 5000
FAX: (703) 264-9494
E-mail: service@cec.sped.org
Internet: www.cec.sped.org
The CEC works to advance the special education needs of children with specific learning disabilities. It also serves children with emotional, cognitive, motor, visual, auditory, or communication handicaps, as well as gifted children. The CEC maintains a collection of special education literature for parents, teachers, and administrators through its Department of Information Services. It also coordinates and supports a network of local chapters and state and provincial federations, and it represents specific areas of interest within the field of special education as well.

Mainstream Inc
3 Bethesda Metro Center, Suite 830
Bethesda, MD 20814
Phone: (301) 654-2400
Fax: (301) 654-2403
E-mail: info@mainstreaminc.org
http://www.mainstreaminc.org
Mainstream Inc is a nonprofit organization dedicated to improving competitive employment opportunities for people with disabilities. The organization provides its constituents with training, educational publications, and videos on disability employment issues. Educational materials include a magazine titled "Employment in the Mainstream" that reports on the latest trends and developments affecting the employment of Americans with disabilities. Programs include Project LINK, a model employment service program for persons with disabilities in Dallas or Washington, DC, and the Disability Employment Network, a pilot program that provides counseling and referral services to job hunters in the New York City area.

National Parent Network on Disabilities (NPND)
1130 17th Street NW, Suite 400
Washington, DC 20036
Phone: (202) 463-2299 (V/TTD)
Fax: (202) 463-9403
E-mail: npnd@cs.net
http://www.npnd.org
The NPND is a volunteer not-for-profit coalition of parent organizations, specific disability organizations, and professionals who work with people with disabilities. NPND provides up-to-date reporting on governmental policy and planning, provides a strong advocacy voice to communicate the needs of its members, and maintains a system of sharing experiences that can be used to develop effective policy recommendations. It offers a variety of educational and support materials including, brochures, reports, and a regular newsletter.

Parents Helping Parents (PHP)
The Family Resource Center
3041 Olcott Street
Santa Clara, CA 95054
Phone: (408) 727-5775
Fax: (408) 727-0182
E-mail: info@php.com
http://www.php.com
PHP is a multifaceted, comprehensive parent-directed family resource center for children with any kind of special need (mental, physical, emotional, or learning disabilities). PHP was founded as a parent support group. Now parent support is only one of numerous services offered by this organization.

CHAPTER 54

DOWN SYNDROME

WILLIAM I. COHEN, MD

Down syndrome (DS) is the most commonly occurring genetic disorder associated with mental retardation. Its physical characteristics are distinctive enough that health care providers who have early contact with the newborn— including obstetricians, delivery room and maternity nurses, and primary care physicians—can recognize the disorder relatively easily. This offers the advantage of early identification and treatment of associated serious and potentially life-threatening congenital abnormalities. Nevertheless, families often struggle with the fact they have not had the developmentally typical child they expected.

Physicians should be mindful of the significant difference in perspective between health professionals and educators caring for children with DS and these children's parents. As health professionals, we are educated in a deficit or pathological model (discovering and defining what is wrong with the child). Consequently, we often come in conflict with parents who recognize the value and potential of their child, celebrating their child's achievements and abilities measured against his or her own previous attainment, rather than against a community or general standard. This pride in their child's accomplishments has been augmented by the conscious decision to include these children in the life of the family and, more importantly, the community. In response to the efforts of families, the educational community has begun to appreciate the value of integrated education in preparing young people with DS to live and work in their communities. These changes have accelerated since the closing of public residential institutions, which began 20 to 30 years ago. Previously, infants and babies were removed from their homes and communities when well-intentioned individuals thought that raising a child with a disability at home would be too burdensome. Recent experience has shown how well these children thrive when raised in a personalized, loving environment. The goals of treatment and intervention focus on identifying and treating medical conditions that would serve as barriers to optimal function, overcoming the frequently encountered nihilistic stance: "what do you expect: this baby has DS." As has been true with most of the advancements in caring for people with DS, activist parents have been at the forefront of the movement to encourage the discovery of what might be possible. The recent developments in understanding the biological basis of neural functioning in DS, which have resulted from the Human Genome Project, have provided an enormous amount of information that suggests that it may be possible to enhance cognition, memory, and language skills for people with DS. These exciting developments will be detailed below

Background

In 1865, the British physician John Langdon Down described a group of individuals who were residents of the Earlswood Asylum for Idiots in Surrey, England, where he was superintendent. These individuals with mental retardation had a particular facial appearance and resembled each other. Although they shared many characteristics in common, the biologic basis for this disorder remained unknown until 1959, when Jerome LeJeune determined that all the individuals with these characteristics had a third copy of chromosome 21. The phenotype of DS was found, in 95% of individuals, to represent the genotype of trisomy 21. Trisomies, in general, result from nondisjunction during the first meiotic division, and although they can occur in either parent, 95% of the extra chromosome 21 are of maternal origin. There is a well-documented age related increase in nondisjunction, which has been described as reflecting the loss of particular proteins that play a role in the completion of meiosis I at the time of ovulation. Trisomy 21 is a sporadic, noninheritable event. Nevertheless, the

empirically observed increased risk of having another child with trisomy 21 is reported to be 1:100, or approximately 10 times the base rate of 1:800 to 1,000 live births.

Of babies with DS, 3 to 4% have a translocation (the long arm of chromosome 21 is attached to either chromosome 14 or chromosome 21, resulting in 14/21 or 21/21 translocation). Although two-thirds of these translocations occur at the time of recombination in meiosis, one third of these children will have inherited this translocated chromosome from a parent. That parent is called a balanced carrier, because he or she has only two copies of chromosome 21. It is recommended that parents of children with translocation DS have chromosomal studies to be certain they are not carriers and at risk for having another child with DS in a subsequent pregnancy.

A small percentage of individuals with DS have mosaicism. They have two different types of cells in their bodies: some with the normal number of chromosomes, some with an extra chromosome 21. It is usually thought that children with subtle facial features or with cognitive abilities close to or within the average range invariably have the mosaic form of DS. This has been shown to be incorrect. The degree of mental retardation and the presence or absence of congenital abnormalities or medical problems is related to the specific tissues in the body that contain the extra chromosome.

Diagnosis

The DS phenotype is varied but includes a commonly occurring constellation of features. Hypotonia is most common and, along with characteristic facial features, often suggests the diagnosis in the newborn period. In fact, approximately 75% of all children with DS are identified by 6 months of age. Characteristic features include flat profile, epicanthal folds, upslanting palpebral fissures, depressed nasal bridge, brachycephaly (short anteroposterior measurement of the head), and short ears. Often, there is excess neck skin (nuchal fat pad). In addition, there is often a variety of diagnostic clues in the extremities: clinodactyly (shortened, curved fifth fingers), single palmar crease, wide gap between the toes, and plantar crease (Table 54-1).

In any event, clinical suspicion of DS should lead to determination of the karyotype. When a physician suspects DS, parents often ask how certain they are of the diagnosis. In fact, most physicians have a high degree of certainty in the diagnosis when they order this test. However, it can be useful to express some uncertainty: "I think it's likely, but we won't know with certainty until we get the results back." Families tell us that the possibility of a normal result can be helpful when waiting to find out if the child has DS. It allows them to begin to get used to the idea.

TABLE 54-1. Diagnostic Features of Down Syndrome

Upslanting palpebral fissures	98%
Wide gap between the toes	95%
Nuchal fat pad	87%
Depressed nasal bridge	83%
Brushfield spots	75%
Brachycephaly	75%
Epicanthal folds	60%
Clinodactyly	50%
Single palmar crease	50%

After establishing the diagnosis of DS, the responsible physician has several other important duties: referral to genetics services, medical diagnostic services, developmental services, and family support.

Genetics

A consultation with a medical geneticist or genetics counselor can provide important information about the origin of DS (ie, the nature of nondisjunction) and the risk of having a subsequent child with DS. This is especially important for the child with translocation DS.

Medical Diagnostic Services

Babies with DS have an increased risk for various congenital malformations and appropriate diagnostic evaluations are warranted. Congenital cardiovascular abnormalities occur in approximately 50% of infants with DS, and the high frequency of atrioventricular septal defects, which frequently present without cardiac findings or symptoms, warrants a complete cardiologic evaluation. The high incidence of these abnormalities has led to the availability of screening echocardiography in some tertiary-care centers. DS is associated with a risk of hearing loss (sensorineural as well as conductive), and all infants should be evaluated with an objective measure of hearing, such as an auditory brainstem response test or transient evoked otoacoustic emission test as soon as the diagnosis is made. In hospitals that have instituted universal newborn hearing screening, the primary physician may often get the results of the screen at the same time the diagnosis of DS is considered. On the other hand, these screenings missed 14% of all infants (2003 data) and, therefore, the primary physician must be vigilant to be sure this test is performed.

Gastrointestinal abnormalities occur more frequently in children with DS, and some of them, such as duodenal atresia and imperforate anus, are difficult to miss. On the other hand, Hirschsprung's disease may present more

subtly. An awareness of the increased frequency of this condition will lead to earlier diagnosis, which can be lifesaving.

Children with DS have an increased risk of cataracts, and all infants should be evaluated fundoscopically at birth to detect the presence of dense congenital cataracts, which need to be removed immediately to prevent visual loss. Congenital hypothyroidism is more likely to occur in infants with DS than in typically developing infants, and neonatal screening results should be carefully monitored.

Hypothyroidism, both congenital and acquired, is a significant source of developmental morbidity for children with DS.

Infants with DS have increased medical vulnerability in a number of areas, and physicians and families should monitor for these issues. For example, low muscle tone and poor coordination of suck and swallow can lead to feeding difficulties. Such difficulties warrant a referral to a feeding specialist, such as an occupational therapist or speech-language pathologist with expertise in treating oral-motor problems. Feeding difficulties may be further compounded by gastroesophageal reflux disease.

Developmental Services

All children with DS are eligible for early intervention (infant stimulation) services, which are provided for children from birth to 3 years of age by federally funded programs that are administered locally. (There are no out-of- pocket costs to the family, and the services are provided in the family home.) Children are initially assessed and then receive various services appropriate to their ages and needs. These services include those of a developmental specialist and may include, at various times, physical, speech-language, and occupational therapies.

Family Support

Primary-care physicians aid parents by becoming knowledgeable about the kinds of family support available in the local community. Organizations such as Parent-to-Parent or the local chapter of The Arc (a national advocacy organization to support individuals with developmental disabilities) Association for Retarded Citizens can provide information about support groups or one-to-one meetings with parents of children with similar medical and developmental problems. Most parents report that their contact with other families who have experienced similar problems is most useful in developing coping strategies. Your community may have a regional DS organization, affiliated with one of the national DS groups (see Practitioner and Patient Resources.)

Medical Vulnerability

Otolaryngologic Problems

Ears, nose, and throat (ENT) problems are common in children with DS. Because of the characteristic midfacial hypoplasia, manifested as narrow airways, eustachian tubes, sinus ostia, and external auditory canals, children with DS are at increased risk for recurrent otitis media, nasopharyngitis or sinusitis, and the consequences of serous otitis media. This is of particular significance, given the well-known difficulties in expressive language development in children with DS. The medical team caring for the child must ensure his or her hearing is optimized to avoid the undesirable consequence of suboptimal language development. Children with DS have frequent episodes of croup, and this may reflect silent reflux causing upper airway irritation. These children may require laryngobronchoscopy to make the diagnosis.

There is growing evidence of a wide variety of sleep abnormalities in children and adults with DS, and clinicians should consider an evaluation by a sleep center if symptoms are present. Anatomic features contribute to an increased incidence of obstructive sleep apnea. Even normally sized tonsils and adenoids may lead to relative obstruction, and adenoidectomy or tonsillectomy may be indicated in the presence of obvious symptoms. However, children with DS often are restless sleepers, awakening or at least arousing several times during the night. Some youngsters sleep sitting up and leaning forward. It is unclear whether this represents undetected airway obstruction without apnea (related to the collapse of the airway and the arousal of the child in response) or a separate, central phenomenon. In addition to the negative consequences of hypoxemia and disordered sleep on daytime wakefulness (which may lead to behavioral abnormalities such as ADHD symptoms and to learning problems) untreated obstructive sleep apnea has been associated with significant cardiac morbidity, such as pulmonary hypertension. However, parental reports of abnormal sleep do not correlate well with the results of sleep studies. One recent study of children with DS showed that 80% had abnormal sleep evaluations when abnormal arousals were included. Therefore, clinicians should strongly consider an evaluation by a Pediatric Sleep Center in the face of these symptoms, including a full polysomnogram. Although adenotonsillectomy is the first procedure performed, 50% of patients may still have obstruction following this procedure, and therefore, a post-operative sleep study is needed to define the nature of the residual obstruction, which might include glossoptosis, hypopharyngeal collapse, lingual tonsillar hypertrophy, or in the case of previous adenoidectomy, adenoidal regrowth.

Ophthalmologic Conditions

Children with DS have an increased risk of cataracts. All infants should be evaluated at birth to detect the presence of dense congenital cataracts, which need to be removed immediately to prevent visual loss. The midfacial hypoplasia, described above, often leads to nasolacrimal duct stenosis. This can be treated conservatively, although surgical intervention is occasionally required. An increased incidence of refractive errors in children with DS and strabismus is common. Adolescents and adults are at risk for keratoconus.

Endocrine Abnormalities

In childhood and adolescence, hypothyroidism occurs frequently, in approximately 15% of the population. Most of these cases are autoimmune in nature (Hashimoto's thyroiditis). Autoimmune thyroiditis occurs, as well, though less frequently. A recent population-based study of newborns with DS suggests that a "mild form congenital hypothyroidism that is rarely detected by neonatal screening." Thyroid supplementation in a group of these infants led to small but statistically significant increases in motor development, length and weight. These findings have not been replicated as yet, but are suggestive of the need for sensitivity to the subtleties of thyroid disorders in children with DS, where there are mild elevations of TSH in the face of Free T4 levels at the low end of the range of normal.

Hematologic Problems

Infants with DS often present with polycythemia, which quickly resolves. However, partial exchange transfusion may be required to treat symptomatic individuals. Erythrocytes show a persistent macrocytosis in two-thirds of individuals with DS. This may be present in the face of iron deficiency anemia, and give false reassurance. Thrombocytopenia occurs commonly in newborns with DS and it is usually transient although it may be seen as a part of a transient myeloproliferative disorder (TMD), which is found in 10% of infants. This condition, manifested by pancytopenia, hepatosplenomegaly and circulating immature white blood cells regresses spontaneously within the first 3 months of life. However, 20 to 30% of these children go onto to develop leukemia. DS is the most common factor predisposing to childhood leukemia: approximately 1% of children with DS develop one of four kinds of this disorder. This is between 10 to 20 times the frequency that is observed in typically developing children. Half of the leukemias are lymphoid and the other half are myeloid. Most of the myeloid leukemias are acute megakaryocytic leukemia (AMKL). Both TMD and AMKL are associated with somatic mutations of the GATA1 gene, which encodes hematopoetic growth factor. AML in children with DS have extremely high rates of remission and very low rates of relapse, compared with typically developing children. In addition, DS children need lower doses of chemotherapy. Bone marrow transplantation has not been necessary. Most children under 4 years of age who have DS develop nonlymphocytic leukemias, which appear to be extremely responsive to chemotherapy: In one series of 33 patients, all achieved a complete remission and the group had an 80% estimated 8-year survival rate.

Gastroenterology

Gastroesophageal reflux (GERD) occurs commonly in babies with DS, especially those with cardiac disease. The primary physician should be mindful for occult reflux and aspiration, which may present as croup or recurrent pneumonia. Feeding disorders may reflect oral-motor coordination difficulties as well as sensory issues which interfere with the ability to tolerate different textures and tastes. Celiac disease (gluten enteropathy) is reported to occur in 7 to 14% of individuals with DS. In addition to the usual symptoms of bloating, diarrhea, and failure to thrive, children with DS may have no symptoms of malabsorption, and may present with constipation, failure of linear growth or present with behavioral abnormalities. Serological screening using IgA tissue Transglutaminase antibody will indicate those children who need a referral to a gastroenterologist for a biopsy to confirm the diagnosis. This is necessary before beginning treatment with a gluten-free diet. The Down Syndrome Medical Interest Group (US) currently recommends screening children at 2 years of age. Celiac disease can occur as soon as 6 months following the exposure to gluten. Likewise, it may not manifest itself for several years after the initial exposure. Clinicians must be sensitive to the various manifestations of celiac disease, both the gastrointestinal as well as the multiple non-GI symptoms and re-evaluate the child accordingly.

Autoimmune Disorders

The increased incidence of autoimmune disorders leads to a higher incidence of both hypo- and hyperthyroidism (2% in a Swedish longitudinal study), celiac disease, juvenile-onset diabetes mellitus, juvenile rheumatoid arthritis, and alopecia areata.

Musculoskeletal Disorders

Ligamentous laxity is a common finding in children with DS. These children exhibit hypotonia and appear floppy and flexible. It is quite rare to see congenitally dislocated hips in children with DS, although hip problems do occur in adolescence. Adolescents also are prone to patellar dislocation.

The most potentially serious problems caused by ligamentous laxity are related to the occiput and cervical spine. Laxity of the transverse ligaments can lead to

excessive movement of C1 and C2. A small percentage of individuals with DS (estimated at 2%) will develop spinal cord compression from this excess movement. Approximately 13% of individuals with DS have > 4.5 mm distance between the atlas and the dens on lateral cervical spine radiographs when comparing full flexion and full extension. These individuals have been described as having "atlantoaxial instability" (AAI) and have been, in the past, considered at risk for the development of spinal cord compression. The belief that AAI was an asymptomatic precursor of cord compression, as well as the desire to prevent any possible injury, led to the recommendation that all individuals participating in Special Olympics have such studies performed. However, recent reviews of the literature have suggested that such screening may not be necessary and that individuals who are at risk for such spinal cord catastrophes either have symptoms or signs, such as neck pain, gait disturbance, bladder or bowel problems, or hyperreflexia and abnormal Babinski's sign, or have been subject to manipulation of the neck (Cohen, 1998). This has led to the recommendation of universal precautions in administering anesthesia to children with DS, especially for ENT procedures. The presence of signs or symptoms warrants further neuroradiologic evaluation (magnetic resonance imaging). Symptomatic individuals must be referred for neurosurgical evaluation and treatment, which consists of fusion of C1 and C2.

Current recommendations for screening include lateral cervical spine films (flexion, extension, and neutral) and measurement of the neural canal width between 3 and 5 years of age. (The neural canal width should be > 14 mm.) Participants in Special Olympics may need to have more frequent studies. It should be noted that adults with DS are at greater risk for cervical spine abnormalities, as a result of anatomic predisposition as well as the early onset of arthritic changes.

Neurologic Disorders

Epilepsy

Although seizures occur more frequently in individuals with mental retardation than in the typical population, the frequency of seizures in individuals with DS ranges from 5 to 10%. One-half these seizures can be attributed to an underlying medical problem (such as cardiovascular disease, infection, trauma, perinatal problems, or, more rarely, moyamoya disease). Consequently, a full investigation is warranted. The other 50% are idiopathic. A recent retrospective study of 350 Israeli children and adolescents with DS (performed between 1985 and 1997) showed that 8% had epileptic seizures, 47% had partial seizures, 32% had infantile spasms, and 21% had generalized monoclinic seizures. In this group, neurodevelopmental outcome of children with infantile spasms was poor, in spite of adequate seizure control (Goldberg-Stern et al, 2001). In other series, however, timely recognition of this disorder, along with rapid institution of treatment, correlated with better outcomes. Those who had a delay in beginning treatment and who had a long time until the spasms stopped had a lower developmental quotient and a higher incidence of autistic features (Eisermann et al, 2003). Vigabatrin, which is not currently available in the United States, has been associated with rapid cessation of spasms.

Autistic Disorders

These disorders are more prevalent in children and adults with DS. Whereas the incidence of autism in the general population is reported at 15 per 10,000 population, current evidence suggests that the prevalence in DS is approximately 5 to 10%. In addition to an early onset of symptoms, children with DS seem more likely to develop the so-called disintegrative form of autism, in which a child with adequate development of cognitive, language, and adaptive skills undergoes a dramatic regression with the emergence of typical autistic features. These children warrant a full investigation and should be considered for prolonged video electroencephalographic evaluation.

Attention-Deficit Hyperactivity Disorder

This common neuropsychiatric disorder occurs more frequently in children with DS (and mental retardation in general) than in typically developing children. It is important to control for the child's developmental age when using standardized ratings. Be mindful of underlying undiagnosed medical problems, such as hyperthyroidism, hearing loss, sleep disturbances (with or without sleep apnea) which may be responsible for the inattention and/or over activity. Generally, children with DS respond well to current medical management with stimulant therapy although it is wise to start with smaller than usual doses, because of heightened sensitivity to psychoactive medications.

Other Neurobehavioral Disorders in Children

In addition to AD/HD, children with DS commonly manifest oppositional-defiant disorder, disruptive disorder, and stereotypic movement disorder. Adolescents and adults with DS may manifest depressive disorders, obsessive-compulsive disorders, and a peculiar psychotic-like disorder. These are described in greater detail in Capone's (2006) review of the subject.

Alzheimer Disease

Parents of newborn babies with DS have often heard about the association of DS with Alzheimer's disease (AD), and although this is not a condition that appears in childhood, the question of the likelihood of it developing later may well arise. DS has been associated with premature aging.

This has manifested in various ways, for example, early onset of presbyacusis (age-related hearing decline) and changes in skin tone (early wrinkling). A number of studies of institutionalized adults with DS had suggested a very high degree of dementia. Neuropathologic study of these individuals revealed the typical findings of neurofibrillary plaques and neuritic tangles, consistent with AD. The presence of the gene that codes for amyloid precursor protein (APP) on chromosome 21 lent further credence to the anticipation that three copies of this gene lead to an excess of APP and, therefore, AD. However, careful study of this issue has revealed that the incidence of true AD is much lower. The presence of these findings in the brain has not inevitably correlated with symptoms of AD. One of the greatest sources of confusion has been the uncritical attribution of a change in behavior to dementia. Many conditions, most of which are treatable, lead to behavior change in individuals with DS. The most common is depression, either endogenous or exogenous. Undetected hypothyroidism also can lead to depressive symptoms. Furthermore, care must be taken to distinguish normal, age-related decline in function from that seen in individuals with dementia. In a series of 148 adult patients referred to the Adult Down Syndrome Clinic at Lutheran General Hospital in Chicago to evaluate decline in function, only 11 of 148 met the criteria for progressive and nonreversible decline and deterioration and would, therefore, merit the diagnosis of AD (Chicoine et al, 1999).

Complementary and Alternative Therapies

Many parents learn about a variety of complementary and alternative therapies for children with DS, sometimes from other parents, often through the Internet. These include nutritional interventions (such as multivitamin, mineral, and amino acid combinations) that are purported to enhance learning, improve muscle tone, and decrease medical complications. In addition, some parents may pursue chiropractic treatment, neural enhancers, facial plastic surgery, and other interventions they hope will improve the lives of their children. Attempts to scientifically document the benefits claimed have been unsuccessful. (More information about this topic is available at <http://www.dshealth.com.>) The great interest in these treatments reflects parental hopes that their child might be spared the consequences of the cognitive disabilities so often associated with DS. Cooley has provided a compassionate guide for discussing these issues with parents.

Investigations in Interventions to Improve Cognition and Memory

The possibility of enhancing memory and learning now appears to be more than a dream. The development of an animal model of DS (the Ts65dn mouse which is trisomic for about half of the genes on human chromosome 21) has provided molecular biologists the opportunity to explore the consequences of the overexpression of genes contained on chr 21. Neuroscientists have demonstrated the same structural abnormalities of the hippocampus and the cholinergic pathways through the basal forebrain nuclei in these mice as are found in human brains. Further study has revealed abnormalities of synaptic function, with an increase of inhibitory control (specifically an increase in GABA A receptors) which is now believed to play a role in interfering with optimal learning and memory. Other studies of cerebellar structure reveal deficits in the granule cell layer development that may correlate with the decreased cerebellar volume found in these mice and in individuals with DS. The overexpression of APP has been implicated in interfering with axonal function in these mice. Preliminary investigations suggest that a variety of pharmacologic interventions may ameliorate or partially correct these deficits later in life. Although the development of specific treatments will likely take quite some time, these findings have galvanized the biomedical community and families alike.

Developmental and Educational Issues

DS is associated with mild to moderate mental retardation. A number of individuals are more capable, functioning in the normal range of cognitive abilities. Whereas most adults with DS require some supervision in their living and work environments, a small but increasing number of young adults live independently. Many of them are employed as self-advocates for themselves and others with developmental disabilities.

Speech and Language Needs

An important part of the developmental profile of individuals with DS is the greater delay in expressive language function than in cognitive abilities and receptive language. "When will my child start talking?" is the most common question asked by parents of young children. The problem appears to relate to difficulty in phonologic mapping. Speech-language clinicians encourage the use of total communication with young children with DS, including instruction in sign language, as a bridge to effective communication while working on verbal communication as well. Children with DS have strong visual skills, and this has been used to teach reading, which, in turn, has improved language skills. Unlike other conditions with language disabilities, adolescents and adults with DS can continue to develop verbal language, and they should be afforded the opportunity to receive appropriate services in this area. For those individuals who do not develop functional expressive language, augmentative communication devices are indicated.

Education

The Individuals with Disabilities Education Act (IDEA) is a federal law that provides funds for special education for individuals with disabilities. In addition to funding early interventions services for children from birth to 3 years of age, IDEA mandates that the educational system (local school district) take responsibility for providing for the developmental and educational needs of the child through his or her 21st birthday. Many children enter preschool programs for children with developmental disabilities where the same types of services provided by the early intervention system in the home are available. Some parents also enroll their children in preschool programs for typically developing children, recognizing the benefit of exposure to typically developing children.

Traditionally, most children with special needs have been served in categorical programs and segregated environments. Children who were not successful in regular classroom situations were often pulled out for services, which were delivered in resource rooms for children or self-contained classes for children with learning disabilities or mental retardation. Recently, families have become aware of the value of educating their children alongside peers, in so-called "inclusive" settings. The services that the child may need are then provided in the regular classroom. These practices have several advantages. They help the child to generalize information across settings and they allow educators to incorporate physical therapy, occupational therapy, and speech-language strategies throughout the school day.

One warning: inclusive education should be a choice that parents make. Well-intentioned friends, educators, or physicians should not impose this on the family, because in education, as in the rest of life," one size does *not* fit all." Parents should be aware of all methods of educating children with special needs and should have the option of choosing the program in their school district that best meets their child's needs.

Health Care Guidelines

The frequency of detectable and preventable medical conditions has led to the development of various screening protocols for infants, children, and adults with DS. "Health Care Guidelines for Individuals with Down Syndrome" is currently available in a 1999 revision. It lists recommended laboratory tests and medical consultations by age. The current version was compiled by the Down Syndrome Medical Interest Group (United States) and developed in conjunction with the Committee on Genetics of the American Academy of Pediatrics, whose most recent revision of "Health Guidelines for Children with Down Syndrome" was published in *Pediatrics* in 2001. Although not identical, these documents are in general agreement. (Note: These protocols are designed to supplement, not replace, the standard well-child care protocols of the American Academy of Pediatrics and the American Academy of Family Physicians.) An updated version is expected in early 2005.

What follows is a brief summary of screenings and consultations recommended for the optimal care of the child with DS:

Birth

- Cardiac evaluation (should include echocardiogram)
- Objective hearing evaluation (auditory brainstem response test)
- Ophthalmoscopic exam to detect dense congenital cataracts
- Thyroid function testing (check state-mandated screening)
- Referral for early intervention
- Discussion regarding availability of family support
- Medical genetics consultation, as indicated, regarding discussion of future risk in subsequent pregnancies. The parents of any child with translocation genotype must have a karyotype to be certain they are not balanced carriers.

First year of life

- Periodic hearing evaluation (every 6 months) until pure tone audiograms can be performed, then yearly.
- Eye examination by pediatric vision specialist by 6 months
- Thyroid function testing (TSH and free T4) at 6 and 12 months Ages 1 to 12 years
- Continued periodic hearing evaluations
- Continued eye examinations
- Yearly thyroid function testing
- Screening for celiac disease (beginning at 2 to 3 years of age), repeated every 2 years
- Lateral cervical spine radiography (flexion, neutral, and extension), measuring the atlanto-dens interval and the neural canal width, between 3 to 5 years of age, looking for atlantoaxial instability

Adolescence

- Continued yearly thyroid function testing
- Continued periodic vision and hearing assessment
- Adolescent medicine consultation regarding sexual health concerns
- Educational programming with a focus on transition planning

Families currently obtain large amounts of information about DS from a variety of sources. Shortly after the birth of the baby (or after prenatal diagnosis), community-based parent groups (often in partnership with clinical programs providing consultative medical care to individuals with DS) can provide the family with extensive information about

DS. Examples of materials provided include books on health and development, videos describing typical reactions to the unexpected birth of a baby with DS, information regarding parent support meetings, pamphlets on breastfeeding, and information on accessing developmental services. The Internet is often accessed as a source of information about DS, though the reliability of that information can vary. The primary care physician should anticipate that the family will be knowledgeable and often is looking to partner and collaborate with the physician. When based on trust and mutual respect, this collaboration can provide enormous satisfaction to all, focusing on optimal medical, developmental, and emotional outcomes.

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Down Syndrome: Health Issues
http://www.ds-health.com
This is the most comprehensive DS site on the Internet. Developed by Dr Len Leshin, a pediatrician who has a son with DS, it features a comprehensive listing of medical, scientific, and practical information about DS, as well as DS organizations and clinics worldwide. It lists contact information for many local and state or provincial parent groups providing family support.

Down Syndrome Quarterly
http://www.denison.edu./dsq
Down Syndrome Quarterly is an interdisciplinary journal devoted to advancing the state of knowledge on DS and covers all areas of medical, behavioral, and social scientific research. The 1999 "Health Care Guidelines for Individuals with Down Syndrome" are available online at <http://www.denison.edu/collaborations/dsq/health99.html>

National Down Syndrome Society
http://www.ndss.org
The mission of the National Down Syndrome Society is to benefit people with DS and their families through national leadership in education, research, and advocacy.

National Down Syndrome Congress (NDSC)
http://www.ndsccenter.org The purpose of the NDSC is to promote the interests of persons with DS and their families through advocacy, public awareness, and information dissemination on all aspects of DS.

Chapter 55

Other Chromosomal Disorders

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While Down syndrome is the most common chromosomal abnormality that is associated with mental retardation, child neurologists, developmental pediatricians, geneticists, and other specialists will frequently encounter and care for disabled children whose handicaps are secondary to other defects in chromosomal number or structure. Clinicians who provide initial evaluations and long-term follow-up care of these patients should be familiar with the developmental features of these various chromosomal disorders and the genetic mechanisms that underlie their pathogenesis.

Clinicians who evaluate infants and children with mental retardation or birth defects including an assortment of other neurologic manifestations must consider a wide variety of etiologies when attempting to determine the cause of a developmental handicap in any particular patient. A vast number of congenital and acquired disorders of the central nervous system may be responsible for the slow or incomplete acquisition of developmental milestones. As part of the assessment of these patients, a thorough perinatal and family history must be obtained. Together with a complete neurologic examination, these children will also need to be checked for signs of multiorgan involvement. When this history and physical assessment suggest a congenital cause of mental retardation, a primary disorder of chromosomes may be uncovered through a variety of cytogenetic tests.

Chromosomal disorders result from imbalance of genes, either from a gain or from a loss of chromosomal material and may involve either the sex chromosomes and/or the autosomes. This widely diverse group of disorders includes those due to a divergence of chromosome number from the usual diploid count of 46 chromosomes (these disorders are termed aneuploidies), such as Down syndrome, discussed elsewhere in this book. The other main category of chromosomal disorders are aneusomies, which are due to either net loss or gain of genes from a variety of chromosomal rearrangements of either a whole or portion of a chromosome(s). Such rearrangements may include deletions, duplications, translocations, inversions, isochromosomes, supernumerary marker, and ring chromosomes. On occasion, human disorders are also caused by aberrant chromosomal mechanisms, such as disorders, due to imprinting and mosaicism.

Abnormalities in autosomal chromosomes cause mental retardation, growth deficiency, and multiple congenital malformations. Certain features are suggestive of a chromosomal abnormality and necessitate prompt cytogenetic testing. These features include newborns that are small for gestational age and older children with small stature, poor somatic growth, or overgrowth. Further, young adults, children, and newborns with multiple congenital abnormalities (including dysmorphisms, microcephaly, and macrocephaly) also strongly suggest a chromosomal causation. Together with developmental delay and later, frank mental retardation, other neurologic features of children with chromosomal abnormalities would include epilepsy, upper motor neuron signs, central hypotonia, associated congenital ophthalmologic anomalies, and deficiencies of the special senses, as well as recognizable patterns of brain dysgenesis or malformation (such as holoprosencephaly or polymicrogyria). Features such as these should raise the clinician's index of suspicion, and an evaluation for a chromosomal disorder should be initiated, if no alternative diagnosis or single-gene disorder is apparent.

The yield for cytogenetic analysis is higher in those individuals with the early onset of growth and developmental problems including multiple malformations, growth delay, short stature, ambiguous genitalia, tumors and mental retardation, a family history of chromosomal abnormalities in a close relative, and in the offspring of women with a history of prolonged infertility, advanced maternal age, a history of stillbirths, neonatal demise or early pregnancy losses.

Pathogenesis of Chromosomal Disorders

The correct chromosome count in humans, 46, was first made in 1956, and thereafter, the first set of human disorders due to chromosome abnormalities, such as Down, Turner, and Klinefelter syndromes and Cri du Chat syndrome, were identified by investigators. The prevalence of chromosomal abnormalities is, in part, dependent on the time of sampling and testing. In reality, the estimates of prevalence depend, in part, on ascertainment methods/biases and the quality of cytogenetic testing used.

Chromosomal abnormalities are highly prevalent in spontaneous pregnancy losses with at least half of the 15 to 20% of all conceptions that are lost spontaneously being due to a lethal chromosomal abnormality, mainly triploidy (69 chromosomes) and autosomal trisomies (three copies of a chromosome). In newborns, chromosomal abnormalities occur in about 1 in 100 births and are split between sex and autosomal chromosome anomalies. In patient groups with moderate and severe mental retardation, chromosomal disorders may underlie as high as 50% of all cases. With higher resolution of chromosomal testing and implementation of molecular cytogenetic testing, even higher contributions of previously undisclosed chromosomal disorders to these patient groups may be expected overtime. The effect on the child is dependent on the precise abnormality, but in general, aneuploidy affecting the sex chromosomes is much less deleterious to the child than an autosomal aneuploidy.

Human somatic cells are diploid in their chromosome complement (2n = 46 chromosomes with 23 pairs of chromosomes) bearing two copies of the genome. However, some cells, such as myocytes, contain several nuclei, rendered polyploid through cell fusion. Somatic cells divide by mitosis throughout life, and faithful chromosome replication in the cell cycle (mitosis) ensures production of daughter cells with nearly identical DNA and genomes. Rarely, disruption of mitosis may result from single-gene inherited disorders known in the past as chromosome breakage syndromes and now with genetic identification now more precisely classified as DNA repair defects: these are almost all autosomal recessive disorders. Although rare, these disorders include ataxia-telangiectasia (AT), Nijmegen breakage syndrome, xeroderma pigmentosa, Fanconi anemia, cerebro-oculo-facio-skeletal syndrome (COFS)/Cockayne syndrome, and several others. AT is well known to neurologists and is covered elsewhere in this book. In general, these disorders encompass neurologic problems, such as microcephaly, mental retardation, spasticity, basal ganglia calcifications and ataxia, growth deficiency (sometimes extreme), skin photosensitivity and other skin changes, immunodeficiency, eye signs, other congenital anomalies, and early onset often fatal, malignancies. As such, they may well suggest a chromosomal disorder to the alert neurologist. Specialized chromosomal breakage studies are often undertaken as a prelude to precise gene-based DNA confirmation.

Germ cells (sperm and eggs) are haploid ($n = 23$) and result from the reduction-division process known as meiosis; here chromosomes play the pivotal role in determining human variation by way of recombination in the first part of meiosis (meiosis I). Meiosis is preceded by DNA replication (2n to 4n) and then, the two reduction divisions of meiosis, proper follow. The first meiotic division involves pairing of the parental homologues, exchange/recombination of genetic material between chromosome arms then ensues, followed by separation of the homologues (4n to 2n). This separation is termed disjunction and its fidelity is crucial. The second meiotic division (meiosis II) then reduces the spermatozoa and eggs to the haploid state (2n to n). Again, accurate separation or disjunction is needed. Aberrations of meiosis produce the classical chromosomal disorders listed in Tables 55-1 and 55-2 and result in either numerical errors of chromosome number or aneuploidies (see Table 55-1) or structural anomalies involving abnormal chromosome breakage and rejoining or aneusomies (see Table 55-2).

The Cytogenetic Evaluation of Patients for Chromosomal Disorders

Cytogenetic analysis is usually carried out on cultured white blood cells from a peripheral blood sample but may also be performed on skin fibroblasts, amniocytes, chorionic villus cells, bone marrow cells, amongst other cell types. For disorders in which chromosomal mosaicism (where more than one cell line exists in a child which is derived from a single zygote) is suspected then sampling of an additional tissue for chromosomes (usually skin fibroblasts) is indicated as the chromosome abnormality is often not present in peripheral lymphocytes. Suspicion for a mosaicism is prompted either from recognition of a distinctive phenotype, such as tetrasomy 12p/Pallister-Killian syndrome or more often, from particular clinical pointers, such as changes in skin pigment, including the phenotype known as hypomelanosis of Ito and asymmetry of limbs.

TABLE 55-1. Numerical Aberrations: Other Than Polyploidy These are Due to Failed Normal Chromosomal Separation During Meiosis; *Nondisjunction*

Type of Disorder	Example	Outcome
Polyploidy	Triploidy, 69 chromosomes, results from two sperm or egg + polarbody contribution to fertilization	Fetal demise
Aneuploidy (autosomal)	Additional chromosome 18	Trisomy 18: MCA, demise
	Additional chromosome 13	Trisomy 13: MCA, demise
Aneuploidy (sex chromosomes)	45,X	Turner syndrome: MCA
	47,XXY	Klinefelter syndrome: mild
	47,XXX	Triple X syndrome: mild

MR = mental retardation; MCA = multiple congenital anomalies.

TABLE 55-2. Structural Aberrations: Abnormal Chromosome Breakage and Rejoining

Type of Disorder	Examples	Outcome
Deletion	Terminal deletion of chromosome 5p	Cri du chat syndrome: MCA/MR
	Interstitial deletion of chromosome 22q11.2	Velo-cardio-facial syndrome: MR/MCA with CNS malformations
Duplication	Tetrasomy 12p; four copies of the short arm (p) of chromosome 12, present in mosaic form	Pallister-Killian syndrome: MCA/MR
Inversion	Pericentric inversion chromosome 9	No ill effects, normal variant Others may be unbalanced especially, paracentric
Translocation		
1) Reciprocal: Describes an exchange of chromosome segments without (balanced) or with (unbalanced) net gain/loss of genetic material	Balanced: 46,XX,t(7;22) (q32;q11.2)	No ill effect known, unless de novo and then associated with MCA/MR
	Unbalanced: 46, XY, t (4:17) (p15.2;q25)	MCA/MR; effects from trisomy (three copies of chromosome segment, 4pter-15.2), and/or from the monosomy (one copy of a chromosome segment, 17q25-qter)
2) Robertsonian balanced or unbalanced	As above, involves acrocentric chromosome 13, 14, 15, 21, 22 only. Carriers have only 45 chromosomes because the acrocentric chromosome q arms join to make a single chromosome but are not unbalanced (redundancy of the acrocentric short arms)	

CNS = central nervous system; MR = mental retardation; MCA = multiple congenital anomalies.

In the laboratory, mitosis is arrested at metaphase when the chromosomes are most visible and then stained with Giemsa (G-banding), although a variety of other stains are also available for specialized applications. The chromosomes are then analyzed by light microscopy for numerical count and structure. The chromosomal status of any cell is termed the karyotype, and reports of a karyotype follow the International System for Human Cytogenetic Nomenclature (ISCN). The short arm of the chromosome is annotated as "p" (after *petit*, little, from the French language), the long arm is "q" (following p), the centromere as "cen," and the terminus of the chromosome or telomere as "tel."

With the G-banding technique, staining of light (containing GC-rich regions and relatively gene rich) and dark bands (containing AT-rich regions and relatively gene depleted) of the p and q arms of any chromosome occurs. These bands and their positions are then compared with ISCN standards to determine their structural integrity. By this means, a light-microscopy-based karyotype is generated for each metaphase cell examined. However, significant limitations to this light microscopy evaluation exist, notably the lack of resolution or consistent ability to detect either loss (deletion) or gain (duplication) of genetic material below 5 million base pairs, where such intervals may harbor tens to even, hundreds of genes.

In response to the challenge posed by the lack of resolution to the individual gene level of light microscopy, molecular cytogenetic protocols were developed to interrogate submicroscopic genetic regions and hence individual genes. These approaches all take advantage of the ability of short

stretches of single-stranded DNA acting as a DNA probe to hybridize (bind) to its unique location in the genome, in this case conveniently represented as a metaphase spread of chromosomes. The binding of the selected DNA probe or hybridization can be confirmed by detection of fluorescence if the probe is tagged with a fluorescence dye using fluorescence microscopy with appropriate filters.

Currently, these types of evaluation are now commonplace and include fluorescence in situ hybridization (FISH) studies. In this approach, hybridization of a single-stranded DNA probe (labeled with a fluorescent dye) derived from a precise chromosomal/genetic locus to a patient's metaphase chromosomes is performed to determine the integrity; that is, either the presence, absence, abnormal copy number, or changed location of the hybridization signal for that particular locus in the patient sample. In this way, a deletion (absence of hybridization), duplication (increased copy number), translocation, or inversion (changed location) of a genetic locus may be determined using the fluorescent dye-labeled DNA probe.

A FISH study can also be performed using more than one probe in a single study (multiplexing) so that a numerical count can be done usually carried out just for the chromosomes of interest. For example, using FISH probes for chromosomes 13, 18, and 21, the most common human trisomies can be identified in prenatal screening protocols. This latter approach can also be adapted to nonmitotic cells when the chromosomes are resting (in interphase) to obviate the need to induce cell division in the laboratory and thereby significantly reduce the test time (turnover).

Specific structural anomalies can be identified by FISH testing, such that absence of a hybridization signal for a FISH probe reveals a deletion to be present (therefore, causing a monosomy for that gene/locus represented by that probe) or an additional signal for a FISH probe reveals a duplication (therefore, causing a trisomy). If an abnormal location on the chromosomes is detected for the hybridization, this might suggest a translocation, inversion, or duplication to be present.

A well-known example of this diagnostic approach is the routine evaluation of the critical interval for a suspected case of velo-cardio-facial syndrome at chromosome 22q11.2, using the TUPLE1 FISH probe. Again, multiple loci can be evaluated for known or novel structural aberrations using different fluorescence tags for each FISH probe, as occurs in the commonly performed FISH analysis of multiple chromosome subtelomeres to evaluate these relatively gene-rich regions located adjacent to the telomeres of chromosomes for rearrangements in cases of idiopathic mental retardation or unexplained multiple congenital anomalies or growth deficiencies.

Subsequently, screening evaluation of the genome at representative intervals (eg, every 1 million base pairs) or at selected locations associated with human disorders has been proposed and undertaken by extensions of FISH technology using microarray-based comparative genomic hybridization (CGH) studies. Here, a gene chip or microarray is manufactured so that the DNA probes representing the human genome (at the chosen intervals) are immobilized on a glass slide. Patient's fluorescence dye-labeled DNA (eg, labeled with Cy3 green) along with control reference DNA labeled with a different fluorescence dye (eg, Cy5 red) is then simultaneously hybridized to this microarray. Digitized analysis of the microarray dye signals via an automated reader facilitates quantitation of hybridization at all sites performed in replicates for quality control. The quantifiable output of the study ranges from a pure yellow signal (ie, equal red and green hybridizations) representing no departure from normal (wild-type), to an excess of digitized red signal representing potential patient loss of genetic material (a putative deletion), to an excess of digitized green signal representing a potential patient gain of genetic material (a putative duplication). Parental testing is often necessary outside known established diagnoses because some putative deletions or duplications discovered by this approach may actually represent examples of normal human variation (polymorphisms) as evidenced by being present in a healthy parent and therefore noncausative.

Gene chips fall into two broad categories at the present time; specific-targeted arrays designed to test known human deletion-duplication disorders and the subtelomeres, or genomic screening arrays, which have large research applications at this time but in due course will be applied to clinical testing and may eventually provide a high-resolution means of surveying the chromosomes. In the latter instance, it is possible to envisage that this technology may eventually replace conventional light-microscopy-based karyotyping, but rigorous evaluations prior to clinical applications will be needed.

Examples of Chromosomal Disorders with Neurodevelopmental Features

Trisomy 18 Syndrome

After Down syndrome, trisomy 18 is the second most common chromosomal disorder and is associated with a wide variety of congenital anomalies. The incidence of trisomy 18 is 3 per 1,000 births with a 3:1 ratio of females to males. The majority of affected newborns are critically ill and expire within the first weeks of life with a median survival of 14.5 days. Only 5 to 10% of these patients live beyond 12 months of age, and these children have significant mental retardation and motor handicaps. Typical neurologic and dysmorphic features include reduced activity and a week cry, prominent occiput, low-set malformed ears, and micrognathia. Less frequently, these

infants have gross malformations of the central nervous system including microgyria, hypoplasia of the cerebellum, abnormalities of the corpus callosum, hydrocephalus, and spinal dysraphism. Common systemic features of this disorder that are present at birth include a clenched hand with overlapping of the fifth finger over the fourth and the index finger over the third, a short sternum, midline abdominal defects, such as diastasis recti or abdominal hernia, and a cardiac septal defects. A variety of gastrointestinal, renal, skeletal, and cardiac defects have also been reported. Given the severity of this multiple malformation syndrome, once a suspected diagnosis of trisomy 18 is confirmed via cytogenetic studies, a frank discussion with the parents regarding the prognosis needs to be held, and this should include counseling regarding a possible decision to restrict medical procedures that would prolong the survival of the infant. An accurate cytogenetic diagnosis is essential, as cases of mosaicism and partial trisomy 18 variants have been reported. These incomplete cases of trisomy 18 may be less severely affected and have a longer life span with less severe mental and motor handicaps.

Trisomy 13 Syndrome

Infants with trisomy 13 have significant involvement of the central nervous system and as such are at high risk of profound mental retardation. This chromosomal disorder occurs with an incidence of 1 in 5,000 births and the median survival is 7 days. Holoprosencephaly and other forebrain developmental anomalies are common as are midline facial and palatal defects, microphthalmia, and iris and retinal anomalies. Less commonly, these infants may have hypoplasia of the cerebellum, hydrocephalus, and spinal dysraphism. Cardiac involvement is common, and these infants may have a variety of skeletal malformations including camptodactyly, polydactyly, as well as dermatoglyphic features and flexion, and possible overlapping of the digits. As in trisomy 18, infants with trisomy 13 frequently have involvement of the gastrointestinal tract and genitalia, as well as renal anomalies. As a consequence of the developmental abnormalities of the brain, apneic events and epileptic seizures are common in these infants, and hypsarrhythmia has been described in the EEG of some patients. An approach similar to that used in infants with trisomy 18 should be taken when counseling parents and managing infants with trisomy 13. Corrective surgical procedures should be delayed until the full extent of the developmental anomalies is known and survival of the infant beyond the first months of life is more likely. An accurate cytogenetic diagnosis of trisomy 13 is imperative, as mosaicism and partial trisomy 13 cases have been described and these infants may have a somewhat better prognosis.

Deletion 5p Syndrome (cri du chat)

Deletion of a variable amount of genetic material from the short arm of chromosome 5 results in the cri du chat syndrome, a disorder that is characterized by a distinctive cat-like cry in affected infants, growth failure, microcephaly, and mental retardation. Systemic involvement is less common in this chromosomal disorder, but characteristics facies have been described and are more easily recognized in the infant than the older child. Distinctive facial features may include hypertelorism, a round face, epicanthal folds, and downward slanting palpebral fissures. The cognitive performance of affected children is improved over that reported in earlier natural history studies, and with special education intervention, these individuals may achieve motor, language, and social skills equivalent to a 5-year-old child. The 5p deletion syndrome occurs with an incidence of 1:15,000 to 1:50,000 live births, and 85% of cases are due to a sporadic deletion, most commonly of the paternally derived chromosome 5. The severity of the condition is, in part, related to the size of the deletion of the critical 5p15.2 to 5p15.3 region, and some degree of genotype-phenotype correlation is now possible. Several candidate genes have been identified within this region, and deletion of certain genes are felt to be responsible for the presence of mental retardation while deletion of several other genes may be responsible for the characteristic mewing cry of affected infants. While a diagnosis can usually be made via standard cytogenetic techniques, FISH analysis of the critical region may also be helpful to confirm the diagnosis in some cases.

Sex Chromosome Aneuploidy Disorders

A variety of congenital disorders that result from an abnormal complement of sex chromosomes have been described. Many of these conditions have associated neurodevelopmental and psychiatric features. The 47,XYY syndrome is rather common, with an incidence of 1 in 840 newborn boys. However, this disorder does not have an easily identifiable pattern of anomalies, and many affected boys and men are never diagnosed. Features that may be recognized in affected males include growth acceleration starting around 5 years of age, poor development of chest and shoulder girdle musculature that is associated with some degree of weakness and poor motor coordination, and neuro-developmental disabilities that include features of attention-deficit hyperactivity disorder and temper tantrums. A somewhat more common sex chromosome aneuploidy disorder is Klinefelter syndrome, which is due to an additional X chromosome (47,XXY) and occurs in approximately 1 in 1,000 males. These boys more frequently come to medical attention

due to their abnormal growth and the development of hypogonadism, hypogenitalism, and resultant infertility, when many are recognized. From a neurodevelopmental perspective, the IQ of affected males has a wide range, but the mean full-scale IQ is low average. These boys tend to exhibit difficulties in expressive language, as well as learning disabilities and behavioral problems. Boys with 48,XXXY and 49,XXXXY karyotypes have also been reported, and these males have clinical features that show a similarity to Klinefelter syndrome. A spectrum of more severe growth and performance deficits are noted in affected boys with a greater complement of X chromosomes. A number of nonspecific facial dysmorphisms have been described in these syndromes along with forms of brain dysgenesis including anomalies of the corpus callosum, microcephaly, and arrhinencephaly. Seizures have been noted in some individuals and decline in performance with increasing age has been reported. While the extra X chromosome in Klinefelter syndrome may be of either paternal or maternal origin, the additional X chromosomes in males with either the 48,XXXY and 49,XXXXY syndromes are maternally derived. Careful cytogenetic study and molecular analysis of the X chromosomes of affected males are required to make an accurate diagnosis and to determine the source of the aneuploidy, although the assignment of the meiotic error as paternal versus maternal has no impact on the management and is neither routinely required or determined.

Sex chromosome aneuploidy disorders also occur in phenotypic females, with Turner syndrome (45,X syndrome) being the most commonly recognized, occurring in 1:2,500 newborn females. The majority of Turner syndrome fetuses demise spontaneously in early pregnancy. These girls are frequently identified at birth with congenital lymphedema, loose skin particularly about the neck (webbed), a broad chest with widely spaced nipples, and a variety of other dysmorphic features with coarctation of the aorta renal anomalies and streak gonads. However, some affected girls are not diagnosed until later childhood when short stature and clinical signs and symptoms of gonadal dysgenesis are more evident. Later, autoimmune hypothyroidism, obesity, noninsulin-dependent diabetes mellitus, and hypertension frequently appear. Diagnosis is confirmed via routine cytogenetic studies, and the missing X chromosome is usually of paternal origin. Other X chromosomal abnormalities including mosaicism can underlie Turner syndrome. From a neurodevelopmental perspective, these girls only have a mild degree of cognitive impairment, typically a specific spatial-reasoning deficiency, together with some degree of motor in-coordination. Several neuropsychologic features have been described in affected females, and in particular there are deficits in social cognition and the development of low self-esteem and depression in adolescent and young adult women with Turner syndrome. Recent imaging studies have demonstrated regions of cortical maldevelopment that might correlate with the cognitive profile of these women.

The triple X syndrome is also common (1 in 1,200 females) and neurologists may encounter this anomaly, often emerging as a coincidental finding. These girls are taller than expected for their family but are otherwise physically normal. Early developmental delays and later, educational and behavioral problems out of keeping for the family level of function occur (IQ is thought to be depressed about one standard deviation below siblings). Also, mild psychological problems are not uncommon.

Additional Chromosomal Disorders with Neurologic Involvement

Deletions of several contiguous genes may result in clinically identifiable syndromes with characteristic neurologic involvement. Williams syndrome (7q11.23 deletion), Prader-Willi syndrome (paternal chromosome 15q11→q13 deletion or maternal uniparental disomy of chromosome 15), and Angelman syndrome (maternal chromosome 15q11→q13 deletion or paternal uniparental disomy of chromosome 15) are well-known examples, whose neurologic characteristics are described elsewhere in this book. Of particular note is the highly variable associations of the relatively common chromosomal disorder, the velocardio-facial syndrome (22q11.2 deletion), where both polymicrogyria and cerebellar malformations have been described. Of relevance to neurologists is also the association of terminal deletions of chromosome 6p with the Dandy-Walker malformation complex, also associated with other congenital malformations, notably anterior segment anomalies of the eye. Several other forms of chromosomal aneuploidy, deletion syndromes and duplication syndromes have been described, many of which have associated mental retardation, craniofacial abnormalities, and systemic malformations. Characteristic features of some of these syndromes are listed in Table 55-3. For more complete descriptions of these and other chromosomal disorders, the reader is referred to the monographs listed under the Section Suggested Readings. As with all of the chromosomal disorders described in this chapter, a thorough cytogenetic analysis is required to make an accurate diagnosis.

Management of Patients with Chromosomal Disorders

The management of infants and children with chromosomal disorders depends, in part, on the natural history of the particular disorder, but will generally require a multispecialty approach that involves not only physicians but also therapists, educators, and social workers. An accurate

TABLE 55-3. Additional Chromosomal Disorders with Neurologic Involvement

Chromosomal Disorder	Selected Neurodevelopmental Features	Selected Craniofacial Features	Common Systemic Features
Trisomy 8 Mosaic syndrome	Mild to severe mental retardation	Hypertelorism, deep-set eyes, micrognathia, palatal anomalies, auricular anomalies	Camptodactyly of multiple digits, abnormal creases, joint contractures
Trisomy 9 Mosaic syndrome	Severe mental retardation, cerebellar anomalies, choroid plexus cyst, abnormal gyration	Narrow bifrontal diameter, anomalous palpebral fissures, micrognathia, low-set posterior rotated ears	Kyphoscoliosis, multiple joint anomalies, hypoplasia of the sacrum and pelvis
Duplication 3q syndrome	Severe mental retardation, seizures, holoprosencephaly, and other brain dysgenesis	Craniosynostosis, micrognathia, palatal anomalies, short webbed neck, broad nasal root	Cardiac septal defects, flattened chest, omphalocele
Deletion 4p syndrome	Hypotonia, severe mental retardation, seizures	Microcephaly, hypertelorism, beaked nose, carp-like mouth, midline scalp defect	Cardiac septal defects, cryptorchidism, hypospadias, absent uterus, streak gonads
Deletion 9p syndrome	Mild to moderate mental retardation	Trigonencephaly, flat occiput, micrognathia, short webbed neck	Umbilical and inguinal hernias, long fingers and toes
Deletion 18p syndrome	Mild to severe mental retardation, holoprosencephaly, hypotonia	Brachycephaly, micrognathia, ptosis, prominent ears	Glaucoma, cataracts, microphthalmia, short fingers, clinodactyly of fifth finger, cardiac septal defects
Deletion 18q syndrome	Moderate mental retardation, ataxia, hypotonia, aggressive behavior	Midface hypoplasia, deep-set eyes, auricular anomalies	Long hands, tapering fingers, proximal thumbs, genital anomalies

diagnosis must be made as soon as possible after the birth of an affected child, and thorough counseling regarding the natural history of the disorder, its genetic origin, and recurrence risk must be provided to the parents. Depending on the severity and complexity of the malformations and anomalies of the central nervous system and other organ systems, a compassionate discussion should be held with the parents and other family members regarding the pros and cons of life sustaining medical procedures and corrective surgical measures. Consultation with appropriate specialists in neurology, genetics, orthopedics, neurosurgery, ophthalmology, gastroenterology, nutrition, endocrinology, and developmental pediatrics should be requested on a case-by-case basis. For those infants who do survive the neonatal period, a primary care physician should be identified to manage the outpatient treatment of the patient and to help the parents identify community resources and the necessary subspecialty medical care for their disabled child. In particular, the infant should be referred to the local "birth-to-three program" for early intervention services. When the child reaches 3 years of age, school-based special education programs should then be made available. Depending on the location where the family resides, parent support groups may offer additional resources. With the development of the Internet, additional support is becoming more common via disorder-specific Web sites and e-mail correspondence between parents with affected children.

Suggested Readings

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Practitioner and Patient Resources

Chromosome Deletion Outreach, Inc.
<http://www.chromodisorder.org/>
Chromosome Deletion Outreach, Inc. is an advocacy and support group for parents of children with a variety of chromosomal disorders. Their Web site provides an extensive library of information about chromosomal deletion, trisomy, duplication, and other disorders.

Gene Clinics
<http://www.geneclinics.org/>
Gene Clinics is a comprehensive online database, edited by Dr. Roberta Pagon and colleagues at the University of Washington, that includes edited reviews of human genetic conditions (including chromosomal disorders) and available resources for laboratory testing of genetic disorders. Entries are edited and updated on a regular basis.

Genetic Alliance
<http://www.geneticalliance.org/>
The Genetic Alliance provides disease-specific advocacy organizations with a variety of tools to help improve the services that they provide to their members. Their Web site provides an excellent portal to retrieve information about numerous chromosomal and other genetic disorders including support and advocacy groups.

Online Mendelian Inheritance in Man (OMIM), available through the National Center for Biotechnology Information
<http://www.ncbi.nlm.nih.gov/>
OMIM is a comprehensive online database of human genetic disorders (including chromosomal disorders) that is edited by Dr. Victor McKusick and colleagues of the Johns Hopkins University. Entries are edited and updated on a regular basis.

CHAPTER 56

RETT SYNDROME

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*Rett syndrome is a neurodevelopmental disorder predominantly appearing in girls during infancy and early childhood. It is associated in more than 80% of these patients with mutations in the methyl-CpG-binding protein 2 (*MECP2*) gene. Definitive treatment is lacking, but specific clinical issues should be discussed with the parents or principal caregivers, including life expectancy, cognitive impairment, seizures, growth and nutrition, gastrointestinal function, respiratory function, ambulation, scoliosis, and self-abuse, as well as general medical issues relevant to girls.*

Rett syndrome (RS) is a unique neurodevelopmental disorder that predominantly affects females. Since RS was first recognized in the 1960s by Andreas Rett, our understanding of the clinical, molecular, and neuropathologic features of the syndrome has advanced rapidly, culminating in the identification of mutations in the methyl-CpGbinding protein 2 (*MECP2*) gene as the molecular basis for this disorder. Mutations in *MECP2* have been found in more than 80% of girls fulfilling the consensus clinical criteria. RS affects girls throughout the world. Prevalence rates of 1:10,000 to 1:22,000 exceed those for phenylketonuria in girls. In the United States, the International Rett Syndrome Association database lists approximately 3,000 girls or women. However, this number understates the actual number of individuals with RS in the US by as much as four-fold.

The natural history of RS reveals a disease profile consistent with a neurodevelopmental disorder rather than a neurodegenerative condition (Figure 56-1).After an initial period of regression, further deterioration of cognitive function is not seen. Rather, improvement in communicative functions is typical, particularly with regard to eye-gaze, even though motor skills may gradually diminish. Neuropathologic findings suggest an arrest in neuronal maturation and synaptogenesis without evidence of a progressive neurodegenerative process.

FIGURE 56-1. Ten year-old girl demonstrating visual and emotional responsiveness.

Diagnosis

The clinical diagnosis of RS is based on the implementation of consensus criteria (Table 56-1) obtained by a thorough

TABLE 56-1. Rett Syndrome Consensus Clinical Criteria

Criteria	Onset
Normal at birth	—
Apparently normal early development (May be delayed from birth)	6–8 months
Postnatal deceleration of head growth rate in most	3 months – 4 years
Loss of achieved purposeful hand skills	6 months – 2½ years
Psychomotor regression	9 months – 2½ years
Emerging social withdrawal, communication dysfunction, loss of learned words, and cognitive impairment	
Stereotypic movements	1–3 years
Hand washing/wringing/squeezing	
Hand clapping/tapping/rubbing	
Hand mouthing	
Gait dysfunction	1–4 years
Impaired (dyspraxic) or failing locomotion	
Absence of	
Organomegaly, or other signs of storage disease	
Optic atrophy or other retinal changes	
Intrauterine growth retardation	
Evidence of perinatal or postnatal damage	
Acquired neurologic disorders due to infections or head trauma	
Existence of identifiable metabolic or other progressive neurologic disorder	

history and neurologic assessment. These consensus criteria have been clarified recently to allow uniform application worldwide. Clinical assessment should include evidence of pervasive deceleration of growth parameters and the presence of other associated features (bruxism, drooling, periodic breathing, seizures, disrupted sleep, GE reflux, chewing/swallowing dysfunction, inconsolable screaming, self-abuse, and peripheral autonomic involvement, although all may not be noted in every girl). The earliest clinical clue to the diagnosis of RS, albeit nonspecific, is deceleration in the rate of head growth, noted as early as age 3 months. This is followed by deceleration in weight gain and linear growth.

In most instances, the pre- and perinatal periods are normal, and early development appears normal despite subtle deviations. Thereafter, achievement of developmental milestones stagnates between 6 and 18 months, and previously acquired skills are lost, including purposeful hand use, speech, and socialization. During this regression, extended periods of profound irritability may be a dominant feature. Sleep is often interrupted and punctuated by unprovoked screaming or laughter. Teeth grinding (bruxism) and drooling may be prominent. Feeding is slow and tedious due to poor chewing skills and swallowing incoordination. Constipation is a common complaint. Peripheral changes in the form of cool or cold and bluish hands and feet may be seen, along with indifference or delayed response to pain. Periodic breathing, consisting of breath holding, hyperventilation, or both develop from 12 to 36 months and may be very prominent in early school years. Forced expulsion of air (puffing) or saliva may precede or accompany the development of periodic breathing. In some instances, air swallowing (bloating) will occur. Seizures of variable type, including staring spells, complex partial events, or generalized tonic-clonic movements, typically begin after age 2 years. Rarely, seizures begin in infancy and have the appearance of infantile spasms. Behavior patterns in RS, so-called "Rett" behaviors, resemble seizures and must be differentiated from them.

The most prominent and characteristic sign of RS is the development of stereotypic hand movements during or at the end of the regression phase. These movements are quite variable from girl to girl; each expresses her own repertoire, which evolves throughout life. Hand stereotypies may include hand washing, hand wringing, and hand tapping movements with hands together, or hand mouthing, clothes picking, or head tapping. Additionally, finger rubbing and unusual finger postures occur. Stereotypic movements of the feet and toes may also be noted.

During infancy, hypotonia is prominent. Generally, tone will gradually increase during childhood to the point of rigidity by adolescence or early adult years. Progressive dystonic posturing, truncal ataxia, and coarse tremor appear in some. Most girls with RS achieve ambulation that is apraxic and nonpurposeful, although about 20% never do so and another 20% may lose independent gait after the regression phase. Scoliosis and kyphosis are later signs, usually beginning after 5 years of age. Scoliosis may be progressive, particularly in nonambulating and hypotonic girls, ultimately requiring surgical intervention.

Atypical Rett Syndrome

In recent years, girls have been recognized with atypical patterns of RS. These include an early onset seizure variant, a preserved speech variant, and a delayed-onset variant. Whether they represent the same disorder remains to be determined, although < 50% have mutations in *MECP2*. Consensus criteria have also been developed for these variant forms (Table 56-2). In the Swedish series, these atypical forms represent 20% or more of the total.

Differential Diagnosis

Before the worldwide recognition of RS, autism was the most frequent diagnosis given these girls. However, rigorous application of criteria for the two disorders allows clear differentiation. This confusion should occur even less frequently in the future. Static encephalopathy (cerebral palsy) should be considered, although the clinical features and natural history of RS would be atypical. Fragile X syndrome and Angelman syndrome (AS) initially may

TABLE 56-2. Rett Syndrome Consensus Variant Criteria

Inclusion criteria
Meet at least 3 of 6 Main Criteria
Meet at least 5 of 11 Supportive Criteria
Six main criteria
Absence or reduction of hand skills
Reduction or loss of babble/speech
Reduction or loss of communication skills
Deceleration of head growth from first years of life
Monotonous pattern of hand stereotypies
RS disease profile: a regression stage followed by a recovery of interaction contrasting with slow neuromotor regression
Eleven supportive criteria
Breathing irregularities
Bloating/air swallowing
Bruxism (harsh sound)
Abnormal locomotion
Scoliosis/kyphosis
Lower limb amyotrophy
Intense eye contact/eye pointing
Diminished response to pain
Laughing/screaming spells
Cold, purplish feet usually growth impaired
Sleep disturbances including night screaming outbursts

resemble RS. Chromosome analysis with high-resolution banding and fluorescent in situ hybridization (FISH) and methylation analyses for AS are recommended. Other conditions to be considered include the leukodystrophies, neurocutaneous disorders, and metabolic disorders. In particular, the infantile form of neuronal ceroid lipofuscinosis, which is especially prevalent in the Finnish population, can resemble RS during early stages. Neuroimaging (cranial computed tomography or magnetic resonance imaging [MRI]), electroencephalography (EEG), and metabolic studies should exclude these disorders.

Diagnostic Procedures

Confirmation of the clinical diagnosis of RS is based on identifying mutations in *MECP2*. With the recent identification of mutations in exon 1 in a few instances and large deletions in a much larger number, more than 95% of females meeting the consensus criteria will have a mutation in *MECP2*. Moreover, mutations in *MECP2* have also been recognized in females and males who fail to meet these consensus criteria. As such, RS remains a clinical diagnosis. Recommended evaluations also include cranial MRI and EEG, preferably with video monitoring. Cranial MRI is typically normal or shows mild to moderate volume loss. Video- EEG will differentiate seizures from "Rett" behaviors that lack electrographic abnormalities. These include unusual posturing and staring spells. Typically, episodes of periodic breathing and hand stereotypies will only occur during wakefulness. Polysomnography may be useful to define sleep patterns and exclude obstructive apnea. Radiography studies for scoliosis may be required by age 5 years and should be repeated periodically according to rate of progression. An EKG for prolonged QT interval (see below) should be obtained at diagnosis. If normal, this should be repeated every 2–3 years.

Genetic Basis of Rett Syndrome

Because it is an X-linked dominant genetic disorder, RS predominantly affects girls. A much more aggressive phenotype is apparent in boys and RS may even lead to fetal demise. RS is largely sporadic, much less than 1% representing recurrence within a family. In those instances of familial recurrence, the transmitting female is normal or may have mild learning disability. More than 95% of females meeting RS consensus criteria will have mutations in *MECP2*. *MECP2*, located at Xq28, encodes methyl-CpG-binding protein 2 (MeCP2), which is highly expressed in brain and is important as a regulator of gene transcription and RNA splicing. Most females with RS represent de novo mutations. More than 200 different mutations have been defined in *MECP2*, although eight specific mutations account for about two thirds of the total. Most of the known mutations are truncating and lead to an incomplete form of the MeCP2 protein. Missense mutations result in a protein with reduced functional integrity.

Despite the low risk for recurrence, parents who wish to have additional children should meet with a genetic counselor. The feasibility of prenatal diagnosis has been demonstrated. The carrier status of the mother of a girl with an *MECP2* mutation may be assessed, although the failure to identify the same mutation would not exclude the presence of a germline mutation.

Phenotype–genotype correlation studies in girls with classic RS have shown the most important determinant of clinical severity to be variability in X-chromosome inactivation, but the position of the mutation or whether it is truncating or not is also important. More specifically, skewed inactivation of X-chromosomes bearing mutations in *MECP2* may produce milder clinical involvement, whereas skewed inactivation of the normal X-chromosome may produce a more severe phenotype.

The occurrence of RS in boys is exceedingly rare. Boys with Klinefelter syndrome (XXY) have been described with features typical for RS. Other boys possessing *MECP2* mutations have been identified with rapidly progressive encephalopathy, developmental delay and cognitive impairment, or spastic paraparesis. However, aside from boys with Klinefelter syndrome, other males (46XY) with *MECP2* mutations do not fulfill the criteria for RS. In addition, duplication of *MECP2* has been noted in a female with the preserved speech variant form of RS and in males with

cognitive and motor impairments. As such, the spectrum of clinical phenotypes associated with mutations in *MECP2* extends well beyond RS and includes normal individuals and those with mild learning disability, severe encephalopathy, autistic spectrum disorder, Angelman syndrome, and nonsyndromic mental retardation.

Therapy

Definitive treatment is lacking. Nevertheless, several specific clinical issues should be discussed with the parents or principal caregivers. These include life expectancy, cognitive impairment, seizures, growth and nutrition, gastrointestinal function, breathing function, ambulation, scoliosis, and self-abuse. The International Rett Syndrome Association (IRSA) has a useful Web site (see Practitioner and Patient Resources) and many helpful publications bearing on these issues.

Life Expectancy

Survival may extend well into adulthood. Survival follows that of all girls up to age 10 years. However, survival of women with RS to age 35 years is about 70% compared with 98% for girls and women combined. Understanding the possibility of prolonged survival is important in order to guide parents and other caregivers about long-term care.

Cognitive Issues

Assessing cognitive function in girls with RS is extremely problematic. The absence of effective fine motor and communication skills severely limits the application of available standardized tests. Nonetheless, functional assessments indicate a mental developmental age at the 8- to 10-month level and gross motor function ranging from 12 to 18 months. Adaptive skills, including feeding, dressing, and toileting functions, are largely absent, such that individuals with RS will require lifelong support in these areas. The provision of appropriate physical, occupational, music, and speech therapy, including augmentative communication, is essential for individuals with RS throughout their lifespan (Figure 56-2).

Seizures

Reports of seizure frequency in RS range from 30 to 80%. The EEG is invariably abnormal after age 2 years, featuring slowing in background activity, reduction or loss of posterior dominant rhythm, and recurrent spike and slow spike-and-wave activity. Despite these abnormalities, clinical seizure activity may be minimal or absent in the majority. Seizures tend to diminish in adolescence and adulthood. In some adults, the epileptiform features may no longer be present on the EEG. Only rarely will seizures first appear after age 20 in women previously seizure-free. Differentiating behavioral patterns from seizures can be challenging and may often require video- EEG monitoring to resolve the question. Seizure control is typically not difficult in individuals with RS, usually responding to carbamazepine (15 mg/kg/d in two to three doses; blood levels to12–14 μg/mL may be required) or sodium valproate (20–30 mg/kg/d in divided doses; blood levels to 100–120 μg/mL). Lamotrigine (initial dose of 0.5–1.0 mg/kg/d with increases every other week to 4–10 mg/kg/d; blood levels 4–20 μg/mL) has also proved effective. Although generally well tolerated, carbamazepine or valproate may be associated with agitation or self abusive behavior. On occasion, seizure control requires combination strategies.

FIGURE 56–2. Fourteen year-old girl demonstrating intense hand mouthing during period of breath-holding. Note dystonic postures of her upper extremities.

Growth and Nutrition

Growth failure in RS is pervasive, the first evidence being deceleration in the rate of head growth as early as 3 months of age. Median head circumference values fall to the second

percentile for the normal population by age 4 to 5 years. Weight percentiles begin to decline near the end of the first year of life, with the median value falling below the 5th percentile for the normal population by age 7 years. Height or length percentiles fall off around 15 months of age, with the median values reaching the 5th percentile for the normal population around age 7 years. Hand and foot growth is also affected. Feet are more likely to be involved than hands, the reduction in foot growth percentiles paralleling that of height.

Nutrition is often problematic, requiring the guidance of a nutritionist. It appears that girls with RS have increased protein requirements and require dietary supplementation. Ultimately, gastrostomy feeding may be necessary in some girls to preserve growth as such. In adolescence, weight gain may accelerate as caloric requirements diminish. Care must be taken to avoid excessive weight gain as this may diminish mobility in those who are ambulatory and make lifting difficult in those who are not ambulatory.

Gastrointestinal Function

Gastroesophageal reflux and esophagitis are common, and gallbladder disease has been described in many girls and women with RS. Recurrent periods of unexplained irritability or apparent distress may result, requiring appropriate evaluation and treatment by a gastroenterologist. Constipation is also a significant problem in RS. Various strategies, employed with variable success, include highfiber foods, enemas, mineral oil, and milk of magnesia. The frequent use of enemas is discouraged, as it may lead to dependency on this mode of treatment. Furthermore, prolonged use of mineral oil may interfere with proper absorption of fat-soluble vitamins. Most recently, polyethylene glycol (MiraLax®) has proved particularly effective and well tolerated. It is tasteless and odorless and may be dissolved in juice, making it more palatable.

Breathing Function

Irregular breathing during wakefulness is common. This may consist of hyperventilation or breath holding or, in some girls, both. Breath holding may be prolonged and frightening, occasionally exceeding 1 minute. In other girls, it may be quite subtle and, thus, under recognized. Parents and other caregivers should be advised to look for specific features of breath holding or hyperventilation, no matter how subtle, as well as evidence of brief oral expulsion of air or saliva. Air swallowing (aerophagia) may be profound and produce marked abdominal distension. However, the distension will abate, particularly during sleep. Irregular breathing is usually noted first in early childhood (3 to 5 years), reaching maximal levels during the early school-age period (5 to 10 years), when it may dominate much of the waking activities. Thereafter, breathing irregularities diminish in frequency and intensity. Efforts to modify breath holding or hyperventilation medically generally have been unsuccessful. The opiate antagonist naltrexone (1–3 mg/kg/d in single or divided doses) may provide some benefit but not uniformly and may reflect in part the sedating properties of this drug. Irregular breathing occurring during sleep is not a typical feature of RS and should result in a search for causes of obstructive apnea.

Ambulation

Approximately 80% of girls with RS ambulate, about one-fourth of whom will lose their ability to walk during or after the period of regression. Overall, about 60% of girls remain ambulatory. In some instances, ambulation is lost during the regression phase, only to be regained later in childhood. Regardless, ambulation should be encouraged as long as possible, and for those who do not walk, weight-bearing should be encouraged with the use of standing frames. Bones tend to be undermineralized in RS and weight-bearing may be beneficial.

Osteopenia

Osteopenia occurs in virtually all girls and women with Rett syndrome, being more significant in those girls or women who have inadequate calorie and protein intake. Even in those who have adequate calorie-protein intake, osteopenia is present but just to a lesser degree. Due to the frequency and extent of osteopenia, fractures are much more common in the girls or women with Rett syndrome. As such, unexplained disuse of an extremity despite the absence of complaints should trigger assessment for a possible fracture in that extremity. Fractures often go undetected because of the girls' inability to express and localize pain. Consideration should be given to oral calcium supplementation, beginning already in childhood.

Scoliosis

The incidence of scoliosis in RS increases with age. It is noted in about 8% of preschoolers and in more than 80% of girls over 16 years of age. The overall incidence is about 50%. Onset occurs typically at age 8 years or somewhat before. Progression is much more common in girls who are nonambulatory. Bracing is considered with a 25° curvature. However, systematic studies have not established that bracing actually delays progression. Surgery is recommended strongly when curvature exceeds 40°.

Sexual Maturation and Gynecologic Issues

Ordinarily, girls with RS enter puberty at similar ages to their peers. As these young women are quite vulnerable, appropriate consideration should be given to protecting them from unwarranted contact.

Menstrual cycles, once established, generally occur with predictable regularity. Parents and other caretakers may choose to deal with these in the usual fashion or employ one of a variety of strategies to eliminate or minimize menstrual flow. These include birth control pills for menstrual management, endometrial oblation or Depo-Provera® injections. Concerns regarding bone demineralization may limit the appropriateness of this last option. The largest experience is with birth control pills, which have been quite effective. Newer preparations that limit menstruation to quarterly are now available. As with GI issues, unexplained irritability or inconsolable crying should lead to appropriate consideration of problems in the gynecologic system. An abdominal ultra-sound as well as consultation with a gynecologist should be strongly considered.

Self-Abuse

Self-abusive behavior is seen occasionally in the form of hair pulling, biting of the fingers, hands, or other parts of the upper extremities, and hitting about the face. Aggressive behavior toward others, consisting of hitting, biting, or hair pulling, may also occur. Before using medications, care should be taken to exclude other medical problems, particularly gastrointestinal dysfunction (gastroesophageal reflux or constipation) as noted above, and to ascertain whether behavior is a side effect of medications already in use. Otherwise, low-dose risperidone (0.5 mg bid) may be beneficial.

Other Features

These include bruxism (teeth grinding), interrupted sleep patterns, and vasomotor disturbances comprising cold feet and hands, the former more so than the latter. Bruxism tends to be most prominent during early childhood. Attempts to treat have not been fruitful in most instances. Sleep is often fragmented. It is not unusual to find that girls with RS do not sleep well for many nights in succession or are awake in the night, often playing quietly or laughing for no apparent reason and producing very disrupted sleep for the parents. Chloral hydrate (25–50 mg/kg), diphenhydramine (1–2 mg/kg), or hydroxyzine (1 mg/kg) may be required. As significant tolerance may develop to hydroxyzine and diphenhydramine, chloral hydrate is the preferred choice. Vasomotor disturbances represent autonomic nervous system dysfunction. Sympathectomy occurring during surgery for scoliosis may reverse these findings on the operated side. No effective treatment is otherwise available. Prolongation of the QT interval has been noted. As such, an electrocardiogram (ECG) should be obtained in early childhood and repeated periodically, perhaps annually.

Long-Term Management

Long-term management requires physical and occupational therapy, speech therapy, nutritional support, orthopedic intervention, and seizure management. Emphasis should be placed on establishing optimal communication by building on the improved social interaction and eye contact, which develop by school age. Augmentative communication strategies may be quite effective. Failure to maintain proper weight gain may reflect swallowing dysfunction or gastroesophageal reflux and require referral to a gastroenterologist. The principal orthopedic concern is monitoring of scoliosis and surgical intervention with stabilizing rods when necessary.

Long-term planning needs to be considered as well. Given the potential longevity in RS, other health issues must be considered. Women with RS have the same medical and dental needs as other women and require proper attention. An ECG should be performed annually to assess the QT conduction interval. Gynecologic care should also be provided annually.

In summary, women with RS may survive well into middle age. The provision of optimal care and health maintenance to promote both general health as well as those issues specific to RS should be emphasized to parents and caretakers. Paramount among these is maintaining effective socialization and interaction with family and friends.

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Practitioner and Patient Resources

International Rett Syndrome Association (IRSA)
9121 Piscataway Road, # 2-B, Clinton, MD 20735
Phone: (301) 856-3334
http://www.rettsyndrome.org
The mission of the IRSA is to support and encourage research to determine the cause, treatment, and cure for Rett syndrome, to increase public awareness of Rett syndrome, and to provide informational and emotional support to families of children with Rett syndrome.

Kennedy Krieger Institute
Johns Hopkins University School of Medicine
707 North Broadway
Baltimore, MD 21205
Phone: (410) 550-9409
http://www.kennedykrieger.org
Kennedy Krieger Institute is an internationally recognized facility dedicated to improving the lives of children and adolescents with pediatric developmental disabilities through patient care, special education, research, and professional training.

UAB Sparks Clinics Rett Syndrome Research Program
University of Alabama at Birmingham (UAB) School of Medicine
1600 7th Ave South
Birmingham, AL 35233
Phone: (205) 939-6940
http://www.circ.uab.edu/Sparks/Rett/index.html
On the UAB Sparks Clinics Rett Syndrome Research Web site, you will find detailed information about Rett syndrome, along with links to research, clinic appointments, and international online resources related to Rett syndrome.

Blue Bird Circle Rett Center
Baylor College of Medicine
1 Baylor Plaza
Houston, TX 77030
Phone: (713) 798-7388
http://bluebirdrett.bcm.tmc.edu
The Blue Bird Circle Rett Center at Baylor is involved in three major activities: caring, education, and research. The Rett Center at Baylor College of Medicine is one of the few centers in the United States that specializes in the diagnosis and care of girls and women with Rett syndrome, providing care not only for girls and women living in the Houston area, but also to those from all parts of Texas, the United States, and the world.

RettBASE IRSA MECP2 *Variation Database*
http://mecp2.chw.edu.au/
This database has been constructed by merging mutation and polymorphism data from the published literature pertaining to Rett syndrome and related clinical disorders, and by incorporating unpublished mutation and polymorphism data that have been directly submitted. RettBASE is updated on a very frequent basis manually by its curators to ensure the validity of the data.

InterRett—IRSA Rett Phenotype Database
http://www.ichr.uwa.edu.au/rett/irsa/
InterRett is working to provide comprehensive information about the range of clinical features found in Rett syndrome as well as management and treatments used around the world. This project

involves collecting information about the clinical features of Rett syndrome from parents and clinicians and collating those details to form an online searchable database. It will attempt to ascertain whether the differences between the mild atypical cases, the classical cases, and those cases that have an early onset and are perhaps more severe are due to differences in genetic characteristics. It will be helpful in predicting the outcome and severity and how environmental factors such as early intervention therapy or specific treatments can affect the course of Rett syndrome in children with identical genetic characteristics.

Chapter 57

Inborn Errors of Metabolism

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The number of congenital disorders of metabolic pathways is extensive and around 500 entities have been recognized. The specific metabolic deficits causing these disorders and the underlying specific genetic mutations have been identified. However, all these conditions are rare. As a consequence, it is almost inconceivable that physicians, adult or pediatric, would have a ready-to-use knowledge of the clinical syndromes and their biochemical basis. It is, therefore, useful to describe screening procedures that can help in the initial identification of patients with inborn errors of metabolism. This will lead to further biochemical and metabolic characterization and possible referrals to specialists in neurometabolic diseases.

Many symptoms prominent in patients with inborn errors of metabolism are not very specific and can be caused by more common conditions, such as infections, asphyxia, or other neurologic diseases. These conditions are usually easier to diagnose; therefore, these differential diagnoses should always be considered first. The clinical features accompanying neurometabolic diseases seldom permit a specific diagnosis to be made. It is, however, necessary that each physician assessing a child with a number of unexplained symptoms and signs thinks of the possibility of a metabolic disease and further investigates the case. This will be done initially with the indicated screening methods and further with a specific diagnostic workup, in collaboration with a specialist who has a broad knowledge of available laboratory tests and who can help prioritize the ones that could lead to a precise diagnosis.

Progress in the molecular understanding of these disorders has revealed the clinical heterogeneity of some metabolic diseases. This important variability in the clinical syndrome caused by a specific metabolic abnormality can be apparent even among affected members within one family. It is important to be aware of this complicating aspect, as the family history is used as one criterion for the identification of an inborn error of metabolism. To further complicate matters, affected family members sometimes develop symptoms as adolescents or relatively late in adulthood. Most inborn errors of metabolism affect the nervous system. For many of these diseases, little is known about the exact pathogenic mechanism by which the metabolic deficit generates the central nervous system (CNS) anomalies, including the dysmorphogenesis that is often present. Energy deficiency or toxic effects from the storage of certain metabolites leading to neuronal death are possible explanations, but exactly which processes are involved is far from clear. Several diseases can now be diagnosed using specific biochemical assays performed on specific tissues to reveal the enzymatic deficit. With advances in molecular biology, corresponding gene mutations often can be identified and eventually can be used for further family testing and prenatal counseling. Sometimes, one is restricted to a biochemical diagnosis when the gene involved is not yet fully characterized or is too cumbersome to analyze, as can be the case for very large genes. In other cases, the opposite is true, and it is easier to document a specific mutation than to do the biochemical assay.

Early diagnosis of inborn errors of metabolism can prevent severe disease progression. Swift diagnosis also

widens the time window for prenatal diagnosis in subsequent pregnancies. For all this to be possible, the clinician needs to be alert to the possibility that metabolic disease can be the underlying cause of a wide variety of clinical symptoms. Most inborn errors of metabolism are inherited in an autosomal recessive fashion. In most of these cases, the disease can only manifest itself fully in homozygotes for the mutation. This is generally a rare occurrence, except in consanguineous families. However, some inborn errors of metabolism are caused by mutations in genes located on the X chromosome, and the disease is then called "X linked." The effect is two-fold: first, the disease becomes dominant in male offspring inheriting the mutation; second, due to variable random X-chromosome inactivation in various tissues, the expression of the disease can be highly variable from one tissue to another and from one girl to another. Few inborn errors of metabolism are autosomal dominant. Finally, subsets of the respiratory chain genes that are encoded within the mitochondrial deoxyribonucleic acid are maternally inherited.

Metabolic diseases can present with single or recurrent life-threatening events, such as coma due to hyperammonemia or hypoglycemia, or status epilepticus. In other diseases, the clinical picture is that of a chronic progressive process with epilepsy, mental regression, and other organ involvement. In this chapter, we are not catalogueging all possible metabolic diseases but discuss the important alarm signals and clinical presentations that could point to inborn errors of metabolism in different age groups. Some metabolic diseases are diagnosed through systematic neonatal screening programs instituted by government regulation. These screening programs pick up certain of the metabolic diseases with a higher incidence. However, the programs differ significantly from one country to another. Biotinidase deficiency, for example, is an inborn error of metabolism resulting in the defective recycling of biotin. Neonatal screening for this disorder is not universal, and undiagnosed children will develop mental retardation, seizures, and cutaneous findings, although clinical progression could have been prevented by early detection and oral biotin administration. This means that each physician must know which screening tests are or are not routinely performed in their country. Medium chain acyl-CoA dehydrogenase deficiency was found to have a birth incidence of one in 8,930 through a supplemental newborn screening program in Pennsylvania using tandem mass spectrometry, making it one of the more common inborn errors of metabolism. Specific measures in case of illness or fasting can prevent episodes of hypoketotic, hypoglycemic encephalopathy avoiding cerebral injury or death.

On the basis of their pathophysiology, metabolic diseases can be classified into three groups according to Saudubray and colleagues (2006):

1. Disorders of complex molecules. This group includes enzymatic deficiencies that lead to a disturbance of the synthesis or catabolism of complex molecules (eg, lysosomal and peroxisomal disorders, congenital defects of glycosylation [CDG] syndrome, and defects in cholesterol metabolism).
2. Disorders resulting in intoxication. This group includes most of the inborn errors of intermediary metabolism and leads to intoxication because of accumulation of substances that cannot be further metabolized. A classic example is methylmalonic aciduria.
3. Disorders of energy metabolism. Here, the disturbance is also situated in the intermediary metabolism, but the deficiency results in inadequate energy production or use.

For the clinician, a more practical operational approach is needed. Although metabolic diseases are inherited, symptoms often are not present at birth. The age at which first symptoms appear can vary. However, for each particular defect, we can define the age group in which these symptoms typically become clinically apparent. These three age groups are (1) the neonatal period and infancy, (2) childhood, and (3) adolescence to adulthood. In this chapter, we will discuss only the neonatal and childhood periods.

Again, in most metabolic diseases, neurologic symptoms will be present and may even be a significant or dominant part of the clinical syndrome. In a minority of conditions, there are no neurologic findings.

Neonate and Infant

The younger the child, the less well organized is the CNS. As a consequence, neurologic symptoms tend to be nonspecific in young children. In the neonate, general clinical signs are poor feeding, lethargy, hypotonia, and seizures (Table 57-1).

TABLE 57-1. Findings that Suggest Inborn Errors of Metabolism

Neonate and Infant	Older Child
Dysmorphism and malformations	Encephalopathy and coma
Seizures	Stroke
Hypotonia	Extrapyramidal syndrome
Liver dysfunction and hepatomegaly	Acute ataxia
Encephalopathy and coma	Liver dysfunction, cardiac insufficiency
Fat pads, hair, and ophthalmologic abnormalities	Peripheral neuropathies
	Chronic cerebellar ataxia
	Myopathy, rhabdomyolysis
	Intermittentpsychiatric disturbances
	Mental regression, myoclonus, seizures

Often, there is a free interval of a few days between birth and the onset of the symptoms, especially with inborn errors of intermediary metabolism. This is the time needed for the accumulation of toxic metabolites generated by feeding, which starts at birth.

Further important elements for the differential diagnosis are the absence of a history of asphyxia at birth, the presence of consanguinity in the family, prior loss of siblings in the neonatal or infantile period, or previous miscarriages.

Dysmorphism as the Dominant Clinical Symptom

A number of metabolic disorders are associated with dysmorphism, and the clinical presentation, even in the neonate, is not always that of an overwhelming metabolic decompensation. The best example is pyruvate dehydrogenase (PDH) deficiency (most frequently E1 α subunit of the complex), one of the more frequent causes of congenital lactic acidosis. PDH-E1 α deficiency is an X-linked disorder, in which affected heterozygote females present with dysmorphism (hypertelorism, thin upper lip, upturned nose, frontal bossing, low-set ears, and short proximal limbs) and severe cortical atrophy. Systemic lactic acidosis, which is a typical feature, can be absent, and elevated cerebrospinal fluid (CSF) lactate and pyruvate levels with normal lactate-pyruvate ratio may be the only clue to the diagnosis.

These female babies are often erroneously considered to have cerebral palsy, especially when they present with severe developmental delay and eventually develop microcephaly, myoclonic seizures, and severe spastic quadriplegia. Dysmorphism and microcephaly can also be a sign of respiratory chain defects, as was recently described in a child with complex V deficiency due to a mutation in assembly gene *ATP12*.

Another example is Zellweger syndrome, where the association of dysmorphic features (high forehead, epicanthic folds, slanting palpebral fissures), together with hepatomegaly and seizures, should lead to a search for a peroxisomal disorder. The first step toward the diagnosis is the determination of the concentration of the very-long-chain fatty acids (VLCFAs) in plasma; VLCFAs are elevated because of absent biogenesis of peroxisomes. Several peroxisomal disorders due to different enzyme deficits are now known. The genes responsible encode for integral peroxisome membrane proteins or receptors involved in targeting proteins to the peroxisomes. The normal functions of peroxisomes include catabolic activities, as in β-oxidation of VLCFAs, catalase activity, oxidation of phytanic acid and pipecolic metabolism, and anabolic activities, such as biosynthesis of plasmalogens. The increasing number of babies with CDG should not be forgotten; for example, mutations in *COG7* gene in children with dysmorphic features and microcephaly associated with episodes of hyperthermia. The group of CDG diseases can usually be screened by isoelectrofocussing of sialotransferrines in plasma.

A coarse facies can lead to the suspicion of a storage disease, such as mucopolysaccharidoses or oligosaccharidoses. The Smith-Lemli-Opitz syndrome features multiple malformations, such as microcephaly with several developmental abnormalities of the brain, micrognathia, anteverted nares, low-set posteriorly rotated ears, cleft palate, irregular alveolar ridges, limb abnormalities with syndactyly, and genital abnormalities ranging from hypospadias to ambiguous genitalia. Other organs, such as the heart and the kidney, can also be affected. Abnormalities of the gastrointestinal tract also occur, such as Hirschsprung's disease. The diagnosis can be made by measuring plasma 7-dehydrocholesterol (precursor of cholesterol), which is elevated in association with low cholesterol levels caused by a deficiency in the final step in cholesterol biosynthesis. A more extensive malformation syndrome with rocker-bottom feet, defects of the anterior abdominal wall, hypospadias, and enlarged polycystic kidneys can be seen in the infantile form of glutaric aciduria type II (multiple acyl-CoA dehydrogenase deficiency). Progressive macrocephaly with acceleration of head circumference growth percentiles between 3 and 6 months of age is a frequent finding in glutaric aciduria type I. Enlarged subarachnoid spaces and chronic subdural effusions and hematomas are responsible for the presenting feature of this disease and can be demonstrated with computed tomography and magnetic resonance imaging (MRI) of the brain.

Seizures as the Dominant Presenting Symptom

In general, neonatal and infantile myoclonic seizures are often related to a metabolic problem. Seizures in metabolic diseases have no specific characteristics and are indistinguishable from seizures due to, for example, a hypoxic-ischemic encephalopathy. The electroencephalogram can be severely abnormal, with a pattern of burst-suppression, as seen in nonketotic hyperglycinemia or sulfite oxidase deficiency. In nonketotic hyperglycinemia, babies present with intractable seizures but also have severe hypotonia together with apneic spells and hiccups. A trial with pyridoxine (intravenously or orally for several days, with a dose of at least 100 mg/d) is necessary in each infant with unexplained seizures because pyridoxine-dependent seizures are curable. Recently, the diagnosis can be made biochemically (elevated urinary α-aminoadipic semialdehyde) and by analysis the gene-encoding antiquitin A trial of pyridoxal phosphate

should also be considered in children with seizures resistant to pyridoxine.

A few cases of folinic acid–responsive seizures have also been described, and a trial with folinic acid may be considered in some neonates. Another two disorders to consider in the differential diagnosis of neonatal seizures are D- and L-2-hydroxyglutaric aciduria, the genes for both disorders are recently identified.

One should never forget to verify CSF glucose levels in infants with intractable seizures because a deficiency in a glucose transporterb (GLUT1, which can be measured in erythrocytes) needs to be treated early and has a better outcome with a ketogenic diet. These babies present with early-onset intractable seizures, and the sole biochemical abnormality is a low CSF glucose with a low CSF-blood glucose ratio of less than 0.33.

Hypotonia

Hypotonia is another frequent nonspecific finding. Associated findings, such as hepatomegaly, arthrogryposis, and cardiomyopathy, should be looked for, leading to disorders of energy metabolism including those of fatty oxidation. When the hypotonia is severe, Prader-Willi syndrome needs to be considered, and the diagnosis can be confirmed with cytogenetic techniques.

Hypotonia is a frequent sign in adenylosuccinate lyase deficiency, an inborn error of purine synthesis. Neonatal and infantile myoclonic seizures, together with autistic features, are often reported in this disorder. The diagnosis can be made after screening the urine by the Bratton-Marshall test.

Hypotonia and failure to thrive associated with megaloblastic anemia should lead immediately to a search for defects in cobalamin metabolism and to the determination of plasma homocysteine and urinary methyl malonic acid.

Liver Dysfunction

Liver failure associated with neurologic symptoms lead to consideration of a number of disorders characterized by the presence or absence of hypoglycemia and/or metabolic acidosis. Cholestatic jaundice might indicate cholesterol biosynthesis defects and defects of bile metabolism but also Niemann-Pick type C disease, CDG syndrome, or peroxisomal disorder. Clinical syndromes, such as the examples cited above, should trigger further action.

Decreased Consciousness or Coma

With this presentation, further biochemical determination is required as a first-step metabolic acidosis with an increased anion gap, either ketoacidosis or lactic acidosis, neutropenia, and thrombocytopenia (especially in the organic acidurias), are important indicators, together with evidence obtained from MRI of the brain and biochemical analysis of the urine and CSF. To begin with, there should be a general screening followed by more specific diagnostic tests (Table 57-2). To narrow the diagnosis to a defined group of diseases, such as a peroxisomal or mitochondrial disorders, Saudubray and colleagues categorized the neonate and infant with metabolic distress into one of five categories on the basis of the results of a number of

TABLE 57-2. Laboratory Screening

Screening
Blood*
Blood cell count, electrolytes, glucose, calcium, blood gases, magnesium, uric acid
Liver tests and coagulation
NH_3, lactate, pyruvate
Acylcarnitines on filter paper
Urine†
Acetest, DNPH, and Clinitest
Bratton-Marshall test
Sulfite strip test on fresh urine
Uric acid
Specific Tests
VLCFA and phytanic acid (peroxisomal diseases)
7-dehydrocholesterol and cholesterol (SLO)
FFA/3-OH-butyrate (mitochondrial and fatty acid oxidation)
Sialotransferrines isoelectric focusing (CDG)
Homocysteine
Vacuolated lymphocytes in blood (storage disorders)
Urine oligosaccharides, MPS (storage disorders), and guanidinoacetate and urinary creatine/creatinine ratio (creatine deficiency)
Urinary α-aminoadipic semialdehyde levels (pyridoxine responsive seizures)
CSF glucose, GABA, HVA, 5-HIAA, 5-methyltetrahydrofolate, biopterin, protein, lactate, andamino acids (serine, glycine); and freeze 2 mL
Brain imaging (MRI, MRS) and neurophysiology
Radiography of skeleton, echocardiography, and echo liver and spleen
Advanced Specific Tests
Muscle biopsy for microscopy, biochemistry, and mtDNA
Fibroblast or lymphoblast cell culture
Leukocytes for measuring of specific enzymes and DNA
Electron microscopy of the skin or the conjunctiva

*Keep heparinized plasma and EDTA blood at –20°C for amino acids and other determinations.

†Keep urine and freeze at –20°C for organic and amino acids, purines, and pyrimidines.

5-HIAA = 5-hydroxyindoleacetic acid; CDG = congenital defects of glycosylation; CSF = cerebrospinal fluid; DNA = deoxyribonucleic acid; DNPH = dinitrophenylhydrazine; EDTA = ethylenediaminetetraacetic acid; FFA = free fatty acid; GABA = γ-aminobutyric acid; HVA = homovanillic acid; MPS = mucopolysaccharidoses; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; mtDNA = mitochondrial deoxyribonucleic acid; SLO = Smith-Lemli-Opitz syndrome; VLCFA = very-long-chain fatty acid.

these screening tests on (1) blood, including pH and electrolytes, NH_3, glucose, lactate, ketones, blood count, liver function tests, calcium, and (2) urine, including Clinitest and dinitrophenylhydrazine keto acids.

Type 1 presents predominantly with ketosis and is due to maple syrup urine disease. This disease is caused by a disturbance in the metabolism of branch-chain essential amino acids, resulting in an accumulation of keto acids in body fluids. Symptoms appear within the first week of life with vomiting and coma, often with fluctuating ophthalmoplegia.

Type 2 presents predominantly with ketoacidosis and hyperammonemia. This group comprises most of the organic acidurias in which a diagnosis can be made by urinary organic acid analysis and by analysis of the acyl carnitine profile on filter paper. Clues to the diagnosis include the finding of neutropenia, anemia, or thrombocytopenia.

Type 3 presents predominantly with lactic acidosis, with neurologic distress of the energy deficiency type arising from a defect in bioenergetic metabolism, as seen in the mitochondrial encephalomyopathies and PDH deficiency.

Type 4a presents with hyperammonemia without ketoacidosis. This group includes most of the urea cycle disorders. The absence of ketonuria distinguishes this group from the organic aciduria patients (type 2).

Type 4b includes a group of infants with neurologic deterioration without ketoacidosis or hyperammonemia and encompasses various disorders, including CDG and deficiencies in neurotransmitter metabolism. Nonketotic hyperglycinemia and sulfite oxidase deficiency belong to this group. Some fatty acid oxidation disorders also fall into this category and can present with neurologic symptoms, together with liver and cardiac involvement.

In type 5, hepatic dysfunction is the leading symptom. This group includes the glycogenoses and several storage disorders. Using simple basic screening, one can narrow down the differential diagnosis of these diseases to one of the groups. Further specialized tests are the next step.

Other Important Clinical Features

Skin lesions (fat pads on the buttocks in CDG), cardiac arrhythmias (as seen in fatty acid oxidation defects), abnormal hair (pili torti in Menkes' syndrome), skeletal deformities, and ophthalmologic problems, such as cataracts, are all important "red flags" for an underlying metabolic disease.

Childhood Presentation

Repeated episodes of unexplained coma, liver dysfunction, or ataxia can be the presenting symptoms of an inborn error of metabolism later in life (see Table 57-1). Precipitating factors should be identified, such as prolonged fasting, a catabolic state after trauma or surgery, or a severe infection. Fatty acid oxidation defects can present with later onset of hypoketotic hypoglycemia, hyperammonemia, metabolic acidosis, and dicarboxylicaciduria.

For an older child in stupor or coma, an approach similar to that for the neonate should be taken, using the same initial screening tests (see Table 57-2). The concentrations of glucose, ketones, lactic acid, and ammonia need to be measured urgently. Intoxication or CNS infection should be excluded. The differential diagnosis also includes CNS tumors. The clinical history and observation should focus on the child's prior behavior, feeding habits, and possible recurrent vomiting. Migraines preceding a coma can be seen in ornithine transcarbamoylase deficiency in females. The initial presentation can even be delayed until adulthood. Recurrent headache and vomiting are also frequent signs of mitochondrial diseases, which are discussed in Chapter 52,"Mitochondrial Cytopathies."

In some children, coma is associated with focal signs. Strokes and stroke-like episodes in a child or adolescent lead the physician to consider a wide spectrum of differential diagnoses, including urea cycle disorders and organic acidurias, respiratory chain defects (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), homocystinuria (arachnodactyly, ectopia lentis, marfanoid habitus, and mental retardation), Fabry's disease, and CDG syndromes. The latter, a group of inherited multisystemic disorders characterized by aberrant N-glycosylation of proteins, can also present with a failure to thrive, cerebellar degeneration, and pericardial effusions. Coagulation factor deficiencies should also be ruled out in cases of stroke.

When liver dysfunction is present, Wilson's disease should always be ruled out. Here, a defect in copper transport in the bile ducts leads to an accumulation of copper, first in the liver, resulting in chronic hepatic dysfunction or in fulminant hepatic failure, and later to a neurologic extrapyramidal syndrome due to the accumulation of copper in the basal ganglia. Early diagnosis and treatment with chelators, such as penicillamine, or oral zinc administration can prevent the neurologic symptoms. Acute or recurrent ataxia can be a symptom associated with ketoacidosis or lactic acidosis. When accompanied by a skin rash, Hartnup disease, due to a defective transport of neutral amino acids, is a possibility. Acute or intermittent psychiatric symptoms, such as hallucinations, confusion, anxiety, or aggressiveness, may suggest acute intermittent porphyria, ketoacidosis, or hyperammonemia. The older the child, the more structured and definable the neurologic picture will be. Possible neurologic manifestations of metabolic diseases are ataxia, ophthalmoplegia, peripheral neuropathies, spastic paraplegia, or chronic cerebellar ataxia. Further workup includes brain imaging, with a special emphasis on the proportion of white or gray matter involvement. An essential clue to a metabolic etiology is to recognize the progressive

nature of the neurologic picture, in contrast to the more static encephalopathies from nonmetabolic origin. Other possible neurologic symptoms are progressive polymyoclonus and seizures or mental regression. Several diagnostic algorithms in the referenced chapter on clinical phenotypes written by Saudubray and Charpentier (see Suggested Readings) can be used.

A metabolic myopathy with progressive proximal muscle weakness as a major presentation is often associated with intermittent rhabdomyolysis. This subject is reviewed in Chapter 72, "Muscular Dystrophy and Myopathy." Extrapyramidal dysfunction, such as that seen in the L-dopa-responsive dystonia, has been shown to result from an inborn error of metabolism of the guanosine triphosphate cyclohydrolase involved in the biosynthesis of tetrahydrobiopterin, the cofactor for hydroxylation of phenylalanine, tyrosine, and tryptophan respectively to, tyrosine, dopamine, and serotonin, normally leading to the synthesis of homovanillic acid and 5-hydroxyindoleacetic acid. Other defects in this bioamine metabolism are now recognized in a group of patients with dysfunction of the biosynthesis of neurotransmitters. The main clinical symptoms are extrapyramidal dystonia, oculogyric crises, body temperature fluctuation, miosis, ptosis, and hypotension. Early-onset presentation is possible. Replacement therapy treatment can lead to spectacular results and disappearance of all clinical signs.

Recent Progress in Diagnostic Investigation

Proton magnetic resonance spectroscopy (MRS) of the brain can provide important information on biochemical processes. Specific abnormalities can be seen in a certain number of disorders, such as nonketotic hyperglycinemia, Canavan's disease, or congenital lactic acidosis, but also in new, possibly treatable diseases, such as a defect in creatine synthesis or creatine transporter. The abnormal MRS spectrum caused by a lack of creatine led to the detection of an underlying defect in guanidine acetate methyltransferase deficiency or other defects in creatine metabolism, together with accurate analysis of urinary creatine/creatinine ratio and guanidoacetate. In the future, proton MRS may be used for monitoring the effect of treatment in some diseases.

Treatment Strategies

Part of the acute treatment of metabolic diseases involves recognition of factors that precipitate or aggravate symptoms with strict avoidance of these precipitants. Possible elimination of metabolites via alternative pathways should exploited. For example, intravenous sodium benzoate and sodium phenylacetate provide alternative pathways for waste nitrogen disposal in the case of hyperammonemia in the context of urea cycle disorders; 2-(2-nitro-4-trifluoromethylbenzoyl)-1, 3-cyclohexanedione (NBTC) can prevent the formation of toxic succinylacetone in tyrosinemia type 1. Alternative substrates, such as sodium succinate to bypass the block in complex 1 deficiency, can be given. In case of decompensation or intoxication (eg, organic aciduria), a diet supplemented by essential amino acids and stop of catabolism needs to be started as soon as possible.

Deficiencies of specific substances, such as L-dopa, creatine, or biotin, should be treated by exogenous administration. Clear instructions, such as the avoidance of fasting in fatty acid oxidation defects, need to be given to the parents. Children with defects of fatty oxidation should receive a frequent feeding, high carbohydrate, low-fat diet. Many enzymes need cofactors for optimal enzyme activity. In a number of specific diseases, cofactors need to be given, for example, vitamin B_{12} in methylmalonic aciduria because some forms are vitamin B_{12}-responsive. In some defects in cobalamin metabolism, OH-vitamin B_{12} is needed. In mitochondrial diseases, different cofactors, such as riboflavin and thiamine, vitamin C and lipoic acid are given to try to improve or stabilize the disease. Riboflavin may be helpful in certain cases of glutaric aciduria type II. Coenzyme Q_{10} deficiency as the cause of a mitochondrial disease has been reported, with improvement in a number of patients after coenzyme Q_{10} treatment. L-carnitine (25 to 100 mg/kg/d) can be given in mitochondrial respiratory chain defects, where there is a low free carnitine concentration but is essential and lifesaving in the case of the plasmalemmal carnitine transporter defect (100 mg/kg/d), which reverses the disease pathology.

Bone marrow transplantation as a means of enzyme replacement is being used in a number of lysosomal disorders, with variable results. For patients with CNS involvement, the procedure tends to be less effective. Nevertheless, with early diagnosis, at a time of few clinical signs or in slowly progressive diseases (eg, adrenoleukodystrophy or late-onset Krabbe's disease) promising results have been reported, including arrest of disease progression.

More sophisticated forms of engineered enzyme replacement targeting specific cells are increasingly being developed and already being used, for example, in Gaucher's disease, mucopolysaccharidosis I, II, and VI, and Fabry's and Pompe's disease. Liver transplantation has been apparently beneficial in older children (eg, methylmalonic aciduria or tyrosinemia).

Suggested Readings

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Practitioner and Patient Resources

Association for Neuro-Metabolic Disorders (ANMD)
5223, Brookefield Lane
Sylvania, OH 43560-1809
Phone: (419) 885-1497
E-mail: VOLK4OLKS@aol.com
ANMD is a national not-for-profit voluntary organization composed of families with children who have metabolic disorders affecting the central nervous system. Established in 1981, the organization shares support and information with other families through various activities. These include a yearly parent conference featuring discussions by experts on neurometabolic disorders, an annual family picnic, informal meetings, and phone calls with concerned parents. Other activities include formal lobbying, educational efforts, and contact with similar organizations throughout the United States and other countries.

CHAPTER 58

AUTISTIC SPECTRUM DISORDERS

MAX WIZNITZER, MD

Autistic spectrum disorders comprise a group of associated conditions characterized by significant deviations from normal social and communicative development and by idiosyncratic motor and cognitive behaviors. Early identification and intervention and management of comorbid conditions are key to maximizing outcome in this population.

Autistic spectrum disorders (ASDs), also known as pervasive developmental disorders, are described in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) as causing a "pervasiveness of difficulties" with socialization and communication. A listing of these disorders appears in Table 58-1. All are characterized by significant deviation from expected social skills and communication development. Affected individuals also exhibit areas of fascination or repetitive motor behaviors and stereotypies. Although the DSM-IV identifies Rett syndrome as an ASD, its distinct clinical features and course differentiate it from the other members of this group, suggesting it should be categorized differently.

In the past 15 years, the prevalence of ASDs has risen to 3–6:1,000, with *autistic disorder* being the most common (prevalence approximately 10–15:10,000). Most or all of this increase may be due to changes in diagnostic criteria, improved and earlier recognition, possible overdiagnosis, and methodologic differences among studies. However, the possibility of a true change in incidence has not yet been adequately investigated.

There is no difference related to socioeconomic or racial status. Autistic disorder has a male-to-female ratio of 3–4:1, which varies with the presence or absence of mental retardation. Recurrence risk is about 3 to 7% and consistent with a strong genetic component to these disorders. Autistic features are found in up to 25% of the mentally retarded population, usually in those with more severe profound cognitive impairment and are reported in individuals with disorders such as Down syndrome, Williams syndrome, Prader-Willi syndrome, and congenital rubella syndrome. An increased prevalence is present in individuals with fragile X syndrome, tuberous sclerosis, and marker chromosome 15.

TABLE 58-1. Autistic Spectrum Disorders

Autistic disorder
Asperger disorder
Childhood disintegrative disorder
Rett syndrome
Pervasive developmental disorder – not otherwise specified

Diagnosis

A definitive biologic marker or test to identify individuals with ASDs is not available. Therefore, diagnosis is made on the basis of behavioral and clinical features that, when combined, are unique to ASD. The criteria for autistic disorder have been adequately defined (Table 58-2). Appropriate diagnosis is important for intervention planning, family counseling, and monitoring for potential complications.

The "classic" form of ASD is autistic disorder. Diagnosis is usually made when a child is 2 to 3 years old, with subtle features frequently having been present during infancy (decreased eye contact, absent wave and pat-a-cake) and differences in joint attention, verbal language, shared affect and repetitive behaviors) and caregivers concerned about development in the second year of life. The most profound impairment occurs in the early preschool years, with a gradual, although not total, improvement in

TABLE 58-2. Diagnostic Criteria for Autistic Disorder

Significant Impairment in Socialization
Markedly impaired nonverbal social behaviors
Failure to develop developmental age-appropriate peer relations
Impaired empathy
Absent social reciprocity
Significant Impairment in Communication
Poor verbal and nonverbal language development
Problems starting or sustaining conversation
Immediate/delayed echolalia
Absent symbolic and developmental level appropriate play
Restricted Interests and Behaviors
Major area of fascination
Rigidity in routines
Stereotypies
Greater interest in parts, rather than use, of object

functioning over time (Table 58-3). All have deficits in joint attention, turn-taking, and imitation that interfere with their ability to learn from others.

In the early preschool years, social impairment is manifest by "aimless" wandering, social unavailability, and failure to seek consolation when distressed. Socialization improves over time. At first, a child may engage in solitary activities with little or no interest in children and some interaction with adults. Eventually the child may make inappropriate attempts to interact with peers and later develop "pseudosocial" skills that are stilted and pedantic in nature and associated with a topic-specific fascination.

TABLE 58-3. Autistic Disorder: Developmental History

1–2 years old
No separation anxiety
No imitation (wave, pat-a-cake, peek-a-boo)
Word development limited and use not meaningful
Socialization and eye contact decrease
Poor play
2–3 years old
Wanderer; interaction with caregiver, not with others
Limited or no speech/uses jargon
Poor response to voice
No symbolic play
Fascinations/stereotypies noted
No gesturing, but takes by hand to location
3–4 years old
Social loner
Some words and echolalia
Puzzle play
4–5 years old
Interaction with adults, but watches peers
Echolalia; phrases and requests
Phrases and requests
School age
May have improved, but limited, peer interaction
Language, if present, used for needs and simple communication
No or restricted imaginative play
Fascinations (physical actions or cognitive) persist

Children with ASD can have a language impairment affecting comprehension or grammar or relatively intact expressive language with an impaired abstraction and literal interpretation of others' comments. Most will develop communicative strategies for requests or needs. However, the persistent core deficit in language is impaired social communication, ranging from an absent desire to communicate to excessive talking to, rather than with, others (pedantic speech as in "little professors"). All children have pragmatic impairment, including poor eye contact and voice modulation, difficulties interpreting and using body language, and poor use of gestures. Immediate and delayed echolalia become apparent in the later preschool years and manifest as pronominal reversal, use of scripts, and repetition of television, video, and movie lines. Difficulty with insight regarding social and emotional function and with the ability to evaluate their actions from other people's perspectives reflect the impairment in social understanding in this population.

Play in ASD has restricted, if any, imaginative and pretend features and varies from absent copying and oral exploration to repetitive stereotypic play without variation or empathy to circumscribed play based on fascinations. Interactive play, if present, is frequently limited to areas of fascination. Children with ASD usually do not seek to continue playing if others stop the activity.

Restricted activities and interests include repetitive actions such as opening and closing doors and playing with light switches, water play, paper shredding, motor stereotypies such as finger-flicking and self-spinning, and apparent obsessive–compulsive behavior such as lining objects and preserving sameness and a fascination in mechanical or cognitive themes (eg, cars, dinosaurs, trains, weather, numbers and letters, books, telephone directories, escalators, and elevators). Most children resist changes in routine, which can include new foods or textures, unexpected stimuli, or rearrangement of furniture, items in the environment, or the schedule of daily activities.

By definition, onset of autistic disorder is prior to age 36 months. It may be gradual, with preexisting evidence of difficulties with socialization and communication, or may consist of an autistic regression in a child who had previously normal development, the latter occurring in about 20 to 40% of this population.

Asperger's disorder is a nonautistic ASD with less severe impairment in socialization that includes difficulties in interpreting and using social cues and naïve or peculiar behavior. Language development, while superficially normal, shows problems with abstraction, interpretation, and pragmatics. Clinically, the children are concrete and literal, with a poor understanding of sarcasm, irony, and cynicism. These individuals have cognitively based fascinations with limited, if any, stereotypies. All have normal or near-normal intelligence and motor incoordination (dyspraxia).

Whether this is a separate disorder or a milder manifestation of autistic disorder requires further clarification.

Childhood disintegrative disorder, previously known as *disintegrative psychosis* or *Heller's syndrome*, shares behavioral features with autistic disorder and has a worse prognosis for functional improvement. Onset is between age 2 and 10 years. These children comprise about 5% of the autistic population and have a history of prior normal development. This condition sometimes is associated with specific medical disorders, such as epileptic encephalopathy and progressive neurologic syndromes.

Pervasive developmental disorder not otherwise specified (PDD-NOS) is the diagnosis for those with some, but not all, of the features of autistic disorder (either quantitatively or qualitatively). All have problems with social interaction and either impaired communication or restricted interests and activities but do not meet full diagnostic criteria. This category is not well defined and may be inadvertently applied to children who, on later evaluation, are found to have significant cognitive impairment or other conditions causing social immaturity (such as attention-deficit hyperactivity disorder [ADHD]) or impaired social development (Table 58-4).

Evaluation

The diagnosis of ASD is usually most easily made in the preschool years. Early detection is important because of the positive impact of early intervention programming on potential outcome. Recommended evaluation includes screening for autism risk (usually through the primary-care provider and using general developmental screening tools such as the Parents' Evaluation of Developmental Status [PEDS], Ages and Stages Questionnaire [ASQ], and Child Development Inventories [CDI]), confirmation of the diagnosis and medical evaluation by a practitioner with expertise in autism (as part of a multidisciplinary assessment), and determination of needed intervention (Figure 58-1). Autism specific screening tools such as Modified Checklist for Autism in Toddlers (M-CHAT), Pervasive Developmental Disorders Screening Test, Screening Test for Autism in Two Year-olds (STAT), and Social Communication Questionnaire and diagnostic tools, including the Childhood Autism Rating Scale (CARS), Gilliam Autism Rating Scale, Behavioral Summarized Evaluation, Autism Diagnostic Interview–Revised, and Autism Diagnostic Observation Schedule–Revised, can be used, although the evaluator's clinical expertise is reported to be the most valuable assessment tool, especially in the preschool years. Laboratory testing may identify chromosomal abnormalities in 5 to 10% and epileptiform activity in 10 to 20% of individuals with ASD. In those with autistic regression, there is a twofold increase in the percentage with epileptiform discharges. The presence of epileptiform activity can be enhanced by doing a prolonged awake and sleep electroencephalogram (EEG) that, at a minimum, captures a complete sleep cycle and may require an overnight sleep study. About 10% of these children will show an increase in epileptiform activity during sleep such as that seen in individuals with acquired epileptic aphasia or electrical status epilepticus in slow-wave sleep. The significance of these EEG findings in children with no history of seizure activity is still uncertain, although a possible relationship to epilepsies with cognitive symptomatology has been considered.

TABLE 58-4. Differential Diagnosis of Autistic Spectrum Disorders

Significant cognitive impairment
Anxiety disorder (especially social anxiety)
Attention-deficit hyperactivity disorder with social immaturity
Mood disorders
Childhood schizophrenia
Child abuse or neglect
Sensory impairment
Epileptic encephalopathy
Motor overflow or mannerisms
Dementia or neurodegenerative disorder
Allergy testing

Intervention

Treatment of children with autism requires early identification. No medication or treatment will cure the disorder. Early and intensive educational intervention that is child-specific, addresses core needs (Table 58-5), and contains proven treatment components (Table 58-6) has been shown to improve the prognosis for many children. This is done in a highly structured environment with individual attention, well-trained staff, parental involvement, programming for more than 20 hours weekly, and institution of strategies proven effective in this population. Behavioral intervention should identify unwanted target behaviors, determine the controlling variables, develop an intervention strategy, and evaluate the effects of treatment.

Medications can be useful when targeting specific symptoms or presentations (Table 58-7) that have been determined to be potentially medication responsive after a functional analysis of behavior. Because of potential sensitivity to medication effect, the principle rule of pharmacologic treatment is to "start low and go slow." Risperidone and other atypical antipsychotic drugs can target aggression, behavioral outbursts, and mood instability. Serotonin reuptake inhibitor antidepressants can reduce anxiety, decrease stereotypies and perseverative behaviors, and diminish anxiety and mood fluctuations. Their effectiveness may be correlated with a family history of major affective disorder.

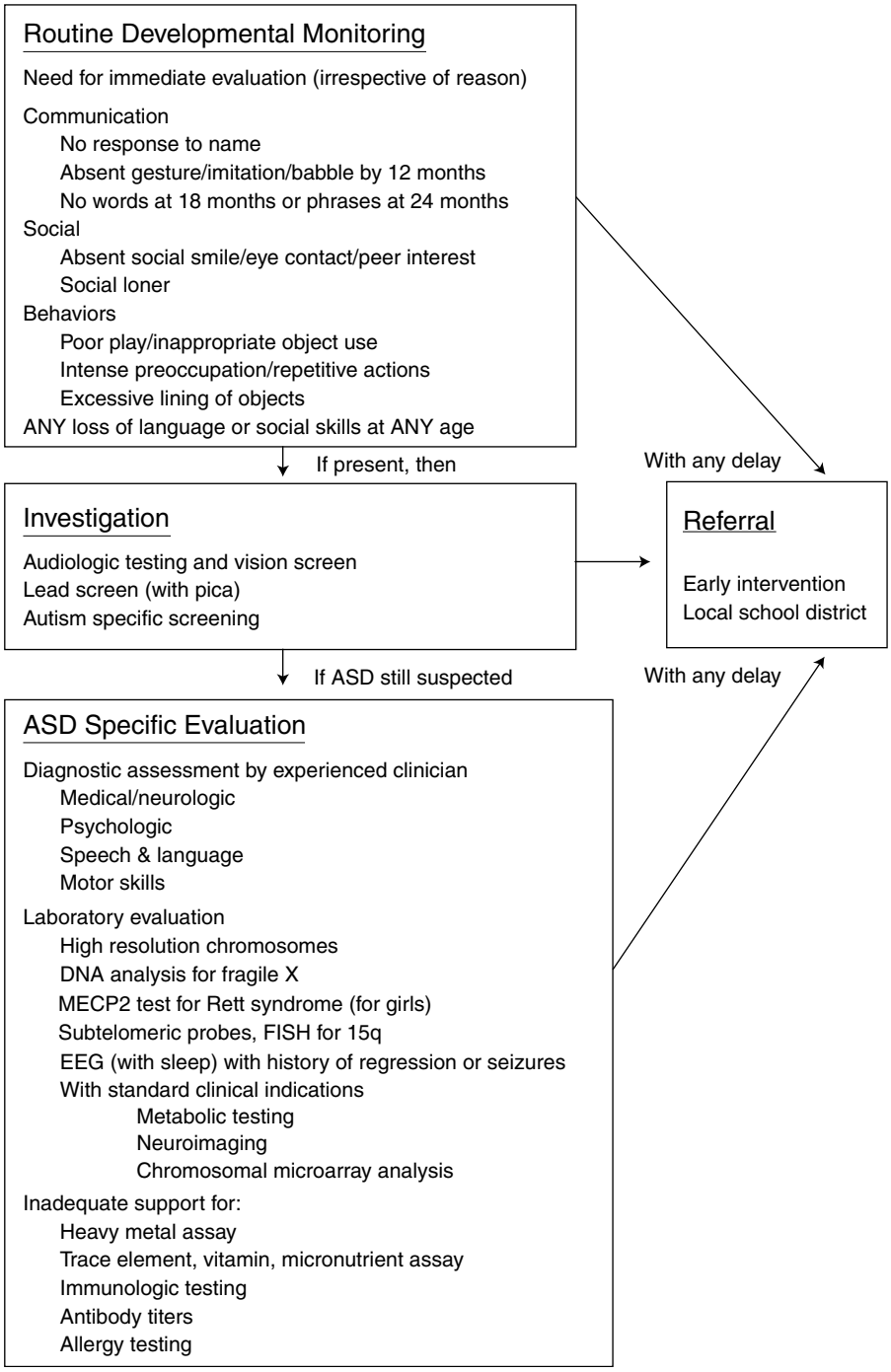

FIGURE 58-1. Evaluation for autistic spectrum disorder (ASD). DNA = deoxyribonucleic acid; EEG = electroencephalogram.

Stimulant medications and antidepressants that impact norepinephrine function improve attention in children with features characteristic of ADHD, but may also produce increased stereotypies, affective blunting, and agitation. Self-injurious behavior and tantrums or aggression of unclear etiology sometimes respond to therapy with naltrexone. Studies with a small number of subjects have reported positive effects of clonidine, mood stabilizers (lithium and antiepileptic drugs, such as valproic acid and carbamazepine), buspirone for aggression and agitation, and cholinesterase inhibitors for impaired language and inappropriate behavior. Anxiety, mood disorder, and other

TABLE 58-5. Autistic Spectrum Disorder: Areas for Educational Intervention

Attention (especially joint attention)
Imitation
Communication (including social)
Socialization
Cognitive deficits
Impaired motor abilities
Purposeful play
Daily living skills

TABLE 58-6. Autistic Spectrum Disorders: Components of Educational Intervention Program

Earliest intervention
Full time programming
Structured environment
Well-trained staff
Good school–parent communication
Family involvement in educational program
Small student–teacher ratio
Intensive treatment (at least 20 h weekly)
Use of developmental task analysis
Development of social and communication skills
Development of leisure skills
Sensory supports
Generalization of curriculum
Functional analysis of behavior
Periodic assessment of progress

TABLE 58-7. Problem Behaviors in Autistic Spectrum Disorders

Specific Features	Medication-Responsive Conditions
Aggression	Attention-deficit hyperactivity disorder
Tantrum	Anxiety
Agitation	Obsessive–compulsive disorder
Self-injury	Affective or mood disorder
Irritability	Seizures or epilepsy
Rigidity or desire for sameness	Tic disorder
Hyperactivity	Sleep disturbance
Repetitive actions or thoughts	Unclear etiology

specific diagnoses can improve with judicious use of appropriate medication and, when indicated, behavioral therapy. Epilepsy occurs in 20 to 30% of individuals with autism by adulthood. Complex partial seizures may start during adolescence and be manifested by unwanted or aggressive behavior. Evaluation and treatment is similar to other individuals with epilepsy. Claims of improvement in the core features of ASD with complementary therapies, such as vitamin B^6 or magnesium, nystatin, and food modifications, are not supported by the available research.

Comorbid disorders and problem behaviors are present, especially in the preschool years. Many individuals have difficulties with fine and gross motor coordination, including speech production. Children are at risk for accidental injury and require close supervision. Stimulus hypersensitivity may influence reactions to sound, food, touch, and visual stimuli. Children frequently have restricted dietary choices. Sleep disturbances, present in 40 to 70% and affecting sleep induction or maintenance, usually respond to nonpharmacologic treatments. Individuals with autism also may have common childhood ailments but may not be able to effectively communicate discomfort or be hyposensitive to pain. For example, challenging behaviors can be produced or aggravated by treatable possible gastrointestinal disorders such as gastroesophageal reflux and disaccharide malabsorption. Therefore, close monitoring for allergies, food sensitivities, and conditions such as migraine headaches or fractures is needed.

Prognosis

Individuals with ASD improve over time, especially after initiation of an early intervention program. Predictors of good outcome include language onset prior to age 6 years, intelligence quotient > 50, and a functional skill (such as computer or filing skills). Past reports of no functional speech in 50% and mental retardation in 60 to 70% of this population may need to be altered because of the impact of effective intervention programs. More recent reports of improved competence and language, job placement (20 vs. 5%), and independent living (12 vs. 0%) need to be interpreted in relation to differences in intervention programs and definition of the target population. Some individuals with ASD and normal intelligence can develop a special interest that allows them to function independently and become self-supporting. Alternate communication systems can circumvent communication difficulties related to verbal dyspraxia or decreased interest in social communication. Ongoing issues for adults with symptomatic ASD include housing, job placement, and health care delivery.

Suggested Readings

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Practitioner and Patient Resources

Autism Society of America (ASA)
7910 Woodmont Avenue, Suite 300
Bethesda, MD 20814-3067
Phone: (301) 657-0881 or (800) 3AUTISM
Fax: (301) 657-0869
http://www.autism-society.org
The mission of the ASA is to promote lifelong access and opportunity for all individuals within the autism spectrum, and their families, to be fully participating, included members of their community. Education, advocacy at state and federal levels, active public awareness, and the promotion of research form the cornerstones of ASA's efforts to carry forth its mission.

Center for the Study of Autism
P.O. Box 4538
Salem, OR 97302
http://www.autism.org
The center provides information about autism to parents and professionals and conducts research on the efficacy of various therapeutic interventions.

National Alliance for Autism Research
99 Wall Street, Research Park
Princeton, NJ 08540
Phone: (609) 430-9160 or (888) 777-NAAR
Fax: (609) 430-9163
http://www.naar.org
The mission of the National Alliance for Autism Research is to fund, promote, and accelerate biomedical research and science-based approaches that seek to determine the causes, prevention, effective treatments, and, ultimately, a cure for autism spectrum disorders.

Cure Autism Now
5455 Wilshire Boulevard, Suite 2250
Los Angeles, CA 90036-4272
Phone: (888) 828-8476
Fax: (323) 549-0547
http://www.cuareautismnow.org
The mission of Cure Autism Now is to promote biomedical research in autism through support for research projects, education and outreach. Cure Autism Now has merged with Autism Speaks but will maintain its own offices.

Autism Speaks
2 Park Avenue
New York, NY 10016
Phone: (212) 252-8584
Fax: (212) 252-8676
http://www.autismspeaks.org
The mission of Autism Speaks, now a merger of Autism Speaks and the National Alliance for Autism Research, is to fund, promote and accelerate biomedical research and science-based approaches that seek to determine the causes, prevention, effective treatments and, ultimately, a cure for autism spectrum disorders and to advocate in the public and private sector on behalf of the autism community.

Centers for Disease Control and Prevention
Phone: (800) 311-3435
http://cdc.gov/ncbdd/autism
The Centers for Disease Control and Prevention is the United States government agency whose mission is to promote health and quality of life by preventing and controlling disease, injury and disability. They encourage developmental monitoring, promote healthy lifestyles and develop public health policies. As part of this mission, they offer an autism information center.

Chapter 59

Child Abuse and Neglect: Issues for Neurologists

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Child maltreatment is the most common cause of preventable developmental and psychiatric disorders. It is essential that pediatric health care providers develop expertise to appropriately assess and *recognize all types of child abuse and neglect and intervene and refer cases as appropriate. Biologic research is leading to a greater understanding of the pathophysiology underlying these deficits and empirically based research is leading to effective treatment strategies.*

Maltreatment of children is a major public health concern that can lead to significant lifelong psychological and medical morbidity and even death. Annually, millions of children in the United States are the subjects of maltreatment reports (5 million reports in 2001), and approximately 1,300 of these youth die. Maltreated children come to the attention of pediatric neurologists because many have behavioral or neurologic disorders that place them at risk of abuse or they develop disorders that result from abuse and neglect. As such, neurologists must be familiar with associated risk factors, be able to readily identify abuse and neglect, and be knowledgeable about evidence-based treatments for related disorders. Given that professionals from multiple disciplines (eg, physicians, therapists, law enforcement, child protective services caseworkers) are involved in abuse cases, pediatric neurologists must also work closely and collaboratively with the multidisciplinary team.

This chapter provides (1) a brief overview of the definitions and prevalence of forms of child maltreatment; (2) a review of the medical, psychiatric, and neurodevelopmental sequelae of child maltreatment, including research that is helping us to understand the pathophysiology; (3) an outline of the basic strategies for identifying child maltreatment; (4) basic strategies for intervention and treatment, and (5) tips for working collaboratively with other professionals.

In 2004 approximately three million children alleged to have been maltreated with sufficient concerns for child protective service investigations. Almost 906,000 were substantiated child victims and 60% of reports were in 2004 "unsubstantiated" (ie, not sufficient for ongoing child protection involvement). The victimization rate has dropped from 12.5 in 2001 to 11.4 per 1,000 children. Of these youth 60% were due to neglect, 18% were physically abused, 10% were sexually abused, 7% were emotionally maltreated, and 15% had "other." A child could be a victim of more than one type of maltreatment. African-American children, Pacific-Islander children, American-Indian and Alaskan-Native children had the highest rates of victimization at 19.9, 17.6, and 15.5 per 1,000 children of the same race or ethnicity respectively. White children and Hispanic youth had approximate rates of 10.7 and 10.4 per 1,000 youth of the same race or ethnicity, respectively. Overall rates are approximately 54% white, 24% AA, 11% Hispanic. Children in the age group of birth to three years had the highest rate of victimization at 16.1 per 1,000. Girls were slightly more likely to be victims than boys.

Fatalities

The most tragic consequences include more than 1490 children that died due to child abuse and neglect and

more than 80% of these were less than four years of age (NCANDS 2004, 2007).

- Child maltreatment, depending on the severity, can lead to
  - poor physical health throughout the life
  - adverse health effects and behaviors such as smoking, alcoholism, drug abuse, eating disorders, depression, suicide, sexual promiscuity
  - correlation to juvenile delinquency and adult criminality
  - victims becoming perpetrators of child abuse and neglect in adulthood.

This public health problem has tremendous emotional cost but is also a huge financial cost.

- Recurrence influenced by
  - nature of intervention
  - family acknowledgement
  - motivation
  - level of cooperation
- Direct costs associated with hospitalization, chronic health problems, mental health care, child welfare, law enforcing and judicial systems is estimated at $258 million per day or $24 billion per year. Indirect costs (special education, medical and mental health care, juvenile delinquency, lost productivity) approximately $70 billion per year.

Definitions and Prevalence

Health professionals are required to report suspected child abuse or neglect to the state Child Protective Services (CPS) agency. Failure to do so can result in criminal prosecution. Professionals who are mandated reporters do not have to wait to report abuse until it reaches a certain definition or criteria; they must simply report suspected abuse. Once an abuse report is made, CPS determines whether the event or injury meets an abuse definition. Such definition varies by state. In the following sections, we discuss common definitions of different types of child abuse and neglect, although there is no broadly accepted national definition.

Child Neglect

Definition and Identification

Child neglect involves acts of omission by adult caregivers. There are four subtypes of neglect:

- *Physical neglect*: refusal to provide or delays in seeking out needed health care, abandonment, lack of supervision, and failure to provide for a child's basic needs of nutrition, clothing, hygiene, and safety
- *Medical neglect*: a delay in obtaining or failure to seek appropriate medical treatment
- *Emotional neglect*: refusal to obtain or delays in seeking psychological care, inadequate attention to a child's needs for affection, emotional support, or attention, or exposure of the child to extreme domestic violence and permitting a child's maladaptive behaviors
- *Educational neglect*: permitting chronic truancy, failure to enroll a child in mandatory schooling, and inattention to a child's special needs

Prevalence

Child neglect is the most common form of maltreatment, leading to one-third of all child fatalities. Neglect accounts for 45 to 55% of reported maltreatment cases.

Physical Abuse

Definition and Identification

The definition of physical abuse generally includes intentional injury to a child less than 18 years of age by an adult. Types of injuries involve bruises, welts, fractures, burns, bites, poisoning, internal injuries, drowning, smothering, gagging, shaking, and cutting. Special subtypes include substance use in utero; factitious disorder by proxy, in which a parent induces or fabricates an illness or physical or psychological symptom in an otherwise healthy child; shaken baby syndrome, which is not always easily identified and can result in death; and parent-induced apnea, mistaken as sudden infant death.

Prevalence

Roughly 25% of reported maltreatment cases are for physical abuse. Even more startling is the finding in both the First and Second National Family Violence Surveys that abusive physical punishment in reaction to parent-child conflict occurred with about 10% of children in a given year. A recent study of physical abuse in the Carolinas found physical abuse to occur many more times than state statistics indicate. In the same LONGSCAN study of mothers, harsh physical discipline meeting criteria for physical abuse was found to have a prevalence of 4.3%. Shaking had a 2.6% prevalence in children less than two years old. Physical abuse was found to be 40 times more common than indicated by state statistics. This indicates a frequent lack of identification of child abuse and neglect victims.

Sexual Abuse

Definition and Identification

Sexual abuse is identified as any sexual activity by an adult with a child where consent is either not given or cannot be given. In addition, sexual activity by an older child with a younger child can be considered sexual abuse if there is a significant difference in age (generally 5 years), development, or size, and the younger child is unable to

give consent. Sexual abuse can include voyeurism, showing children sexually explicit materials, or actual sexual penetration with penis, fingers, or objects. Regardless of the child's age, incest is illegal.

Prevalence

Most sexual abuse is not reported, so establishing prevalence rates is difficult. National surveys have revealed that 20 to 25% of girls and 5 to 15% of boys experience some form of sexual abuse.

Multiple Abuse Experiences

Most frequently, victims of child abuse and neglect are subjected to multiple types of maltreatment. Child neglect is the most common form of child maltreatment, yet little is known about the consequences of neglect in the presence or absence of other forms of maltreatment (eg, physical or sexual abuse).

- Risk factors of child physical abuse and child neglect overlap. Eighty percent of families referred for family preservation following physical abuse have a history of referral for neglect. Forty percent of referrals for neglect have a history of physical abuse.

In some states, cases are recorded as neglect, as doing so may prevent court involvement required in cases with suspicions of physical and sexual abuse. One of the primary dangers of not distinguishing pure types of maltreatment from mixed groups is that effects attributed to a particular form of maltreatment (eg, sexual abuse) may be overestimated, underestimated, or misattributed to the inclusion of children in a group who have also experienced other forms of maltreatment. Little attention has been paid to distinguishing developmental effects of single versus multiple forms of maltreatment or to "dose-related" responses of chronic versus acute maltreatment.

Child Neglect

Children that experience abuse or neglect may exhibit a variety of emotional or behavioral problems across multiple domains. Neglected children mainly show difficulties in social and physical development. Physical development problems may include failure-to-thrive syndrome in infants, indicated by growth delay with postural signs (poor muscle tone, persistence of infantile postures) and behavioral signs (unresponsive, minimal smiling, few vocalizations). Delays in cognitive functioning may include deficits in language, academic delays, and lowered intelligence scores. Delays in social or behavioral development may be manifested through avoidant or resistant attachment to the primary caregiver, passivity, reduced play interactions with mothers, isolative play in preschoolers or school-aged children, and an increased risk for delinquency and criminal behavior in adolescents. Some of these youngsters attach "too eagerly" to a health care professional because they are so hungry for love and attention.

Child Physical Abuse

The most common behavior related to the experience of child physical abuse is aggression. The aggression can be toward adults or peers and persists through the lifespan without intervention. Physically abused children also may show poor social competence in making friends and personal problem-solving. For infants, there may be a tendency to have an insecure attachment to the caregiver and later difficulties sustaining relationships. With regard to cognitive functioning and academic performance, physically abused children tend to score lower on intelligence tests because of expressive and receptive language deficits. In school, they show lower achievement than nonabused peers and also exhibit school discipline problems. Finally, physically abused children may show emotional difficulties such as depression, anxiety, and posttraumatic stress disorder (PTSD).

Child Sexual Abuse

As with other forms of abuse, a wide range and array of outcomes is associated with childhood sexual victimization. The sequelae associated with sexual abuse covers the entire spectrum of mental health problems, but when symptoms are present, they vary by developmental level. Preschoolers are more likely to show anxiety symptoms, nightmares, PTSD, internalizing and externalizing behaviors, and sexual acting out. School-aged children are more likely to experience fears, aggression, and school problems. Adolescents are more prone to depression, withdrawal, suicidal or self-injurious behavior, somatic complaints, illegal acts, running away, or substance abuse.

Perpetrators and Risk or Recurrence

Pediatric health care professionals assess and meet regularly with caregivers and their children, so they often have the best opportunities for interventions and prevention identification of at risk situations. The very people charged with the responsibility of caring for and ensuring the safety and well-being of the child are often the perpetrators. In 2003, parents made up approximately 80% of the perpetrators of child abuse and neglect. Fifty-eight percent of all perpetrators were female; and were mostly mothers and 42% were males and mostly fathers. The risk of recurrence of maltreatment is greatest in the first year after it has been identified yet child protective services may be closed

before the next incident is identified. In Baltimore, only 25% of families had a recurrence while CPS was still involved. Oklahoma found the recurrence rate was 49% within 850 days and Missouri found re-reporting to CPS for any type of CM was 42.4% in a 4 y period. Percentage of recognized repeat CM cases increases with longer follow up. Factors that predict recurrence include child vulnerability and interaction between stress and social support deficits. Recurrence risk is increased for youth living in poverty and especially if a child has psychiatric or behavioral disturbance.

Special Considerations for Neurologists

The most reliable indication that a child has been abused is disclosure to the health care professional. Otherwise, the assessment of whether maltreatment happened and what exactly happened is best left with CPS, medical abuse specialists, or law enforcement. We know that certain behaviors such as attention-deficit hyperactivity disorder (ADHD) and oppositional-defiant disorder (ODD) and developmental disabilities put youth at a higher risk for physical abuse and neglect. It is important to keep in mind that not all maltreated children will experience psychosocial or psychiatric difficulties. However, anxiety, sadness, and fear can be present. The presence of a behavior often seen in maltreated children in no way verifies that abuse or neglect has occurred.

If social, emotional, or psychiatric problems are identified in maltreated youth, the family should be encouraged to seek further psychological or psychiatric evaluation. Recognizing children's symptoms of stress and mood disturbance is not easy. Some reactions to individual or family violence may include sleep disorders, persistent thoughts of trauma, fear and belief that another bad event will occur, conduct disturbances, hyperalertness, and avoidance of stimuli (ie, trauma triggers) or similar events (ie, boating, swimming, baths, traveling, increased fidgetiness, regression, thumb sucking, dependent behaviors, time distortion, an obsession about a traumatic event, feeling vulnerable, and excessive attachment behaviors).

When the pediatric neurologist suspects that child maltreatment has occurred and makes a report to CPS, a crucial next step is to ensure that the child is referred for appropriate treatment. To do so, the neurologist will need to be familiar with common behaviors and disorders associated with child abuse and neglect and determine with the child and parent if these problems are present. Screening for psychosocial problems in an outpatient pediatric setting is difficult, given the time constraints and limited resources. Although many medical care providers have longstanding relationships with families, the brevity of the typical pediatric primary care visit (mean time 11 minutes) hampers the ability to judge parent–child aspects of diagnostic dilemmas. A brief psychosocial checklist, such as Jellinek's Pediatric Symptom Checklist, can be a useful quick screen for behavior and mood problems if identified concerns are followed by consultation with a mental health professional. Multidisciplinary collaborations between health care and legal and law enforcement professionals also are needed if we are to eliminate maltreatment of children and adolescents. Early identification and intervention can stop or at least decrease the frequency and intensity of maltreatment episodes.

In a primary-care or specialty clinic setting, such as neurology, children may present with injuries clearly resulting from physical abuse (eg, shaken baby, scald burns, or spiral fractures) but may also display medical and behavioral symptoms with unclear etiology (eg, factitious disorder by proxy, failure to thrive, medical neglect, or psychosomatic illness).

Often, primary-care providers or school personnel refer children to a neurologist in hopes of finding a reason for their mysterious symptoms. Medical providers must be prepared to rule out abuse or neglect as contributing to the etiology of the presenting problem, especially in ambiguous cases. Some types of child maltreatment may be obvious (ie, bruise that looks like a handprint) and acutely life threatening (ie, shaken baby syndrome), but other types may be disguised. Some practitioners might find it easier to ignore these difficult-to-confront possibilities, but doing so can lead to future significant injury to a child. Factitious illness by proxy is a rare, but baffling form of child abuse. Medical neglect is sometimes not considered in medical settings until puzzling symptoms lead to this consideration (ie, uncontrollable seizures may be brought on by the parent not giving appropriate medication because the parent is overwhelmed by their own issues which may include substance abuse). The etiology of psychosomatic symptoms can be related to undiagnosed child maltreatment, exposure to stress, violence, or loss.

Symptoms of neglect can present a puzzling dilemma. The most common form of medical neglect involves a lack of adherence to appointments or recommendations, resulting in actual or potential harm (eg, Frank not getting his HIV medications). When adherence is a concern, it is useful to document and review precise directions in simple language. It is frequently useful to have the parent sign a "contract" with the health care provider and to include documentation of the need to involve CPS if guidelines are not followed. Young children can present with small stature secondary to nonorganic failure to thrive associated with absence of food and poor nutrition. The etiology of psychosomatic symptoms ie, nonepileptic seizures, conversion disorders can be related to threat of harm, undiagnosed child maltreatment, or exposure to violence or traumatic bereavement. When a patient presents to a neurology clinic

with vague psychosomatic symptoms suggestive of a neurologic disorder, it is useful to find out details about family and social stressors and how these are temporally related to the onset of symptoms. Maltreated youth may fail to mention or hide a history of experiencing or witnessing violent or traumatic events. Anxiety associated with PTSD or fear may be a primary source of neurologic symptoms (ie, headache, numbness, tingling, and dizziness).

The most serious causes of morbidity and mortality from child abuse are injuries to the central nervous system. The term *shaken baby syndrome* is applied to infants who undergo vigorous shaking that leads to acceleration–deceleration injuries to the brain. These infants generally present at less than 1 year of age with seizures, vomiting, lethargy or bradycardia, hypotension, respiratory irregularities, coma, or death. Initial medical efforts for any traumatic brain injury require immediate attention to life-threatening concerns, such as increased intracranial pressure, abnormal tone, evaluation for skull fractures, contusions, risks for ischemia, and axonal damage. Retinal and subarachnoid hemorrhages may confirm a shaking injury diagnosis. Favorable prognostic indications after a shaken baby injury include absence of hypotonia and prolonged intracranial pressure, coma lasting less than 24 hours, and a score of less than 6 on the Glasgow scale at 72 hours. However an infant or child who sustains an ITBI may look well immediately after the trauma yet be left with serious and permanent disabilities. Autopsies have revealed brain parenchymal lesions that were not visible radiographically.

Predictors of poor neurobehavioral outcome in children with diffuse head injury in children younger than 10 years, and most notably children under 4 years include, absence of pupillary reaction, posttraumatic amnesia lasting more than 1 week, findings of diffuse swelling or mass lesions on CT scan, and cortical-subcortical and white matter changes on MRI. The diagnosis of Munchausen by proxy syndrome (MBPS) is made when a child's caregiver systematically fabricates an illness in the child or intentionally makes the child ill. The caregiver brings the child for medical treatment while denying knowledge of the cause of the symptoms. This diagnosis should be considered when a child presents with one or more medical problems that do not respond to treatment or has a puzzling medical course. This is especially true if the physical or laboratory findings are highly unusual, discrepant with the history, or clinically impossible.

MBPS often involves a mixture of exaggeration, false reporting, and symptom induction but can lead to serious damage and, occasionally, death. The abuser is usually a parent, most often the mother, with no clear psychiatric disorder. In physical abuse there are usually obvious signs of rage, but in MBPS the mothers often appear as wonderful parents with falsely reassuring close relationships with their children. The parent typically has an emotionally distant relationship with her spouse, who often fails to visit the patient and has little contact with physicians. Hospitalization and careful monitoring may be necessary to establish the cause of the symptoms. Video sleep electroencephalograms (EEGs) sometimes provide a useful way of monitoring if symptoms are suggestive of seizure-like activity. If foul play is suspected, hospitalization may be the only way to thoroughly evaluate the ill child, observe parent–child interactions, assess the symptoms, and develop a plan of surveillance. Documentation of the time-course of the illness may help identify causal relationships. It is useful to convene an interdisciplinary team of professionals and to involve social service and psychological or psychiatric staff for consultation and evaluation of suspected MBPS as soon as possible to compare impressions and form a plan. Careful documentation of all suspicions and historical inconsistencies is needed to verify a MBPS diagnosis. Documentation of feeding, diapering, and handling of equipment or invasive lines is useful, but staff must institute controls so the suspected parent does not have access to the provision of medical care or the child's records. Clinicians must remember possible medical comorbidity (ie, it is possible to have an explained medical disorder coexisting with MBPS). The local CPS agency or the police should be brought into the case before the parent is confronted.

It may be useful for involved health care professionals to consult with the hospital attorney or legal counsel with CPS prior to making a MPBS report as the level of sophistication and understanding of this disorder can vary. It may also be beneficial to bring in extended family members so that they understand the ramifications of the parental behavior. Often the caretaker will deny any purposeful negligence or intended harm. Caregivers "caught" in this act may be at risk of serious psychiatric issues such as suicide. It is often the responsibility of physicians and mental health professionals to help educate other professionals about MBPS and ensure safety for all family members.

Child Maltreatment and Adverse Brain Development

Animal studies have established that nurturing by a caregiver is a biologic necessity for physical and psychological growth and that experience affects physiologic variables, brain structure, and function. Studies of infant rats and monkeys show that early deprivation of frequent touching by the maternal caregiver results in persistent deficits in social, behavioral, and cognitive development. Even brief maternal separations or exposure to trauma during infancy have been shown to affect the functioning of the limbic hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoid receptor gene expression in the hippocampus and frontal cortex in rats. Individual differences in mothering

of rat pups affect their catecholamine regulation and fear response.

Cognitive problems are prominent long-term effects of abuse. Research from a study by Caldwell in 1992 revealed that childhood victims of abuse experience notable educational difficulties. Emotional problems and language or cognitive impairments were present as well as learning disorders.

- All mental processes, even the most complex psychological processes, derive from operations of the brain. A combination of genes, exert a significant control over behavior and can be turned on and off by life experience.
- Behavior and social factors can modify the expression of genes and thus the function of nerve cells. Learning can produce alterations in gene expression. Alterations in gene expression induced by learning give rise to changes in patterns of neuronal connections.

Traumatic physical abuse, specifically SBS, is the fundamental cause of organic neurological morbidity and equals the intensity of the trauma inflicted. However, neurological sequelae may result from additional forms of child abuse, such as malnutrition. Specifically, severe malnutrition during the first 6 months of life is connected to permanent neurological damage that can exacerbate any additional nervous system injury.

Brain development is regulated by genes, which interact profoundly with densely interconnected, neurobiologic systems that influence physical and cognitive development and emotional and behavioral regulation. Recent research in adults and children indicates that the acute and chronic stress of maltreatment in childhood is associated with alterations in the stress systems that play a role in the manifestations of neuropsychiatric disorders, in cognition and adaptation, and in adverse brain development. Birth to adulthood is marked by progressive physical, behavioral, cognitive, and emotional development, with parallel changes in brain maturation. Neuronal pathways must be stimulated during critical periods of development for natural maturation, pruning, synaptogenesis, and myelination to occur. The process of neural plasticity continues throughout childhood and into adulthood, with genderand age-specific differences in brain development.

Maltreatment in childhood may be more detrimental than trauma experienced in adulthood because of interaction between the psychological impact and plasticity involved in brain development. The neurodevelopmental psychopathology associated with child maltreatment may be regarded as an environmentally induced complex developmental disorder with biologic-induced mechanisms. The influence of maltreatment is related to the complex interaction between psychosocial factors, the environment, genetics, and crucial periods of vulnerability and resilience, and to how these factors influence changes in biologic stress systems. Current research is starting to provide information about these complex alterations in stress systems and the role they play in the manifestations of neuropsychiatric disorders and adverse brain development.

A brief review of the major biologic stress systems is important because (1) these are the major systems implicated in mood, anxiety, and impulse control disorders; (2) there are pharmacologic treatments to target these systems; (3) alcohol and various illicit substances are sometimes used in an attempt to "self medicate" and target these systems by damping down hyperarousal or dysregulated stress systems; and (4) a hyperaroused or primed stress system may lead to behavioral manifestations of motor restlessness and learning and memory deficits that may be secondary to trauma-induced anxiety.

The stress response is a physiologic coping response that involves the HPA axis and the sympathetic and immune systems. Endocrine factors, the microenvironment of cell alterations, and the action of stress-sensitive hormones, such as glucocorticoids, are important in determining gene expression. There is increasing evidence that maltreated children can have HPA-axis, growth hormone, and catecholamine dysregulation and that the neuroendocrine and noradrenergic levels vary depending on chronicity, severity, and types of maltreatment. The specific brain regions most vulnerable to excessive pruning associated with early stress and adverse circumstances appear to include the hippocampus, amygdala, prefrontal cortex, and corpus callosum, and these appear to be influenced primarily by the HPA axis and catecholamines. The hippocampus, crucial to memory storage and retrieval, appears to play a dominant role in the pathophysiology of PTSD, generalized anxiety, and panic disorder. There is increasing evidence that if specific pediatric neurodevelopmental pathways are altered because of stress-sensitive hormones, they will stay altered, even after the insult or problem is corrected. After neuronal damage (perhaps influenced by cortisol and catecholamine levels) is done, the brain may not be able to compensate for the neurodevelopmental skills lost during the crucial time for learning, establishing relationships, or mood stabilization. Normally, there is a diurnal variation in cortisol, with higher levels found in the morning, but this appears altered in adults with PTSD. Typically, acute environmental stress leads to elevation of serum cortisol, which has been found to have harmful effects on brain development, but chronic stress can lead to cortisol reduction and be associated with impaired attachment and biologic depression.

A few studies in adults and preliminary studies in children are demonstrating neurotransmitter and neuroendocrine dysregulation as well as volumetric brain differences associated with PTSD and other psychiatric disturbances. According to research conducted by DeBellis and colleagues, compared with demographically

matched control subjects, sexually abused girls exhibited significantly greater total catecholamine synthesis, as measured by the sum of the urinary concentrations of metabolites of epinephrine, norepinephrine, dopamine, and their metabolites. Hyperactivity of the catecholamine system has been recognized in childhood PTSD but not in nonmaltreated children with anxiety symptoms.

Magnetic resonance imaging technology has been used to further examine changes in brain development in maltreated children. This method provides a noninvasive and safe way to examine differences in brain morphology, physiology, and function between maltreated and nonmaltreated people. A cross-sectional investigation of brain development in medically healthy clinically referred children and adolescents with chronic PTSD secondary to maltreatment and nontraumatized healthy control subjects demonstrated that maltreated children and adolescents with PTSD had smaller structural measures of intracranial volumes, cerebral volumes, and midsagittal corpus callosum areas and larger lateral ventricles than did controls after adjustment for intracranial volumes and socioeconomic status. Intracranial volumes positively correlated with abuse age of onset and negatively with abuse duration and PTSD symptoms. The positive correlation of intracranial volumes with age of onset of PTSD trauma suggests that traumatic stress is associated with disproportionately negative consequences if it occurs during early childhood. Most PTSD subjects experienced multiple types of maltreatment, particularly experiences of sexual abuse and witnessing of domestic violence. Most PTSD subjects studied have comorbid disorders, with many subjects also complaining of comorbid mood disorders (major depression or dysthymia), ODD, or ADHD (mainly inattentive subtype).

It is unclear whether neurobiologic mechanisms of stress are the same in adults as those that exist in children. The severity and chronicity of maltreatment modulates the neurobiologic stress response, and there is some indication that this may be a dose-related response. A better understanding of the neurobiologic consequences of child maltreatment is necessary if we are to optimize effective treatment interventions.

Challenges and Strategies for Identifying Child Maltreatment

Health care providers are trusted adults that are in a special position to identify child maltreatment in their patients. The major barriers to identification of child maltreatment in a medical setting include lack of training and time limitations. Recently trained physicians are more likely to have received essential specialized training on the many manifestations of child maltreatment and thus have expertise in differentiating accidental from nonaccidental injury and in assessing behavioral symptoms that result from maltreatment. For pediatric physicians, specialized knowledge and training are essential. Otherwise, referrals should be made to colleagues who have expertise in the assessment of maltreated children.

There is general consensus that a multidisciplinary assessment is required for a comprehensive diagnostic evaluation, including a physical examination and psychologic forensic interview of the child and the caregiver suspected of abuse. Strategies for the pediatric neurologist trying to screen for child maltreatment include the following:

1. Taking a detailed history from the child and parent individually, with particular emphasis on specific chronologic events that occurred at the time of an injury, on differential diagnosis, and on associated features.
2. Obtaining information from medical records and other health-care providers (and CPS if already involved) regarding history of domestic violence, substance use, and psychiatric disorders.
3. Administering a brief behavioral screen, such as Jellinek's Pediatric Symptom Checklist, to assess behavioral difficulties that may be occurring.
4. Consulting with medical and mental health professionals who are involved with child maltreatment work on a regular basis. No health-care professional should attempt to manage a child maltreatment case in isolation of other professionals who are or should be a part of the multidisciplinary hospital team.
5. Calling the county CPS hotline if child maltreatment is suspected.

Interventions and Treatment

Family situations can vary widely, and the resulting sequelae of common child maltreatment differ greatly from case to case. In recent years, empirically supported treatments have been developed to address the problems associated with child maltreatment. Treatment can be very complex and must be individualized. A large body of research indicates that multiple factors are related to an increased risk for child maltreatment. In a given family, factors within the parent, child, school, community, and social network interact and may increase or attenuate the child maltreatment risk. Thus, to adequately reduce the risk of further abuse, treatment will need to cover multiple problems and address multiple systems. Below, we briefly summarize some of the current approaches to treatment.

Family Treatment

To decrease the risk of child maltreatment, it is important to alleviate family distress. Families need professional

and personal support to help them deal with guilt and frustration, and to change negative interactions that foster conflict. In some cases, partner violence is occurring and must be addressed to produce a safe environment for the child.

Parent Training

Behavioral parent training is an effective treatment for parents who have low parenting skills. This involves teaching basic parenting techniques that include setting up rules, limits, consequences, rewards, and basic discipline in the home. Specific examples of effective parenting group training include Systematic Training for Effective Parenting of Teenagers (STEP-TEEN) and Triple P that was developed and validated in Australia.

Individual Therapy

In some cases, parents or youth will have a history of maltreatment or other trauma and may need individual cognitive behavioral therapy to resolve that experience. Cognitive behavioral strategies may be used to decrease symptoms of PTSD, depression, and anxiety. Attachment disorders can be seen in traumatized victims and careful diagnostic and treatment considerations are needed.

Substance Abuse Treatment

Parental substance abuse is a major risk factor for child maltreatment and may be involved 50% of the time, especially in neglect cases. To assure safety for the child and increase the parent's capacity to parent, specific substance abuse treatment, such as the Community Reinforcement Approach for cocaine addiction, should be applied.

Pharmacotherapy

Pharmacologic interventions to reduce or eliminate PTSD and other mood or anxiety symptoms may be indicated in the treatment of traumatized children or their parents. The selective serotonin reuptake inhibitors (SSRIs) inhibit serotonin transport and can be effective antianxiety agents. There is a relatively safe side effect profile, but medication needs to be tapered if it is discontinued. Akathisia, skin rash, and mania are possible side effects. A government financed study has recently shown that talk therapy and use of the SSRI fluoxetine produced the best result in helping teenagers overcome depression, which is a disorder commonly associated with victimization.

Mood instability can occur following an interpersonal trauma. Minimal information and studies are available concerning the use of mood stabilizers. The disadvantage of using them is the need for routine serum-level monitoring, as well as monitoring thyroid and renal function with lithium, white cell counts with carbamazepine, and liver function with valproic acid. All mood stabilizers require comprehensive medical evaluation and follow-up. This class of medications can be potentially fatal in overdose. Stimulant medication use may be helpful in people with a history of trauma who also have comorbid ADHD. Youth with ADHD are at higher risk for physical abuse than same age peers without ADHD. Stimulants can be helpful for short attention span, hyperactivity, and impulsivity in some individuals; however, close follow-up is needed, as stimulants may potentially worsen the behavior and stereotypies in some individuals with anxiety, PTSD, or bipolar illness. However, this medication can be useful in reducing the risk of recurrence of physical abuse in youth with ADHD.

The hyperarousal behaviors (eg, hypervigilance and hyperactivity) evident with many individuals with PTSD have been successfully treated with clonidine, an α_2-adrenergic receptor agonist. Tolerance may develop to the sedative, but not therapeutic, effects of clonidine. Guanfacine, another α_2-agonist, has less sedative side effects. β-Adrenergic blockers such a propranolol can be useful in the management of agitation and anxiety. However, the short 4-hour half-life of propranolol means frequent administration is necessary. Side effects include hypotension and bradycardia. It can cause increased airway resistance and is therefore contraindicated in asthmatic patients.

Comprehensive Treatments

Comprehensive treatments target multiple systems for intervention. As such, these treatments provide interventions for parents, children, family, and school officials. Two comprehensive models that have been scientifically evaluated are Multisystemic Therapy and Project 12-Ways.

Parent and Child Dyadic Work

In recent years a treatment called Parent–Child Interaction Therapy has been empirically supported with young and school-aged children with a history of maltreatment. The unseen therapist observes the parent–child interaction while they are engaged in specific tasks and directly coaches the parent via an electronic device worn in the ear. The parent is coached on appropriate ways to interact with his or her child during certain tasks.

School-Based Interventions for Learning Problems

In some instances school behavioral and learning problems may contribute to risk of abuse. When parents receive frequent calls from the school due to their child's lack of progress, these contacts can be perceived as a personal attack and frustration may ensue from the parent's difficulty in resolving the school issue. Often behavioral problems are due to a child's difficulty in understanding and producing academically. Parents may feel some of these

behaviors are purposeful *vs* due to a cognitive weakness. Regardless of whether the problem is reported as academic or behavioral, the child should undergo an academic assessment. In most cases a school psychologist best accomplishes this and most school districts have psychologists available for such assessments. However, if a long waiting list exists, the neurologist can refer children to private practice psychologists or other specialty clinics that may exist in communities or universities.

Collaboration of Medical and Mental Health Providers

As noted earlier, no professional handling a child maltreatment case should try to manage it alone. Child maltreatment is a complex problem that is commonly addressed by medical, mental health, legal, and child protection professionals. Through collaboration, professionals can assure that all aspects of a child and family's care receive the best attention. Important considerations include (1) whether there is a suspicion of or risk for child maltreatment; (2) preparations for documentation or photography if the child is in need of a medical examination due to a possible injury; (3) whether a mandated report to CPS should be made; and (4) recommendations for mental health assessment or treatment. If a report is to be made to CPS, parents should be informed, as anonymous reporting leads to greater distrust of medical assistance.

Collaborative professional efforts can help reduce the adversarial results that may come with reporting and help to ensure that a family follows through on treatment. Even when health-care providers are angry with the family, the parents should be encouraged to view themselves as a part of the team that is working to keep the child safe.

Some health-care providers may not feel that patients who have been maltreated need mental health treatment and may not make a referral. However, almost always, at least a mental health evaluation is indicated.

Families referred for mental health services may fail to actually engage in treatment. It is important that referrals be made in a nonjudgmental way (ie, "I need help in providing comprehensive care for your child"). Barriers to families' participation in treatment include lack of transportation, no telephone, treatment being unavailable during parents' hours away from work, being placed on a waiting list for treatment, fear of being mentally ill, the stigma of mental health treatment, and not valuing mental health treatment. Medical and mental health staff can assist families with overcoming these barriers and maintaining treatment compliance.

When collaborative care providers work for separate agencies, difficulties may exist in sharing verbal and written information. During the initial contacts with the family, the Health Insurance Portability and Accountability Act (HIPAA) and written agreements regarding exchanges of information should be reviewed with the parent or legal guardian. If the two providers are from the same agency, families should be informed of the in-house confidentiality policy. In situations where providers represent different agencies, letters of agreement between the agencies may be necessary to clarify issues of confidentiality. Documents of this nature should form the basis of client discussions. In all cases, clients should be informed about any potential limits or exceptions to confidentiality (eg, suspected abuse or neglect, subpoena of records by a judge). The importance of detailed, accurate, and up-to-date documentation must be realized. Detailed medical histories from the patient and other family members should be verified with actual medical records. It is important to remember that it is possible to have an explained medical or developmental disorder coexisting with symptoms associated with child maltreatment. Several studies suggest that vulnerable youth (ie, those with high-prevalence, low-severity disabilities) are more prone to child maltreatment. A paper trail documenting phone calls, missed appointments, and suspicious observations may be key to whether protective services investigates or dismisses a reported case.

Conclusion

Pediatric neurologists may be asked to evaluate or treat children who have been abused or neglected. It is well known that histories of child maltreatment are associated with poor parenting skills and a higher risk of intergenerational transmission of substance abuse, problematic parent–child interactions, domestic violence, and child maltreatment. These poor outcomes appear to be mediated through developmental consequences and negative effects on biologic stress systems and on brain development. To provide safety for their young patients and guide the family toward a peaceful, healthy solution, physicians must be well equipped to (1) determine if they suspect maltreatment by understanding the definitions of abuse and neglect; (2) understand potential sequelae associated with child maltreatment and be able to identify such in the patients; (3) conduct an assessment to determine whether the case has met a threshold of suspicion for making a report to CPS; (4) understand basic treatment strategies to make an appropriate referral; and (5) immediately engage in the process of communicating and working collaboratively with other professionals. Families will need to be carefully monitored to ensure they are fully engaged in treatment and are benefiting from the services being provided. All disciplines should strive to maintain positive relationships with key personnel from law enforcement, the courts, and child protective services. Health-care professionals are encouraged to provide community

support to young victims. Careful identification, reporting, referral, and collaboration are all needed to protect children, our most vulnerable patients.

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Practitioner and Patient Resources

American Professional Society on Abuse of Children (APSAC)
http://www.apsac.org
APSAC is a membership society dedicated to serving professionals who work in child abuse and neglect and thereby improving the quality of services to maltreated children and the adults who share and influence their lives.

National Clearinghouse on Child Abuse and Neglect Information
http://nccanch.acf.hhs.gov
The mission of the Clearinghouses is to connect professionals and concerned citizens to timely and well-balanced information on programs, research, legislation, and statistics regarding the safety, permanency, and well-being of children and families.

National Data Archive on Child Abuse and Neglect (NDACAN)
http://www.ndacan.cornell.edu
NDACAN promotes scholarly exchange among researchers in the child maltreatment field. NDACAN acquires microdata from leading researchers and national data collection efforts and makes these datasets available to the research community for secondary analysis.

Pediatric Symptom Checklist
http://psc.partners.org
The Pediatric Symptom Checklist is a brief screening questionnaire used by pediatricians and other health professionals to

improve the recognition and treatment of psychosocial problems in children.

Helping and Lending Outreach Support (HALOS)
http://www.charlestonhalos.org
HALOS is a public–private partnership that provides much-needed resources and services to abused and neglected victims served by the Charleston County Department of Social Services.

Somatoform Disorder: Somatization
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CHAPTER 60

REHABILITATION: THE ROLE OF OCCUPATIONAL THERAPY AND PHYSICAL THERAPY

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Medical and technologic advances in the care of children with neurologic conditions have resulted in a greater focus on developmental morbidity and, subsequently, a higher demand for pediatric rehabilitation services. Pediatric neurologists need to appreciate the roles and functions of physical and occupational therapists as part of the management of children with or at risk for developmental disabilities.

Rehabilitation focuses on restoring or optimizing abilities and capacities of individuals through training, compensation, and adaptation of the task or environment. The primary goal is to promote autonomy, productivity, and life satisfaction. Rehabilitation services for children and youth must consider their changing developmental needs and demands and must also appreciate the intense involvement of the family in the rehabilitation process. Children who experience loss of function due to injuries or diseases will undergo rehabilitation interventions to restore or optimize functioning as they continue to grow and develop; however, more frequently, pediatric rehabilitation involves the facilitation of the acquisition of developmental skills and activities in children with a developmental disability. Rehabilitation services may be offered acutely, typically in a hospital setting, or as part of an outpatient service, typically in a community-based setting. In hospitals, rehabilitation specialists play an important role in the diagnostic work-up of children presenting with neurologic conditions. Impairments and delays across developmental domains are identified using objective, age-appropriate evaluation tools. Therapeutic interventions may begin acutely for children with either sudden or newly identified disability (eg, traumatic brain injury, encephalitis, cerebral palsy), with complications resulting from chronic disorders (eg, myelomeningocele, bronchopulmonary dysplasia), or after specialized medical or surgical interventions (eg, selective dorsal rhizotomy, open heart surgery). An important role of rehabilitation specialists in acute care is the identification of ongoing rehabilitation and resource needs of children and families and coordination of such services after discharge. Community-based programs in rehabilitation centers and outpatient clinics and home and school-based services provide ongoing therapeutic interventions to children with health risks or chronic developmental disabilities. This may include monitoring of progress and identification of new resource needs and periodic assessments and interventions at key points in the lifespan to enhance function. Interventions in the community focus primarily on promoting independence, maximizing function at home and at school, and facilitating participation and integration in the community. Working on skills and

activities in the child's "natural environment" ensures that all elements of the child's environment are considered and modified if necessary. Furthermore, everyday activities with respect to personal maintenance, mobility, academic performance, leisure, and recreation are more readily addressed as part of rehabilitation interventions.

Rehabilitation interventions include a number of approaches. *Remediation* emphasizes improvement in the areas of difficulty. For children, this may include restoration of developmental skills and abilities or facilitating the successful acquisition of developmentally appropriate skills. Often, deficits cannot be changed and therefore *compensatory* techniques (eg, using aids and adaptations, modifying the task, or altering the environment) are used to promote function and minimize the effect of the child's problems or difficulties. Increasingly, rehabilitation specialists are applying disease *prevention* and health promotion strategies (eg, developmental stimulation programs and injury prevention strategies) to individuals at risk for developmental disability or secondary complications.

Rehabilitation Process

Emphasis is placed on interdisciplinary collaboration. Each discipline brings complementary expertise to the team, to best meet the needs of the child and family. The specific guidelines and procedures for referring a child to rehabilitation specialists are largely determined by the policies and procedures of the facility within which each therapist works. Once a child is referred, rehabilitation specialists may carry out a *screening* to determine whether services are necessary or may perform a formal *assessment*. A variety of standardized and nonstandardized assessment tools may be administered (Table 60-1) to identify the child's strengths and limitations. As part of the evaluation, particular concerns of the child (if appropriate) and the parents are identified and prioritized. Appreciation of the child's physical and social environment, family functioning, and available resources are also part of the assessment process. If *treatment* is required, interventions may be carried out directly (ie, therapist works individually with the child) or indirectly (ie, therapist consults with parents, teachers, or other caregivers and recommends strategies to promote function). An individualized treatment plan is formulated to address short-term and long-term goals, and the most appropriate treatment modalities are selected (Table 60-2). Periodic *reassessments* ensure that goals are being achieved, and treatment strategies may be subsequently adjusted or refined. *Discontinuation of services* may be accompanied by referral to other programs or periodic follow-up to address new needs or concerns.

Role of Occupational Therapy

Occupational therapy (OT) uses purposeful activity and task analysis to prevent and minimize the impact of disability on functional independence and facilitates the development of those skills and behaviors essential to meeting the demands of everyday life. Philosophically, OT is predicated upon a developmental perspective, with the goal of meeting an individual's occupational performance needs throughout the lifespan. The term "occupational performance" refers to those tasks in which individuals engage as part of their normal, everyday routine. In childhood, these tasks may include play and recreation, self-care activities, functional mobility, peer and family relationships, schoolwork, and community living skills. Performance in any of these areas is dependent on the individual's skills within the motor, sensory, cognitive, behavior, and social domains. The focus of occupational therapy is not on the neurologic disease itself, but rather on the impact a disorder has or potentially will have on a child's ability to function in life roles. The primary goal is to facilitate occupational performance and prevent

TABLE 60-1. Examples of Assessment Tools Used by OT and PT

Assessment Tool	Area(s) Evaluated
Alberta Infant Motor Scale	Spontaneous gross motor movement repertoire of infants in supine, prone, sitting, and standing positions (weight-bearing, posture, and antigravity movements)
Batelle Developmental Inventory	Motor, adaptive, communicative, cognitive, and personal–social skills
Canadian Occupational Performance Measure	The client's self-perception of their performance in everyday activities (problem areas and satisfaction with performance)
Gross Motor Function Measure	Gross motor functioning (developed for children with cerebral palsy)
Miller Assessment of Preschoolers	Mild to moderate developmental delays
Motor Free Visual Perception Test	Visual perceptual processing ability (without motor response)
Peabody Developmental Motor Scales	Gross motor and fine motor skill acquisition (mastered or emerging)
Pediatric Evaluation of Disability Inventory	Functional status (functional skills, caregiver assistance and modifications)
Test of Infant Motor Performance	Evaluates motor control and organization of posture and movement for functional activities in newborns and young infants
Vineland Adaptive Behavior Scale	Adaptive behaviors of children (communication, motor, daily living skills, socialization, behavior)
Functional Independence Measure for Children (WeeFIM)	Degree of disability in terms of the need for supervision or assistance in functional activities

TABLE 60-2. Selected Examples of Treatment Approaches Used by OT and PT

Treatment Approach	Primary Focus
Biomechanical	Re-establish or promote the biomechanical aspects of movement
Developmental	Facilitate the mastery of developmental skills
Motor Control/Motor Learning	Apply practice and feedback techniques to acquire or modify movements using functional tasks
Neurodevelopmental	Decrease the influence of abnormal muscle tone and postures, prevent contractures and deformities, promote normal movement patterns
Occupational Performance	Enhance functioning in self-care, productivity and leisure areas important to the client
Rehabilitative	Maximize independence in spite of residual impairments through the use of compensatory techniques
Sensory Integrative	Promote adaptive responses by organizing and integrating sensory processing

dysfunction by providing the child with opportunities to develop, restore, and maintain those skills and behaviors necessary for independent living.

Pediatric occupational therapists service children from the newborn period to adolescence. Once a child with a neurologic disorder is referred to OT, a formal assessment assists in the diagnosis of specific disabilities, establishes a baseline level of performance, and determines whether a child requires OT. The major purpose of testing is to provide a comprehensive evaluation of function by determining the child's strengths and activity limitations. This requires communication with the child's primary caregivers, as well as an understanding of the medical, psychological, and social factors that can interfere with function.

The evaluation of a child's functioning in occupational performance areas (ie, activities or occupations) includes assessment of self-care, feeding, functional mobility, play, community living skills, and school related and prevocational tasks. In addition, the assessment of the performance components (skills or abilities) that may influence functioning may include evaluation of reflexes, range of motion, strength and muscle tone, sensory modalities, perceptual motor skills, cognitive abilities, eye–hand coordination and in-hand manipulation skills, concentration, and organizational abilities. Consideration of these elements provides the therapist with a holistic view of the child's abilities. The actual areas evaluated will vary depending on the age of the child, their developmental level, and the family's primary concerns. With a neonate, for example, assessment may focus on identifying skills in neurobehavioral organization, movement patterns, and oral-motor control, whereas for a preschooler, more emphasis may be directed toward independence in dressing, preacademic skill acquisition, and cooperative play. A wide variety of standardized assessments are used by occupational therapists, and many require training in the administration and interpretation of these tests.

Until recently, most pediatric occupational therapy services were provided predominantly through individual one-on-one therapy. In the past decade, current practice has changed to include a number of service delivery models. Advancements in health care that have improved life expectancy in children with complex health problems, a shift toward shorter hospitalizations, and the integration of disabled children into mainstream schools collectively have created a need to expand OT services from traditional acute-care facilities to community, home-based, or school-based services.

Because young children frequently display patterns of behavior that only suggest difficulties in future developmental status, different intervention strategies are required. In addition to traditional remediation, which is aimed at improving areas of difficulty by teaching specific skills in occupational performance (eg, learning to tie shoelaces or to draw a circle), both compensatory and prevention intervention models may also be used. Compensatory mechanisms may be used when a problem within the child cannot be substantially changed, regardless of how early the intervention process begins. Environmental adaptation may be necessary when a child is unable to compensate for a disability and requires specific environmental modifications to perform a task more efficiently. Examples of functional adaptation include restructuring the physical environment in the neonatal intensive care unit, using ramps to assist with functional mobility or positioning in the classroom to optimize learning. Preventive strategies address children who are at risk for developing problems but who have not as yet demonstrated delays in development. For example, the occupational therapist may provide suggestions that enrich the environment so as to decrease the long-term effects of risk factors.

Various treatment approaches are used in pediatric OT (see Table 60-2). They provide a systematic way to consider performance problems and identify priorities for intervention. The intervention approach within which activities are presented varies depending on the nature of the dysfunction. For example, play can be used within a biomechanical framework to promote range of motion and muscle strength or within a psychoanalytical framework to facilitate emotional expression. Occupational therapists apply various treatment approaches when providing services and the choice depends upon the age and specific needs of the individual child and the therapist's expertise and background. Many occupational therapists choose to use a combination of approaches to best meet the specific needs of the child and family.

Among the unique services offered by occupational therapists working in a pediatric setting are feeding and oral motor interventions; selection of adaptive equipment; fabrication or purchase of splinting, orthotics, and seating devices; and facilitating independence in activities of daily living and developmental progress.

Occupational therapists use purposeful activity (or occupation) to promote adaptive skills in children with disabilities. For an activity to generate a response, it should be developmentally appropriate, interesting, and motivating to the child and address specific therapeutic needs. Various activities are used depending on the particular goal for each child. For example, activities that require antigravity movements (eg, game mounted on the wall) or that offer resistance (eg, modeling clay) may be used to increase strength and dexterity, whereas paper and pencil activities may be chosen to improve visual acuity and the ability to discern patterns. The occupational therapist may use meaningful activities combined with physical handling and positioning techniques to facilitate the child's development of higher-level skills, such as postural control, visually directed reach, grasp, and manipulation of objects. Occasionally occupational therapists may design or fabricate environmental and equipment adaptations, such as positional seating, feeding devices, toys, or orthotics to enhance the acquisition of age-appropriate functions.

In summary, occupational therapy aims to improve the child's abilities while modifying the tasks or environment so as to maximize functioning, allowing the child to meet his or her full potential. Developmental activities such as feeding, moving, communicating, and playing are primary activities of children. Through the use of purposeful, ageappropriate activities and intrinsic motivation, the occupational therapist encourages the child to acquire an increasing repertoire of developmental skills.

Role of Physical Therapy

Physical therapy is a profession with the mandate to assist in the development or restoration of optimal gross motor function. The child with a neurologic or developmental disorder may present with a variety of impairments and subsequent limitations in activity and participation. The pediatric physical therapist uses various assessment tools to determine whether impairments and activity limitations are in fact present and evaluates the extent of the impairment and the degree of the activity limitation in motor function. The physical therapist collaborates with the child and the family to establish realistic intervention goals, with the objective of developing or restoring gross motor function.

The physical therapy assessment allows for the determination of the child's muscle strength, range of motion, reflex activity, postural control, and gross motor function. When evaluating strength, the therapist not only assesses the force of individual muscles but also the functional strength of the child during specific gross motor activities. Postural control is assessed in isolation and in the context of its contribution to motor function. Gross motor development is assessed using a variety of standardized tools, such as the Alberta Infant Motor Scale (AIMS), the Peabody Developmental Motor Scales (PDMS), and the Test of Infant Motor Performance (TIMP). All these measures compare the child with the norm and help to establish the degree of activity limitation. The level of gross motor function of the older child can be determined using the Bruininks-Oseretsky Test of Motor Proficiency (BOTMP). The Gross Motor Function Measure (GMFM) has been developed specifically for use with children who have an established diagnosis such as cerebral palsy. It allows for the evaluation of the amount of change over time in several gross motor domains such as lying, sitting, and walking. The Gross Motor Performance Measure (GMPM), which has recently been developed, allows for the evaluation of qualitative changes in gross motor function. This should prove to be an important measure, as often the child with a disability shows improvement in the quality but not the quantity of movement following an intervention program.

Once the evaluation is complete, the therapist works with the child and the family to establish treatment goals and the intervention plan. The plan takes into consideration the needs of the child and the dynamics of the family unit. Intervention strategies are developed by analyzing a gross motor task and determining which components are missing or impaired. In the past, traditional physical therapy intervention was composed of hands-on treatment with the goal of inhibiting abnormal movement patterns and facilitating more normal motor responses from the child. Current principles of motor learning encourage the child to initiate the movement with the therapist acting only as the guide or coach. Movements are repeated in a simple environment, then expanded into more complex situations with regular feedback of performance and results given to the child. This enables the child to better learn and retain the motor task. Strengthening activities were once contraindicated for the child with spasticity, as these exercises were thought to increase the abnormal muscle tone. Recent literature suggests this is not the case, and that, in fact, strengthening of a spastic limb may improve its ability to function. Muscle strengthening in the very young child presents an interesting challenge for the physical therapist. The child may be unable or uninterested in doing specific muscle-strengthening exercises. It is then necessary for the physical therapist to incorporate strengthening into a play activity that suits the age and cognitive level of the child.

The intensity and type of physical therapy intervention varies during the course of the child's growth and development. During infancy and preschool years the child may receive frequent intervention, with the goals of maximizing gross motor performance and preparing for entry into school. This may also involve evaluation of the need for assistive devices such as orthotics, walkers, and wheelchairs to promote best function in the child's environment. When the child reaches school age, physical therapy may continue as regular treatment but at a less frequent intensity. The therapist may also act as a consultant to ease integration into the classroom and school setting.

As the child grows, the physical therapist carries out periodic reevaluations, in collaboration with other members of the medical team, to determine whether any new impairments have arisen such as a scoliosis or joint contractures. The therapist works with the child, the family, and the medical team to develop new intervention strategies to minimize the impairments. Should the child require surgery, the intensity of physical therapy intervention increases in the preoperative period to prepare the child for the surgery and in the postoperative period to return the child to the preoperative level of function.

The child with a neurologic impairment may demonstrate a tendency to be less active than other children. This can lead to deconditioning, poor physical fitness, and weight gain that may further impair the child's mobility. The physical therapist has an important role and responsibility to assist the child with the development and maintenance of both physical and cardiovascular fitness. The therapist can work with the child and the family to determine the child's exercise and sporting interests and to direct them to the appropriate resources for adaptive fitness and sporting activities.

As the child progresses through adolescence to adulthood, the physical therapist can assist the family with the transition from pediatric to adult medical and therapeutic services. This is usually a difficult transition for both the child and the family. The family may find that the services may be dispersed throughout several different institutions with little or no coordination or communication among centers. The physical therapist not only assists the family in determining the appropriate resources but also acts as an advocate for the young adult to ensure that adequate follow-up is obtained. Together with other health professionals, physical therapists are involved in transitions programs, which address the many challenges associated with adulthood and independent living.

In summary, the physical therapist assists in the development of gross motor skills, which enable the child to be mobile and achieve active participation in his or her environment.

New Directions in Rehabilitation Practice

Rehabilitation specialists increasingly adopt a biopsychosocial view of pediatric rehabilitation, recognizing that developmental disability not only results from the medical (biologic) condition, but is also in part a socially created process (psychosocial). Activity limitations may occur because of deficits or impairments of the nervous system but may be further exacerbated by environmental factors (eg, physical, attitudinal, or social barriers) that inhibit functioning. As such, occupational and physical therapists increasingly appreciate the importance of personal and environmental factors that can influence health and wellbeing. Recently, the World Health Organization endorsed this broader perspective of functioning in their new International Classification of Functioning, Disability, and Health. This holistic view defines health as encompassing body structures and functions (organ system level), activity (individual level) and participation (societal level). This conceptual framework recognizes the importance of contextual factors (personal and environmental) as mediators of functioning and health. With this framework in mind, rehabilitation specialists increasingly use a transactive approach to the therapeutic process, recognizing there is a dynamic interplay between the child's abilities and deficits, the daily tasks and activities that are expected for their age and culture, and the environmental context (home, school, and community) in which they live. As such, treatment not only focuses on "fixing" or minimizing deficits (eg, spasticity, restricted range of motion, coordination difficulties, and perceptual deficits), but also applies strategies (eg, using aids and adaptations, or simplifying the task) to promote functional independence in spite of the child's impairments. Rehabilitation specialists are increasingly involved in health promotion initiatives that encourage greater participation in social, cultural and recreational activities in the community. Children and youth with disabilities may be encouraged to participate in therapeutic recreational programs such as hippotherapy (horseback riding) and aquatic activities, or the therapist may provide strategies to overcome obstacles that limit integration and participation in leisure activities at home and in the community that are enjoyable for the child.

Family-centered care is a service delivery model that recognizes that the family knows their child best and therefore should work collaboratively with health professionals to prioritize goals and assist in the decision-making process for program planning. Family members are encouraged to participate actively in the rehabilitation process. Therapists provide information and support, thus enabling families to become more competent and confident as caregivers of a

child with a disability. Increasing evidence supports the benefits of a family-centered approach to practice in terms of family satisfaction with service and optimizing functional outcomes for the child. Rehabilitation specialists are increasingly embracing the use of a family-centered model of care in practice.

In recent years, budgetary constraints coupled with a greater demand for pediatric rehabilitation services have meant health professionals have needed to be even more accountable for the benefits of their interventions. Therapists must now make clinical decisions based on the most current available scientific evidence and new theoretical models in the field. In particular, there has been tremendous development in the area of standardized pediatric outcome measures, enabling therapists to objectively document degree of responsiveness to treatment across a wide range of outcomes of interest. Most recently, measures are being developed to quantify change in discrete performance areas (eg, gait analysis or assessment of sensory modalities) and to ascertain benefits in health-related quality of life, level of functioning, and participation. Therefore, clinicians are now expected to build on their core professional knowledge by keeping up to date with new knowledge, to ensure best practice. This concept of - evidence-based practice has been accompanied by the advancement of the professional training programs in occupational and physical therapy to a master's level across North America.

Summary

Medical and technologic advances in the care of children with neurologic conditions have resulted in a greater focus on developmental morbidity, and subsequently, a higher demand for pediatric rehabilitation services. Pediatric neurologists need to appreciate the roles and functions of physical and occupational therapists as part of the management of children with or at risk for developmental disabilities. Rehabilitation specialists work collaboratively with the child and family to develop or restore function, increase competency, autonomy, and community integration, and also to prevent disability, social isolation, and family stress. As members of an interdisciplinary team, occupational therapists and physical therapists collectively help neurologically impaired children meet their daily needs and demands in the context of their environment and enable families to become effective caregivers.

Suggested Readings

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Helders PJ, Engelbert RH, Custers JW, et al. Creating and being created: the changing panorama of paediatric rehabilitation. Pediatr Rehabil 2003;6:5–12.

Practitioner and Patient Resources

American Occupational Therapy Association (AOTA)
http://www.aota.org
AOTA is the nationally recognized professional association of approximately 40,000 occupational therapists, occupational therapy assistants, and students of occupational therapy. AOTA advances the quality, availability, use, and support of occupational therapy through standard-setting, advocacy, education, and research on behalf of its members and the public.

American Physical Therapy Association (APTA)
http://www.apta.org
APTA is a national professional organization representing more than 63,000 members. Its goal is to foster advancements in physical therapy practice, research, and education.

Canadian Association of Occupational Therapists (CAOT)
http://www.caot.ca
CAOT provides services, products, events, and networking opportunities to help occupational therapists achieve excellence in their professional practice. In addition, CAOT provides national leadership to actively develop and promote the client centered profession of occupational therapy in Canada and internationally.

Canadian Physiotherapy Association (CPA)
http://www.physiotherapy.ca
CPA is the national professional association representing approximately 9,000 members distributed throughout all provinces and territories. CPA's mission is to provide leadership and direction to the physiotherapy profession, foster excellence in practice, education, and research, and promote high standards of health in Canada.

International Classification of Functioning, Disability and Health (ICF)
http://www3.who.int/icf/icftemplate.cfm
The World Health Organization's ICF describes how people live with their health condition. ICF is a classification of health and health-related domains that describe body functions and structures, activities, and participation. The domains are classified from body, individual, and societal perspectives. Because an individual's functioning and disability occurs in a context, ICF also includes a list of environmental factors.

CHAPTER 61

SMALL, LARGE, OR ABNORMALLY SHAPED HEAD

WILLIAM DEMYER, MD

Head circumference in infants correlates with brain size and growth. This measurement should be part of routine clinical assessment because it helps gauge a child's development. The size and shape of the head have important implications for the diagnosis and prognosis of many conditions.

Monitoring and Charting the Head Size of Infants

To measure the occipitofrontal circumference (OFC), the most important physical dimension of an infant, extend a tape snugly around the head from the glabella to the external` occipital protuberance and record the maximum reading. At term, the OFC is about 35 cm. The range for statistically defined normocephaly is ± 2 standard deviations (SD) (Figure 61-1).

An OFC > 2 SD below the mean is microcephaly and > 2 SD above the mean is megalocephaly (macrocephaly). The range between ± 2 SD mostly reflects normal genetic variation in somatotype. During the first year of life, the OFC increases by an average of about 1 cm per month but most rapidly in the first 6 months. By 1 year of age, the infant's OFC normally had increased about 12 cm, to around 47 cm. The brain weight nearly triples from 360 g at birth to about 950 g at 1 year, or about 70% of its final weight of 1,350 g.

Because a deviant OFC warns of an abnormal brain, measure every infant's head regularly, starting at birth. In the first year of life, measure the OFC monthly, in the second year every 3 months, and in years 3 to 5 every 6 months. Plot the successive OFCs for comparison with the normal curve (Figures 61-1 and 2). When an infant has a small or large OFC on one measurement or when successive OFCs cross the graph lines upward or downward, always suspect an abnormal brain (see Figure 61-2).

The OFC of premature infants increases more rapidly for a period than in term infants, which is a normal phenomenon to distinguish from evolving hydrocephaly. Neonatology texts contain the appropriate curves for premature and very-low-birth weight infants. The OFC depends on the factors listed in Table 61-1.

Relation of OFC to Brain Size

Because an infant has a thin skull and the scalp and the sinuses are underdeveloped, the infant's OFC correlates more closely with intracranial volume than in older people. Microcephaly, a small head, necessitates micrencephaly—a

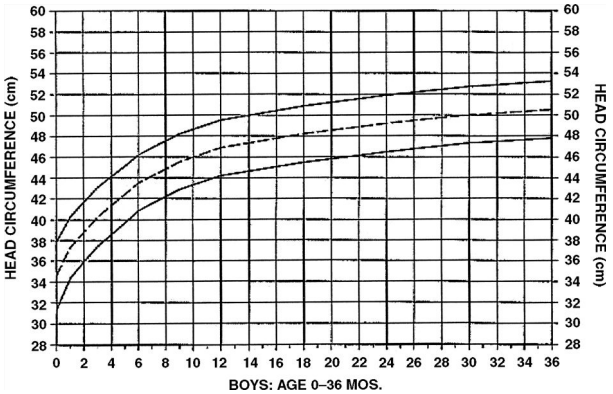

FIGURE 61-1. Normal curve for the occipitofrontal circumference of boys from term birth to 3 years. The occipitofrontal circumference (OFC) for girls is 0.5 to 1.0 cm less. The interrupted line is the mean. The solid lines are ± 2 standard deviations. Data from Roche AF, et al. Head circumference reference data: birth to 18 years. Pediatrics l987;79:706–12.

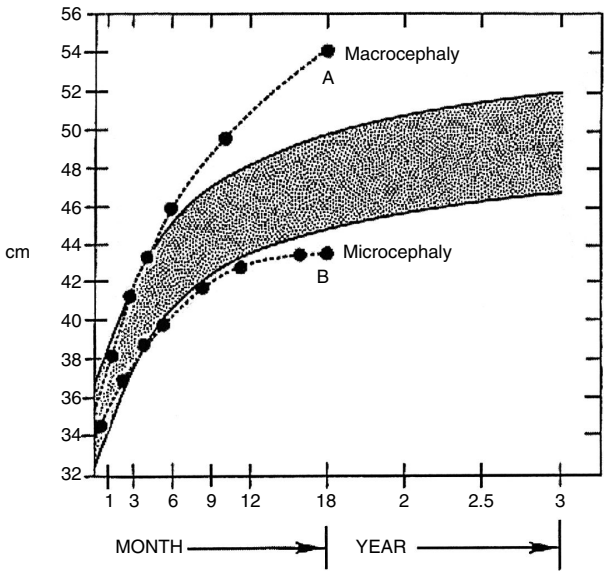

FIGURE 61-2. Successive plots of the occipitofrontal circumference may remain within ± standard deviations in normal individuals or may cross graph lines upward or downward, even if normal at birth. Reprinted from DeMyer W. Technique of the neurologic examination: a programmed text. 5th ed. New York: McGraw-Hill; 2004.

small, underweight cerebrum or brain. In contrast, a large head may contain a large, overweight cerebrum as in megalencephaly; an underweight cerebrum as in hydrocephalus with a thinned cerebral wall; or no cerebrum, as in some patients with hydranencephaly, in whom the supratentorial space, while enlarged, contains only fluid. Thus, a given patient may have megalocephaly and micrencephaly if the pathologic process has both reduced the size of the brain and greatly increased the amount of fluid in or around it. Megalocephaly is a statistical description of head size, not a diagnosis and not a synonym for megalencephaly.

Brain Size and Intelligence

A rough correlation exists between brain size and scores on intelligence tests in normal individuals. College students with intelligence quotients (IQs) higher than 130 have slightly larger OFCs than otherwise normal students with IQs around 100. Apart from this fact, the degree that the OFC approaches or exceeds ± 2 SD increases the likelihood of an abnormal brain.

Microcephaly

Microcephaly, statistically defined, means an OFC > 2 SD below the mean for the person's age and gender. Microcephaly implies neurologic impairment, but the OFC of 2.5% of normal people will fall below 2 SD, as will the OFC of pygmies and some dwarfs with normal intelligence. To evaluate the clinical significance of the OFC, consider gender, age, body size, and the family somatotype. Thus,we may distinguish a benign or asymptomatic familial microcephaly, which is a normal genetic variant, from symptomatic microcephaly with neurologic deficits.

Microcephaly may already exist at birth, and the head may remain small throughout the patient's life. An OFC small at birth obviously implicates a prenatal cause. An OFC that is normal at birth but drops down across percentile lines suggests a perinatal or postnatal cause. If the OFC begins to drop across percentile lines several months after birth, suspect a progressive degenerative disease, inborn error of metabolism, systemic disease, or profound malnutrition. Nevertheless, some infants with dysgenetic or primary microcephaly may have a fairly normal OFC at birth that then fails to keep up with the normal growth curve.

Table 61-2 classifies microcephaly by causes identifiable from thorough clinical and laboratory investigations. However, the cause for microcephaly often remains unknown, in spite of an exhaustive work-up.

The agents that cause microcephaly may also cause megalocephaly due to hydrocephaly or due to excessive fluid accumulation in cysts or the meningeal spaces. In destructive microcephaly, a potentially normal brain has suffered a prenatal or perinatal insult, usually hypoxia or inflammation. Typical lesions in acquired microcephaly consist of single or multifocal porencephaly, thickened meninges, ventriculitis, periventricular calcifications, vasculitis, cortical laminar necrosis, ulegyria, or periventricular leukomalacia.

In dysgenetic or malformative microcephaly, an error occurs in chromosomal morphology or at the gene level. Typical malformations include macrogyria, microgyria, migratory disturbances, holoprosecephaly, lissencephaly, and agenesis of the corpus callosum.Viral infections, exogenous teratogens, and some inborn errors of metabolism can cause phenocopies of primary malformations.

Both genetic disorders and exogenous teratogens may cause microcephaly vera, a miniaturized brain that often has a coarse gyral pattern but a fairly normal overall contour and no overt destructive lesions or overt gross malformations.

TABLE 61-1. Determinants of the Occipitofrontal Circumference

Age, sex, and genetic background
Volume of the intracranial contents
Brain weight and size, normal or as altered by disease
Amount of cerebrospinal fluid in the ventricles or subarachnoid space
Volume of intracranial blood
Space-occupying lesions
Ability of the sutures to expand
Thickness of the calvaria, scalp, and hair

TABLE 61-2. Common Causes of Microcephaly

Destructive lesions
Hypoxic: periventricular leukomalacia, porencephaly, ulegyria, and cortical laminar necrosis
Postinflammatory: see TORCH screen in Table 61-3
Dysgenetic malformation
Chromosome errors: trisomies, deletions, and translocations
Gene errors: various dominant and recessive patterns
Exogenous teratogens
Alcohol
Prescription drugs, including anticonvulsants
Street drugs
Radiation, environmental or industrial toxins, and carbon monoxide
Maternal predispositions
Diabetes
Phenylketonuria
Severe malnutrition
Eclampsia
Faulty placenta
Acquired immunodeficiency syndrome and syphilis

Craniosynostosis may cause a small OFC because of the absence of sutures. It is easily recognized because the infant has palpably ridged sutures and an abnormal head shape.

In searching for the cause for a baby's brain defect, the physician should always consider the risk factors listed in Table 61-2. Many of these risk factors are correctable or can be eliminated or reduced during early pregnancy, during the most susceptible periods of organogenesis and histogenesis.

Draw up a complete pedigree by interviewing parents and grandparents. Always measure the OFC of siblings, parents, and available relatives and evaluate the stature and somatotype of the family. Table 61-3 summarizes the steps to consider in the diagnosis of microcephaly.

Asymptomatic versus Symptomatic Familial Microcephaly

Every primary-care physician will have the task of identifying those infants whose OFCs fall in the lower 2.5% of the normal curve but who are neurologically normal. Assurance of a normal infant comes from the absence of any risk factors for acquired microcephaly (see Table 61-2), relatively small OFCs in neurologically normal family members, proportionately small body size, and, finally, a normal examination and developmental course. In familial symptomatic microcephaly, the inheritance may be X-linked dominant, autosomal recessive, or polygenic.

Recurrence Risks

A major justification for an exhaustive diagnostic work-up is to determine the risk of microcephaly in subsequent children and the possibility of preventing it. The recurrence risk obviously is the risk of the same etiologic agent acting again plus the baseline risk of any pregnancy. Without a specific etiologic diagnosis, the empiric recurrence risk is around 5%.

Communicating the Diagnosis and Prognosis to Parents

Meet with the parents in a private office, not in a hospital corridor or at the bedside. Begin by voicing concern that the infant *may* have a brain problem that may affect development. Speak conditionally, not dogmatically. First of all, demystify the diagnostic process. Parents always wonder, "Does this doctor really know what he is talking about?" They have all heard stories of misdiagnoses or dismal prognoses that proved untrue. Clearly detail the evidence for your concerns by reviewing the physical findings and laboratory test results. Often, I show the infant's magnetic resonance imaging (MRI) scan to the parents, alongside a normal scan.

Never, ever declare that the infant is hopelessly retarded or is only a vegetable and belongs in an institution. Even with unequivocal lesions, such as a hydranencephaly, alobar holoprosencephaly, or lissencephaly, the parents will resist and resent any such dogmatic declarations. Never insist that the parents institutionalize the infant. Let them ultimately raise that issue.

Having voiced and documented your concerns, enter into a parent–physician alliance to monitor whatever development might occur. Describe the development milestones to look for and their normal time of appearance. For example, mention head control and ocular fixation and following.

TABLE 61-3. Procedures for Differential Diagnosis of Microcephaly

1. Complete history and physical examination of the patient.
2. Complete pedigree, obtained from grandparents as well as parents.
3. Inspection and measurement of family members and physical examinations as needed.
4. Retinal examination. Dilate the patient's pupils and search entire retina. Obtain ERG in selected patients.
5. Catalog all malformations, internal and external, and consult a syndrome compendium (K.L. Jones; Buyse; Gorlin, Cohen, and Levine).
6. MRI or CT scan. The MRI is superior, except for bone lesions or calcifications.
7. TORCH screen for prenatal or perinatal infection. What was once a TORCH screen for perinatal infection today becomes a STORCHA screen: S = syphilis; T = toxoplasmosis; O = other; R = rubella; C = cytomegalovirus and coxsackievirus; H = herpes; and A = acquired immunodeficiency syndrome.
8. CSF examination: culture, cytology, PCR, immunologic investigation, and biochemistry, as indicated from the history.
9. Urinary or blood screen for inborn errors of metabolism, especially for postnatal onset of microcephaly.
10. Karyotype or probe selected gene sites. Consult a geneticist.
11. Lysosomal enzyme battery and skin or muscle biopsy if the patient displays developmental regression.
12. Electrophysiologic work-up: consider EEG, BAEP, ERG, SSEP, and EMG, if indicated by the history or physical examination.
13. Consider testing the mother for predispositions (see Table 61-2).

BAEP = brainstem auditory evoked potentials; CSF = cerebrospinal fluid; CT = computed tomography; EEG = electroencephalography; EMG = electromyography; ERG = electroretinogram; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; SSEP = somatosensory evoked potentials.

Explain that at follow-up visits, you will ask the parents about and check the baby for these achievements. Thus, physician and parents collaborate as equals in monitoring the infant's development. In this way, the parents themselves discover the infant's developmental fate. You have become an ally who helps confirm their own observations, not their adversary or merely the bearer of bad news.

Today's mixed families cause difficulties in obtaining the pedigree and in counseling because children can originate in four ways: his previous children, her previous children, their ownchildren together, and neither of theirs (an adopted child). Thus, any given child may be his, hers, theirs, or neither's. Interns and young residents often fail to determine which children come from the current union and which come from previous unions and thus misinterpret the family history. Further difficulty arises when one mate, let us say the father, has had normal children by a previous union, but the first child with a new mother has a brain abnormality. The new mother may feel extreme anxiety, insecurity, and sometimes jealousy. This additional burden increases the guilt that, to some degree, afflicts most mothers of affected children. It makes the recriminating questions "What did I do wrong?" or "Why is God punishing me?"even more painful for the mother to face. The physician can comfort the mother by anticipating these states of mind and by explaining how little medical science knows about the exact causes of malformations, genetic errors, and teratogens. Point out the possibility that any couple can have a baby with brain abnormalities. Explain that reproduction carries an inherent risk that we cannot eliminate.

If some overt act of the mother, such as in fetal alcohol syndrome, has caused the brain defect, prepare to help the mother work through extreme guilt. Similarly, if the pedigree and the genetic work-up clearly establish one parent as the source of the defect, that parent will experience similar emotions. In such cases, it is helpful to explain that the genetic heritage of each one of us contains the potential for error. In one family the result is hypertension, in another, arthritis or cancer—and in another, a brain defect.

Because neurologically impaired infants may have trouble feeding and breathing and may require gastrostomy and respiratory assistance, consider early referral to a developmental center that offers such services as monitoring caloric intake and weight gain, physical therapy, speech therapy, and social support. Often, referral to a lay support group provides additional help.

Megalocephaly and Megalencephaly

Megalocephaly, statistically defined, means an OFC > 2 SD above the mean for the person's age and gender. Megalocephaly implies a neurologically defective individual, but the OFC of 2.5% of the normal population will exceed 2 SD. A common office problem, as with microcephaly, is to separate benign asymptomatic familial megalencephaly from symptomatic types. The OFC already may exceed 2 SD at the time of birth, or the infant may have a normal OFC at birth, and then it may accelerate upward (see Figure 61-2). Most megalocephalic patients have hydrocephaly or megalencephaly. Both conditions may cause successive OFC measurements to accelerate upward across graph lines (see Figure 61-2). Table 61-4 lists the most common causes of megalocephaly.

No known exogenous teratogens cause megalencephaly, although overweight babies of diabetic mothers may have large OFCs. Similarly, although dysgenetic causes for megalencephaly (such as fragile X syndrome, neurofibromatosis, and achondroplastic dwarfism) are fairly common, most dysgenetic syndromes, as well as exogenous teratogens, cause microcephaly rather than megalencephaly. Fragile X syndrome is second only to Down syndrome as a dysgenetic cause of retardation, but patients with Down syndrome have microcephaly.

History and Physical Examination in Megalocephaly

Determine whether the patient is improving developmentally or regressing. Regression indicates a worsening pathologic process, thus differentiating these patients, particularly those with evolving hydrocephaly, from those with static causes for megalocephaly. Inquire about poor feeding, vomiting, irritability, and a disturbed sleep pattern, which together suggest increased intracranial pressure. Carefully assess facial features for clues for craniofacioskeletal dysplasia syndromes. Survey

TABLE 61-4. Common Causes of Megalocephaly

Hydrocephaly
Malformation: Chiari's malformation, aqueductal stenosis, arteriovenous malformation, or arachnoid cyst
Other: meningeal fibrosis, (postinflammatory or posthemorrhagic), dural sinus thrombosis, neoplasms, subdural fluid, extraventricular hydrocephaly (widened subarachnoid space), or porencephaly
Megalencephaly
Anatomic
Asymptomatic familial (upper 2.5% of the normal population)
Symptomatic familial
Metabolic: heredofamilial degenerative diseases
Subdural fluid
Posttraumatic hematoma, accidental injury, or child abuse
Hygroma
Empyema
Toxic-metabolic brain edema
Vitamin A intoxication
Tetracyclines
Lead poisoning
Idiopathic (pseudotumor cerebri)
Thickened skull
Familial bone dysplasia
Severe anemia

the facial gestalt, the interorbital distance, and the proportions of the forehead, midface, and jaw. Determine the size and contour of the fontanelles and palpate the sutures. Increased intracranial pressure will cause a bulging fontanelle and widened sutures, whereas craniosynostosis causes closed, ridged sutures.

Physicians often mistakenly describe the normal anterior fontanelle as "flat." With the infant relaxed and upright, the normal anterior fontanelle is slightly concave. A truly flat contour suggests some degree of increased intracranial pressure. In hydrocephaly, the fontanelle usually bulges, whereas in anatomic megalencephaly, it remains concave. In the metabolic types of megalencephaly, the fontanelle may also bulge. To judge the fontanelle contour, run the tip of your index finger across the fontanelle in the anteroposterior and lateral planes. The fingertip will dip down a little as it moves across the normal fontanelle. Also, a light beam that crosses the fontanelle tangentially will cast a shadow on the concavity of the normal fontanelle.

Attempt to transilluminate the head and complete the rest of the neurodevelopmental examination. Include a funduscopic examination through dilated pupils and a careful search of the skin surface for neurocutaneous stigmata, especially for the café-au-lait spots of neurofibromatosis, the ash-leaf spots of tuberous sclerosis, and multiple hemangiomas. Record the pedigree, as described for microcephaly, including measurement of the OFC of near relatives, and examine their skin surfaces for neurocutaneous stigmata.

Laboratory Investigation of Megalocephaly

To quickly reduce the differential diagnosis to one of the five types listed in Table 61-4, first obtain an MRI scan of the head. For a premature or very young infant, an ultrasonographic scan may suffice for quick screening. MRI scans in benign anatomic megalencephaly may show ventricles that appear somewhat enlarged and wide subarachnoid spaces, neither of which require shunting or tapping. Next, consider the laboratory procedures listed in Table 61-3 for microcephaly.

If the patient has a dysplastic body or if an endocrine or metabolic disorder is suspected, consider radiography of the bones for configuration and bone age and a metabolic-endocrine work-up. Consider testing for blood vitamin A and lead levels, depending on the history.

Abnormal Head Shape

In the neonate, scalp edema (caput succedaneum) and molding of the head during birth are common causes of a misshapen head. Cephalohematomas are hemorrhages beneath the periosteum of one of the large flat bones of the calvaria, most commonly the parietal bone. They cause a localized bulge, limited by the line of a suture. The mass does not pulsate, differentiating it from a meningocele or any other lesion connected with the intracranial space.

Two of the commonest causes of misshapen heads apart from perinatal complications are positional molding and synostosis of the cranial sutures. Craniosynostosis alters the head shape by arresting growth at right angles to the plane of the closed suture. Sagittal suture synostosis results in scaphocephaly, a long, narrow calvaria. Coronal suture synostosis results in acrobrachycephaly, a short, broad cranium. Closure of both sutures causes oxycephaly and often microcephaly and restricted brain growth(Figure 61-3). Craniosynostosis, usually of the coronal suture, with malformations of the face and extremities, implies a genetic syndrome, such as Apert's syndrome (acrocephalosyndactyly).

Deformational or positional molding, with bilateral or unilateral flattening of the occiput, can occur prenatally, or it can occur postnatally when an infant spends excessive time on the back or side. The prolonged positioning of normal infants on their backs to avoid sudden infant death syndrome results in some bilateral or unilateral flattening of the occiput. The heads of premature babies who lie on their sides increase in the anterior-posterior diameter (positional dolichocephaly).With any such positional molding, the sutures remain open. Disorders of the central nervous system or neuromuscular system that prolong the period of recumbency may also lead to unilateral or bilateral positional occipital flattening. Unilateral flattening of the occiput

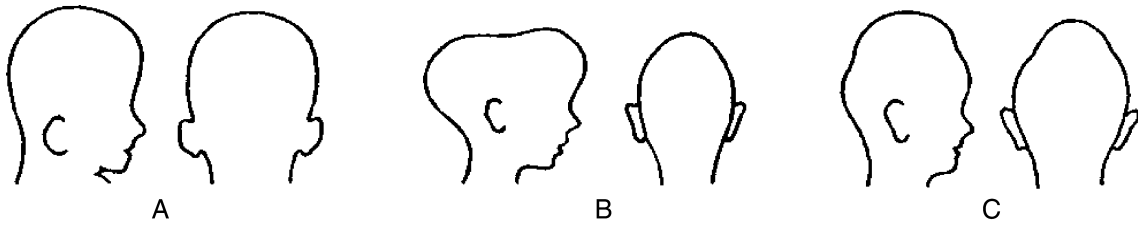

FIGURE 61-3. Silhouettes of some abnormal head shapes caused by craniosynostosis. (A) Acrobrachycephaly (coronal suture synostosis). (B) Scaphocephaly (sagittal suture synostosis). (C) Oxycephaly (coronal and sagittal suture synostosis). (Reproduced by permission from DeMyer W. Technique of the Neuorologic Examination, 5th ed. New York; McGraw-Hill, 2004).

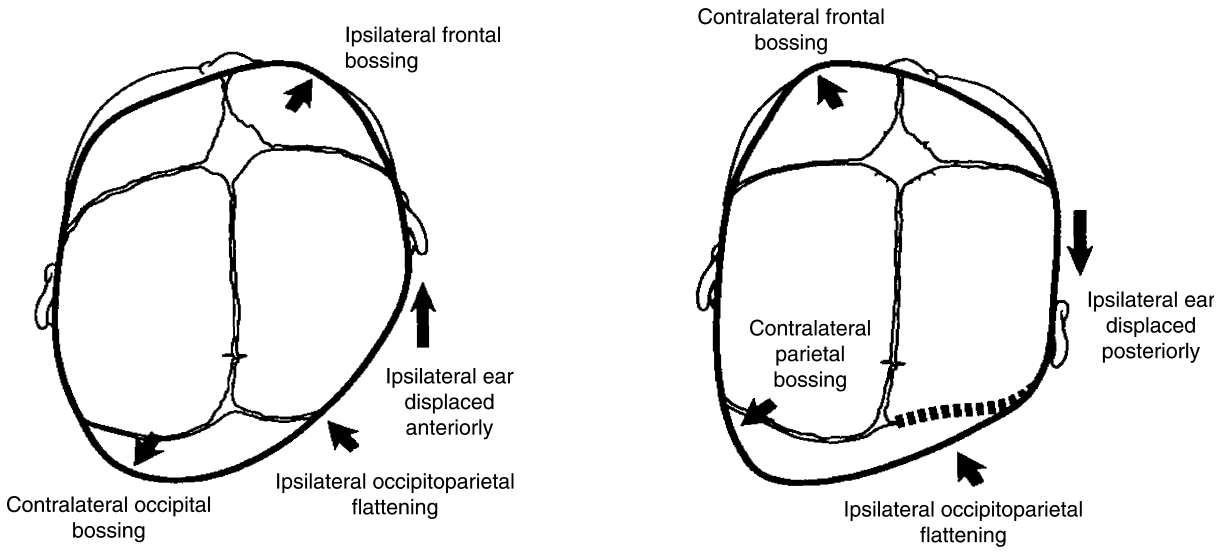

FIGURE 61-4. Top views of head contrasting deformational plagiocephaly (left) and craniosynostotic plagiocephaly from lambdoidal (parieto-occipital) suture synostosis (right). Reproduced by permission from Kabbani H, Raghuveer TS. Craniosynostosis. Am Fam Physician 69: 2004: 2863-2870).

is called *cranioscoliosis* or *plagiocephaly*. Unilateral positional occipital flattening on the "down" side follows any condition that keeps the infant's head to one side. Common associated conditions or causes of positional plagiocephaly include torticollis or a hemisyndrome with a visual field defect or hemiplegia. Long-term follow-up studies show that a significant number of infants with plagiocephaly from any cause have developmental disabilities. Idiopathic and genetic forms of plagiocephaly also occur.

Unilateral positional or deformational flattening of the occiput torques or rotates the skull base, resulting in a lopsided skull. The occiput on one side appears flat, while the cheek and hemicranium on the same side extend forward (Figure 61-4). To check for this type of plagiocephaly, look down on the top of the infant's head. The ear on the side of the forward cheek will sit forward of the opposite ear (Figure 61-4, left). If in doubt, insert the tips of your index fingers into the ear canals, pointing them straight inward. The axis of the finger in the ear on the side of the forward cheek will pass distinctly in front of the axis of the opposite ear canal. The much rarer type of plagiocephaly, *craniosynostic plagiocephaly,* is caused by premature unilateral closure of the lambdoid suture (Figure 61-4, right). The unilateral suture closure restricts the forward growth of the ipsilateral cheek and backward growth of the ipsilateral occiput, causing a small hemicranium and occipital flattening on that side. In addition to characteristic abnormalities in the shape of the head, craniosynostosis causes palpable ridging of one or more sutures.

When the physical examination discloses a misshapen skull, the next step is generally a computed tomography scan with bone windows to visualize the sutures and synchondroses. If any abnormalities of skull bones or sutures are suspected, obtain 3-D CT scans. Obtain an MRI scan if the infant has any neurologic signs or developmental deficits. Obtain the scans early in infancy because surgical correction by linear craniectomy produces better cosmetic results in younger infants and presumably better functional results in patients with oxycephaly that restricts brain growth.

Deformational plagiocephaly tends to self-correct when the infant attains the vertical posture. Photographs of the misshapen head aid in documenting the initial severity of the condition and in monitoring any changes. Growth of the hair as the infant matures tends to conceal the abnormal skull shape, particularly in girls. If the infant lies consistently with the head turned to one side, the parent can orient the crib in such a way as to make the infant turn the head to the opposite side in order to observe the surroundings. For deformational plagiocephaly, the parents should prop up the infant and change the infant's position frequently to avoid the full weight of the head on the occiput until the infant sits up. For severe deformational plagiocephaly, the parents may be referred to a pediatric physical therapy department to fit the infant with a head-molding helmet, although their efficacy is uncertain. Some parents may elect cosmetic surgery, but most patients are best managed conservatively. The only effective treatment for craniosynostotic plagiocephaly is surgery.

Communicating the Diagnosis and Prognosis of Neurodevelopmental Disorders to Parents

Meet with the parents in a private office, not in a hospital corridor or at the bedside. Begin by voicing concern that

the infant *may* have a brain problem that may affect development. Always speak conditionally, never dogmatically. First of all, demystify the diagnostic process. Parents always wonder, "Does this doctor really know what he is talking about?" They have all heard stories of misdiagnoses or dismal prognoses that proved untrue. Clearly explain the evidence for your concerns by reviewing the physical findings and laboratory test results. Often, I show the infant's magnetic resonance imaging (MRI) scan to the parents, alongside a normal scan. Never, ever declare that the infant is hopelessly retarded or is only a vegetable and belongs in an institution. Even with unequivocal lesions, such as a hydranencephaly, alobar holoprosencephaly, or lissencephaly, the parents will resist and resent any such dogmatic declarations. Never insist that the parents institutionalize the infant. Let them ultimately raise that issue.

Having voiced and documented your concerns, enter into a parent–physician alliance to monitor whatever development might occur. Describe the development milestones to look for and their normal time of appearance. For example, mention head control and ocular fixation and following. Explain that at follow-up visits, you will ask the parents about and check the baby for these achievements. Thus, physician and parents collaborate as equals in monitoring the infant's development. In this way, the parents themselves discover the infant's developmental fate. You have become their ally who helps confirm their own observations, not their adversary who conveys bad news.

Today's mixed families cause difficulties in obtaining the pedigree and in counseling because children can originate in four ways: his previous children, her previous children, their own children together, and neither of theirs (an adopted child). Thus, any given child may be his, hers, theirs, or neither's. Interns and young residents often fail to determine which children come from the current union and which come from previous unions and thus misinterpret the family history. Further difficulty arises when one mate, let us say the father, has had normal children by a previous union, but the first child with a new mother has a brain abnormality. The new mother may feel extreme anxiety, insecurity, and sometimes jealousy. This additional burden increases the guilt that, to some degree, afflicts most mothers of affected children. It makes the recriminating questions "What did I do wrong?" or "Why is God punishing me?" even more painful for the mother to face. The physician can comfort the mother by anticipating these states of mind and by explaining how little medical science knows about the exact causes of malformations, genetic errors, and teratogens. Point out the possibility that any couple can have a baby with brain abnormalities. Explain that reproduction carries an inherent risk that we cannot eliminate.

If some overt act of the mother, such as alcoholism, has caused the brain defect, prepare to help the mother work through extreme guilt. Similarly, if the pedigree and the genetic work-up clearly establish one parent as the source of the defect, that parent will experience similar emotions. In such cases, it is helpful to explain that the genetic heritage of each one of us contains the potential for error. In one family the result is hypertension, in another, arthritis or cancer—and in another, a brain defect. Offer referral for genetic counseling as needed.

Because neurologically impaired infants may have trouble feeding and breathing and may require gastrostomy and respiratory assistance, refer the parents to a developmental center that offers such services as monitoring caloric intake and weight gain, physical therapy, speech therapy, and social support. Often, referral to a lay support group provides additional help.

Suggested Readings

DeMyer W. Microcephaly, micrencephaly, megalocephaly and megalencephaly. In: Swaiman K, Ashwal S, editors. Pediatric neurology. 3rd ed. St. Louis (MO):Mosby Inc.; 1999.

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Weaver DD, Christian JC. Familial variation of head size and adjustment for parental head circumference. J Pediatr 1980;96:990–4.

Practitioner and Patient Resources

National Hydrocephalus Foundation (NHF)
12431 Centralia Road
Lakewood, CA 90715-1623
http://www.nhfonline.org
The objectives of NHF are to assemble and disseminate information pertaining to hydrocephalus, its treatments, and outcomes; to establish and facilitate a communication network among affected families and individuals; to help others gain a deeper understanding of those areas affected by hydrocephalus, such as education, insurance, tax and estate planning, employment,

and family; to increase public awareness and knowledge of hydrocephalus; and to promote and support research on the causes, treatment, and prevention of hydrocephalus.

National Center for Learning Disabilities (NCLD)
381 Park Avenue South, Suite 1401
New York, NY 10016
Phone: (212) 545-7510
Fax: (212) 545-9665
Toll-free: (888) 575-7373
http://www.ncld.org/index.html
The NCLD Web site strives to be an effective, easy-to-use resource for people seeking authoritative information on learning disabilities. The Web site includes a resource locator, fact sheets, research news, and much more.

National Institute of Neurological Disorders and Stroke (NINDS) Microcephaly Information Page
http://www.ninds.nih.gov/health_and_medical/disorders/microcephaly. htm
Part of the National Institutes of Health, this Web site provides a list of organizations for information and support.

Family Village – Microcephaly Information
http://www.familyvillage.wisc.edu/lib_microc.htm
Family Village is a global community that integrates information, resources, and communication opportunities on the Internet for people with cognitive and other disabilities, for their families, and for those that provide them services and support. This Web site provides links for more information on microcephaly as well as online discussion groups.

CHAPTER 62

MICROCEPHALY—ACQUIRED

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The terminology associated with microcephaly has become so cumbersome that it is counterproductive to meaningful clinical assessment and communication. Variations in standardized head growth curves bring inconsistency to findings and lead to unnecessary parental anxiety. All clinicians have the capability to make cost-effective diagnoses of primary versus acquired microcephaly. A plan to streamline the investigation of acquired microcephaly is presented.

Microcephaly is defined as "abnormal smallness of the head, usually associated with mental retardation." Although microcephaly is thoroughly reviewed in Chapter 61 by DeMyer, it will be useful to re-emphasize some salient points prior to introducing the meaning and significance of "acquired" microcephaly.

Small, Normal, and Large Head Size

The standard head circumference measurement is an occipitofrontal circumference (OFC) that is measured above the eyebrow ridges and around the skull to include the most prominent area of the occiput. If this OFC is >2 standard deviations (SD) below the mean for age and gender, it is considered microcephaly. Normocephaly is defined as within ±2 SD of the statistical norm for age and gender, and macrocephaly is defined as >2 SD above the mean for age and gender. The range within 2 SD, or from the 2nd percentile to the 98th percentile, primarily represents normal familial and ethnic variations in somatotypes.

Variation in Standardized Head Growth Curves

Standardized head growth curves were published by Nellhaus in 1968 and by Roche and colleagues in 1987. In addition, the United States Centers for Disease Control and Prevention (CDC) developed standardized growth charts in 1977, which were revised in 2000. The age range for the 2000 CDC OFC growth charts is 0 to 36 months. There are two sets of 2000 CDC OFC growth charts. Set 1 has the outer limits of the curves from the 5th to the 95th percentile, while set 2 is from the 3rd to the 97th percentile. Set 2 of the 2000 CDC OFC growth charts comes closest to the desired 2 SD from the mean. The 1968 Nellhaus curves encompass the 2 SD measurements by including the 2nd to the 98th percentiles. The Nellhaus curves cover an age range from birth to 18 years. Variable socioeconomic and ethnic variation is accounted for by both the 2000 CDC OFC growth charts and the Nellhaus curves.

The validity of the Roche curves from 1987 is compromised by the fact that they are from a small population of one race in one localized area of the United States. In addition, the Roche curves and set 1 of the 2000 CDC OFC growth charts have "normal" OFC curves that go from the 5th percentile to the 95th percentile. This makes it possible for 2.5% of normal individuals to appear as if they have an abnormally small OFC because they will be plotted below the lowest curve on the OFC growth charts. Set 1 of the 2000 CDC OFC growth charts are currently the predominant charts used by primary health care providers in the United States. This charting snafu has served to create anxiety for the child's parents and family without contributing to any specific diagnosis since the vast majority of these children are normal on evaluation.

Normal Head Growth

The normal mean OFC for a term gestation infant is 34.5 cm for girls and 36 cm for boys at birth. The OFC increases by 0.5 to 2.5 cm per month during the first year with the greatest increase occurring in the first 6 months of life. There is a mean increase of 11.25 cm in the first year of life with a

normal OFC of 45 to 47 cm at 1 year of age. This increase in OFC correlates with brain weight. The mean brain weight is 360 g at term, 950 g at 1 year, and 1350 g at full maturity. An infant has 70% of his or her final brain weight present at 1 year of age.

What Does OFC Measure?

The young child has a thin scalp and skull as well as undeveloped sinuses. As a result, measurement of the OFC is primarily a measurement of the brain matter and any cerebrospinal fluid (CSF) that is present. A small head size or poor head growth velocity detected during a well-child physical examination alerts the clinician to a possible brain abnormality. The OFC should be measured regularly during early growth and development in infants. Because the OFC correlates with brain size and growth and may indicate an underlying brain abnormality, it is imperative that the terminology used by all clinicians be in agreement. While microcephaly (abnormally small head or skull) necessitates micrencephaly (small brain), macrocephaly (large head) does not necessarily mean that megalencephaly (large brain) is present. One should always consider the reference population when measuring OFCs. Longstanding culturofamilial traits for small head size in a normal population (eg, pygmies, dwarfs) can exist and can be a normal hereditary/genetic variant.

Plotting the OFC Curve

A clinical health care provider needs to plot multiple successive OFC points to develop a meaningful curve. However, it only takes the presence of one abnormally small OFC and/or any significant crossing of percentiles over time from successive OFC measurements to indicate the need for further evaluation. It is not uncommon for this clinical sign to be found on routine examination. Microcephaly is rarely a parental "complaint," and it is often unrecognized by the physician until the measurement is performed.

When Head Size Reflects Brain Size

Although not all children with microcephaly have mental retardation, there is a statistical correlation between brain size and intelligence. As one draws nearer to the outer limits of the ±2 SD curves, there is an increasing likelihood of an abnormality being present. Childhood intelligence is associated with prenatal and infant OFC growth. Commonly, in this situation, the head size reflects the brain size. Brain volume at 1 year of age correlates with intelligence. Growth in brain volume after 1 year of age usually does not totally compensate for lack of normal expansive growth of the gray and white matter in the first year of life. The lack of normal early OFC growth may be due to developmental anomalies, environmental factors, or inborn errors of metabolism that have influenced brain growth.

Prematurity and OFC Growth

A special note needs to be made for normal OFC growth in premature infants. The OFC of premature infants normally increases more rapidly during the weeks/months that they are less than the equivalent of a term infant. This rapid increase in OFC typically occurs until "catch-up" growth is attained in 6 to 9 months. Commonly, a premature infant's OFC, no matter how early his or her birth, should be within ±2 SD of the mean prior to or by 1 year of age. It is very difficult to make up for inadequate brain growth after that time as 70% of brain volume has been achieved by then.

Overgrowth of Classification Terminology

The terminologies and definitions for types of microcephaly in common pediatric, pediatric neurology, and genetic textbooks are numerous. More than two dozen terms are easily found (Table 62-1). The terminologies are so diverse that it is more confusing than helpful to use the current nomenclature.

Adding to the confusion is the fact that definitions for commonly used terms may be different. Relative microcephaly is defined as a "head size that falls within the normal range but is disproportionately small when compared with the patient's length or weight centiles."

TABLE 62-1. Terms for Microcephaly

Absolute microcephaly	Nongenetic microcephaly
Acquired microcephaly	Nonsyndromal microcephaly
Autosomal dominant microcephaly	Postnatal microcephaly
Autosomal recessive microcephaly	Prenatal microcephaly
Borderline microcephaly	Primary microcephaly
Complicated microcephaly	Pure microcephaly
Congenital microcephaly	Recurrent microcephaly
Destructive microcephaly	Relative microcephaly
Dysgenetic microcephaly	Secondary microcephaly
Environmental microcephaly	Severe microcephaly
Familial microcephaly	Simple microcephaly
Genetic microcephaly	Symptomatic microcephaly
Idiopathic microcephaly	Syndromal microcephaly
Isolated microcephaly	True microcephaly
Malformative microcephaly	Unclassified microcephaly
Microcephaly vera	Uncomplicated microcephaly
Mild microcephaly	X-linked microcephaly

Alternative definitions include "an OFC > 10th percentile but small for height and weight" and "a small OFC but proportional to height and weight." Primary microcephaly is often defined as "a small OFC that has been small on the fetal ultrasound or during the newborn exam." Additional definitions include "an abnormal OFC at birth corrected for gestation and length," "an OFC below –3 SD when no other abnormalities are found," and "a group of conditions that usually have no other malformations and follow Mendelian inheritance or are associated with a specific syndrome." Congenital microcephaly likewise has a small OFC and is present on the newborn exam or fetal ultrasound. Conditions that are present at birth, regardless of their causation, are referred to as congenital or natal. In the case of microcephaly, congenital usually implies a hereditary etiology. Many times, congenital microcephaly and primary microcephaly are referred to as "genetic," while secondary microcephaly is considered "nongenetic." Secondary microcephaly occurs when there is a "normal OFC at birth with later acquired microcephaly." Other definitions for secondary microcephaly include "an insult incurred during the last 2 months gestation or perinatally" and a condition that "results from noxious agents that may affect a fetus in utero or an infant during periods of rapid brain growth."

Pruning Terminology for Clinical Usefulness

This menagerie of names and definitions for microcephaly is overwhelming and difficult for clinicians to use. As a result, we propose not to add to the list. Instead, we have selected terms that appear most useful to the clinician seeing children at a center where the technology for in-depth investigations may or may not be available. This condensing of terminologies to have a meaningful diagnostic approach has taken into consideration the classic clinical approach and its descriptive terminology, which includes environmental and genetic etiologies. A contemporary approach is also included in which the use of advanced biochemical analyses, cytogenetics, molecular genetics, and neuroradiology reveals extremely heterogeneous categories blurred by modern technology. Each case should be taken on its own merits and includes the most up-to-date technologies available. Due to the myriad terms and definitions for microcephaly, it is time to simplify the terminology to *primary* and *acquired* microcephaly and expand our differential diagnosis of each group.

Primary Microcephaly

Primary microcephaly exists at birth. The OFC remains small. There is likely a prenatal etiology, if it is not a normal familial variant. Primary microcephaly is discussed at length in all pediatric developmental and pediatric neurology textbooks wherever growth and development is discussed. Primary microcephaly is addressed both as a normal variant and as a disorder with distinct etiologies (Table 62-2). Congenital microcephaly was considered as an alternative term for this group. However, because many health care professionals consider something congenital as having genetic implications, primary microcephaly has been selected as the best term for this category.

Acquired Microcephaly

The child with acquired microcephaly is one that has a normal OFC at birth, and then subsequently the plotting of the OFC crosses percentile lines to >2 SD below the mean. The most likely etiology is perinatal or postnatal in origin. Secondary microcephaly was rejected as an alternative term because some of the etiologies for acquired microcephaly are of genetic origin and have been present since conception, although their presentation is in the postnatal brain.

TABLE 62- 2. Causes for Primary Microcephaly

Prenatal factors	Chromosomal abnormalities
Small for gestational age/extreme prematurity	Deletions and duplications
Prenatal illness/condition	Down syndrome and other trisomies
Acquired immunodeficiency syndrome	Ring chromosomes
Anemia	Sex chromosome aneuploidy
Cytomegalovirus	Genetic
Coxsackie B virus	Bloom syndrome
Diabetes mellitus	COFS syndrome
Malnutrition	Coffin-Siris syndrome
Maternal hyperthermia/significant febrile illness	Cornelia de Lange syndrome
Maternal phenylketonuria	Craniosynostosis (multi-suture)
Rubella	Dubowitz syndrome
Syphilis	Familial
Toxoplasmosis	Feingold syndrome
Varicella	Johanson-Blizzard syndrome
Prenatal Toxic Exposures	Meckel-Gruber syndrome
Alcohol	Mendelian
Anticancer	Autosomal recessive (MCPH)
Antiepileptic	Autosomal dominant
Cocaine	X-linked
Heroin	Neu-Laxova syndrome
Mercury	Nijmegen breakage syndrome
Smoking/tobacco	Roberts syndrome
Toluene	Seckel syndrome
X-irradiation	Smith-Lemli-Opitz syndrome
Anoxia/ischemia/trauma	Brain Malformations
Generalized cerebral anoxia	Atelencephaly (aprosencephaly)
Placental insufficiency	Encephalocele
Porencephaly	Holoprosencephaly
Hydranencephaly	Lissencephaly
	Polymicrogyria

A wide variety of disorders have been associated with acquired microcephaly (Table 62-3). Individuals with certain diagnoses, such as Rett syndrome, have acquired microcephaly as a characteristic finding. Disorders that are commonly associated with acquired microcephaly may have a typical age of onset to help narrow the differential diagnosis (Figure 62-1). With improved documentation of birth OFCs and the successive plotting of OFCs during childhood, the ability to estimate a typical age of onset for disorders associated with acquired microcephaly should improve.

TABLE 62-3. Causes for acquired microcephaly

Perinatal infections	Genetic
Herpes simplex virus*	Chromosome deletions/duplications, eg, del 1p, del 3p, del 5p, dup 17p
Human immunodeficiency virus	Multiple malformation syndromes
Lymphocytic choriomeningitis virus	Aicardi-Goutiéres syndrome
Rubella virus*	α thalassemia X-linked MR syndrome
Post meningitis	Angelman syndrome
Post viral encephalitis	ARX gene mutations
Syphilis*	Cockayne syndrome
Perinatal teratogens	Cohen syndrome
Alcohol	Marden-Walker syndrome
Toluene	MCT8 gene mutations
X-irradiation	Mowat-Wilson syndrome
Perinatal or postnatal insults	Rett syndrome
Anoxia/ischemia	Rubinstein-Taybi syndrome
Trauma	Sturge-Weber syndrome
Birth; accidental; nonaccidental	Toriello-Carey syndrome
Carbon monoxide poisoning	Williams syndrome
Hypoxic ischemic encephalopathy	Xeroderma pigmentosa
Intracranial hemorrhage/ thrombosis†	Metabolic disorders
Lead toxicity	Amino acidurias
Porencephaly/hydranencephaly	Congenital disorders of glycosylation
Post status epilepticus	Galactosemia
Chronic or systemic disease	Glucose transporter defect (GLUT-1)
Adrenocortical deficiency	Leukodystrophies (eg, infantile Krabbe)
Cardiorespiratory	Menkes disease
Hypoglycemia	Mitochondrial diseases
Hypopituitarism	Neuronal ceroid-lipofuscinosis (infantile)
Hypothyroidism	Organic acidurias
Malnutrition/psychosocial deprivation	Pelizaeus-Merzbacher disease
Uremic encephalopathy	Purine and pyrimidine disorders
Structural brain anomalies†	Sulfite oxidase deficiency
Cerebral dysgenesis	
Holoprosencephaly	

*If acquired late in pregnancy/third trimester.

†May also be of genetic etiology.

Frequency in Genetic Syndromes

Microcephaly has been reported as a finding in more than 400 genetic syndromes. However, the majority of these syndromes are extremely rare with few reported cases. In addition, microcephaly is an infrequent finding in many of these disorders. Certain syndromes, such as Coffin-Siris syndrome and α thalassemia X-linked mental retardation syndrome, are commonly associated with microcephaly. However, it is often difficult to determine the proportion of cases with acquired microcephaly due to the fact that head circumferences at birth and other ages may not be reported in the literature. Individuals with Rubinstein-Taybi syndrome and Williams syndrome may be born with small OFCs or develop microcephaly over time. However, the mean OFC for both syndromes demonstrates a normal OFC at birth with the development of acquired microcephaly in childhood. For certain disorders, such as those associated with MCT8 mutations, affected individuals typically have normocephaly but acquired microcephaly has clearly been documented in a minority of cases.

Distinguishing Acquired from Primary

Acquired microcephaly is a unique category, which gets very little specific attention in textbooks when growth and development is reviewed. The ability to characterize the type of microcephaly facilitates a more cost-effective and meaningful evaluation. Distinguishing acquired microcephaly from primary microcephaly should assist in the detection of an underlying etiology. Without an etiology, the empiric risk of recurrent microcephaly is 5 to 20%. A more definitive risk of recurrence, which may be anywhere from 0 to 100%, can be given when a specific etiology is known.

Simple Diagnostic Technique

Acquired microcephaly is unique because of its ability to be diagnosed postnatally by a simple, inexpensive technique: the measurement of the OFC and plotting of that curve against normal populations. Set 2 of the 2000 CDC OFC growth charts is the most accurate to follow children between birth and 36 months of age for evidence of acquired microcephaly. The normal range of OFC measurements for set 2 includes the 3rd to the 97th percentiles. Below the 3rd percentile is abnormal and considered microcephaly. Since the 2000 CDC OFC growth charts do not include a curve for children older than 36 months, the 1968 Nellhaus curves are a satisfactory alternative for older children until more up-to-date curves are developed. The use of the OFC through 18 years of age is informative in that although the majority of head growth

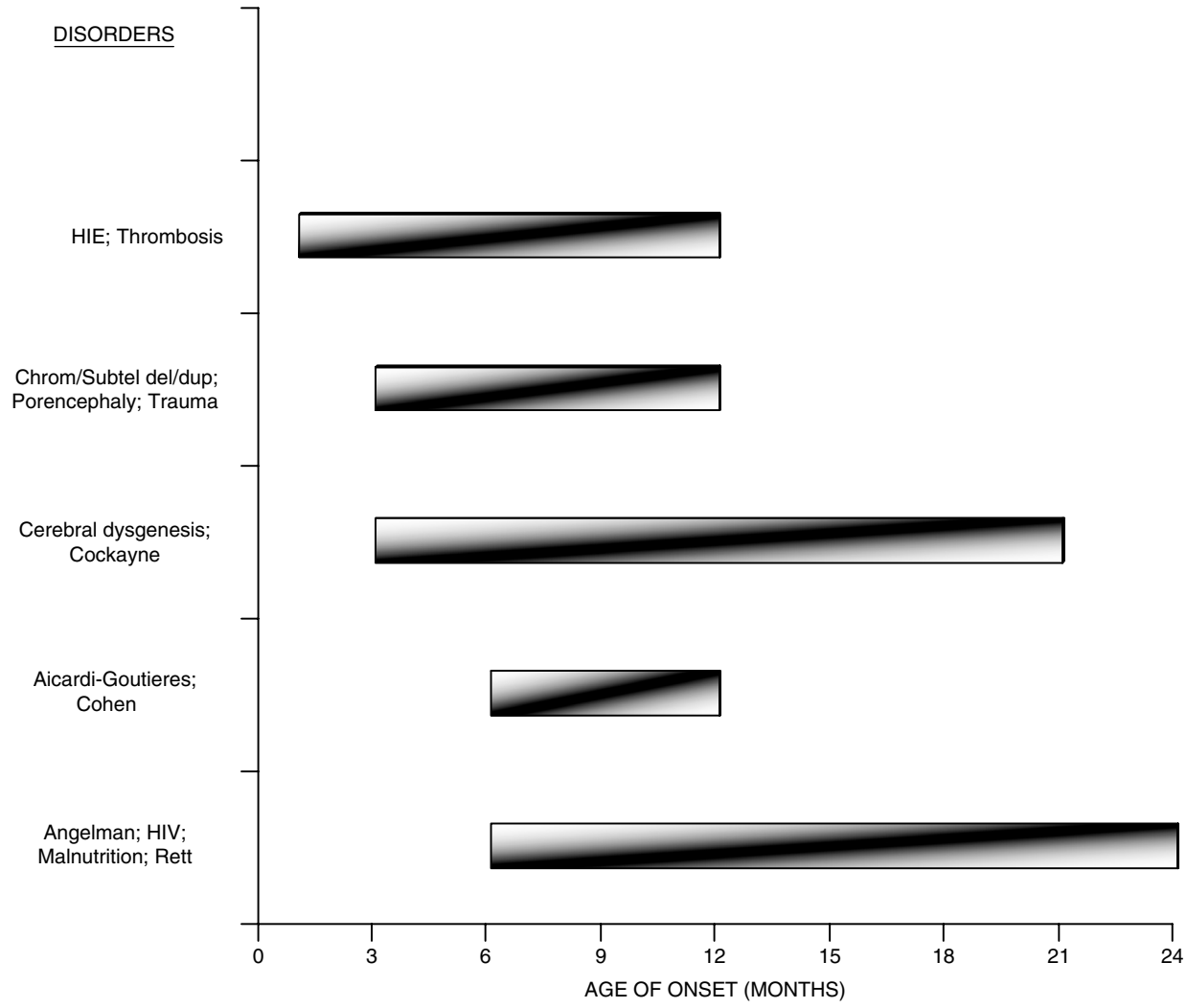

FIGURE 62-1. Age of onset of acquired microcephaly related to specific etiologies.

occurs in the first 2 years of life, there is still significant head growth through 8 to 10 years of age and some continued growth up until 18 years of age.

Etiologic Data Scarce

Although it is unclear why more attention has not specifically been paid to the acquired microcephaly group, there have been two recent abstracts published on the general findings of groups of children in pediatric neurology clinics that present with acquired microcephaly.

The first case series was reported by Rosman and colleagues at the annual Child Neurology Society meeting in 2002. In his case series of 80 patients from Boston, MA, the etiology for acquired microcephaly was found to be encephalomalacia in 24, cerebral dysgenesis in 22, Rett syndrome in 7, and idiopathic in 27. The patients were followed for a mean duration of 51 months with a range of 33 to 87 months. Neurodevelopmental quotients were poor in all the groups except for the idiopathic group, where 11 of the children had normal neurodevelopmental quotients. The Rett syndrome patients had the slowest falloff in head circumference.

A second case series was reported by Baxter and colleagues at the International Child Neurology Congress in 2006. This case series consisted of 55 patients seen in a pediatric neurology consultation clinic in England. Three patterns of acquired microcephaly were generally found as follows: a decrease in head circumference which then grew parallel to the normal curve, a decrease in head circumference that continued to fall away from the normal curve, and a decrease in head circumference with later

recovery. Etiologies most often identified were familial in 15 patients, syndromic in 10 patients, symptomatic postinsult in 11 patients, and idiopathic in 11 patients. Most of the syndromic group was nonspecific. Overall, most acquired microcephaly appeared to be "genetic." It remains to be seen whether specific patterns of head growth unique to acquired microcephaly may be helpful for diagnosis, treatment, and/or prognosis.

Initiate Appropriate Evaluation

The lack of attention paid to acquired microcephaly presents a challenge for clinicians attempting to initiate an appropriate evaluation. As a result, an algorithmic approach to the patient with acquired microcephaly is presented as a guide to the diagnostic workup (Figure 62-2). Some very basic information can be accumulated without a large cost or the need for high-technology genetic and metabolic testing. Initially, the history and physical exam, including a pedigree and obtaining familial OFCs, help to resolve many of the possible etiologies.

Infectious Agents and Other Testing

The history and physical exam may be suggestive of an infectious etiology. "TORCHES" screening and acute CSF screening may be necessary. However, this testing is commonly of minimal help since these infants are often 3 to 6 months old when they are initially evaluated by the examiner. In addition, human immunodeficiency virus testing or other chronic inflammatory titers can be evaluated at this time. There also may be clues to a systemic disease which necessitates screening tests such as thyroid function tests, electrolytes, BUN, creatinine, liver function tests, plasma glucose, growth hormone, cortisol levels, and a lead level.

Ophthalmology Plus

If the initial evaluation of the eyes does not provide sufficient detail or is difficult in an uncooperative child, an ophthalmologic examination under sedation or anesthesia should be considered. This may provide diagnostic clues and potential management or prognostic information. This may include a characteristic eye finding such as pigmentary retinopathy in association with Cohen syndrome. Pigmentary retinopathy can also be found in cases of Cockayne syndrome. However, the characteristic skin photosensivity, as can be seen in xeroderma pigmentosa, would most likely be the earliest diagnostic clue. Other characteristic findings may also be detected by a careful physical exam such as the sparse and twisted hair associated with Menkes disease.

Brain Magnetic Resonance Imaging

A brain magnetic resonance imaging (MRI) is indicated if an underlying etiology remains elusive and/or if there is unexplained nonfamilial neurodevelopmental disabilities with acquired microcephaly. Evidence of calcifications may be suggestive of rare disorders such as Aicardi-Goutieres syndrome. White matter changes may indicate the need to specifically test for leukodystrophies, such as Pelizaeus-Merzbacher disease. If evidence of intracranial thrombosis is found on the brain MRI, a thrombophilia workup would be necessary. Testing of specific genes associated with lissencephaly may be indicated if cerebral dysgenesis is detected.

Genetic Testing

As a significant proportion of acquired microcephaly is due to a genetic cause, high-resolution chromosome analysis and subtelomere analysis may be considered to look for evidence of chromosomal changes as a cause of acquired microcephaly. If a patient with acquired microcephaly appears to have a syndromic etiology, dysmorphic facial features may lead to a clinical diagnosis such as Mowat-Wilson syndrome. Some syndromic causes of acquired microcephaly are not typically associated with dysmorphic features. However, a diagnosis such as Rett syndrome can be recognized by other characteristic phenotypic features such as developmental regression after a period of normal development and loss of purposeful hand movements. Furthermore, there are a number of syndromic causes for acquired microcephaly which have molecular genetic testing available to confirm the diagnosis.

Metabolic Testing

In cases of acquired microcephaly that appear nonsyndromic, metabolic testing should be considered. Metabolic tests may include plasma amino acids, acylcarnitine profile, carnitine levels, ammonia, transferrin analysis, purines and pyrimidines, plasma and CSF glucose, galactose-1-phosphate uridyltransferase, thyroid function tests, lactate/pyruvate, urine organic and amino acids, urine S-sulfocysteine, and possibly additional mitochondrial studies.

Conclusions

With an emphasis on the evaluation of the child with acquired microcephaly, as well as a review of terminologies for microcephaly in general, the following conclusions can be drawn:

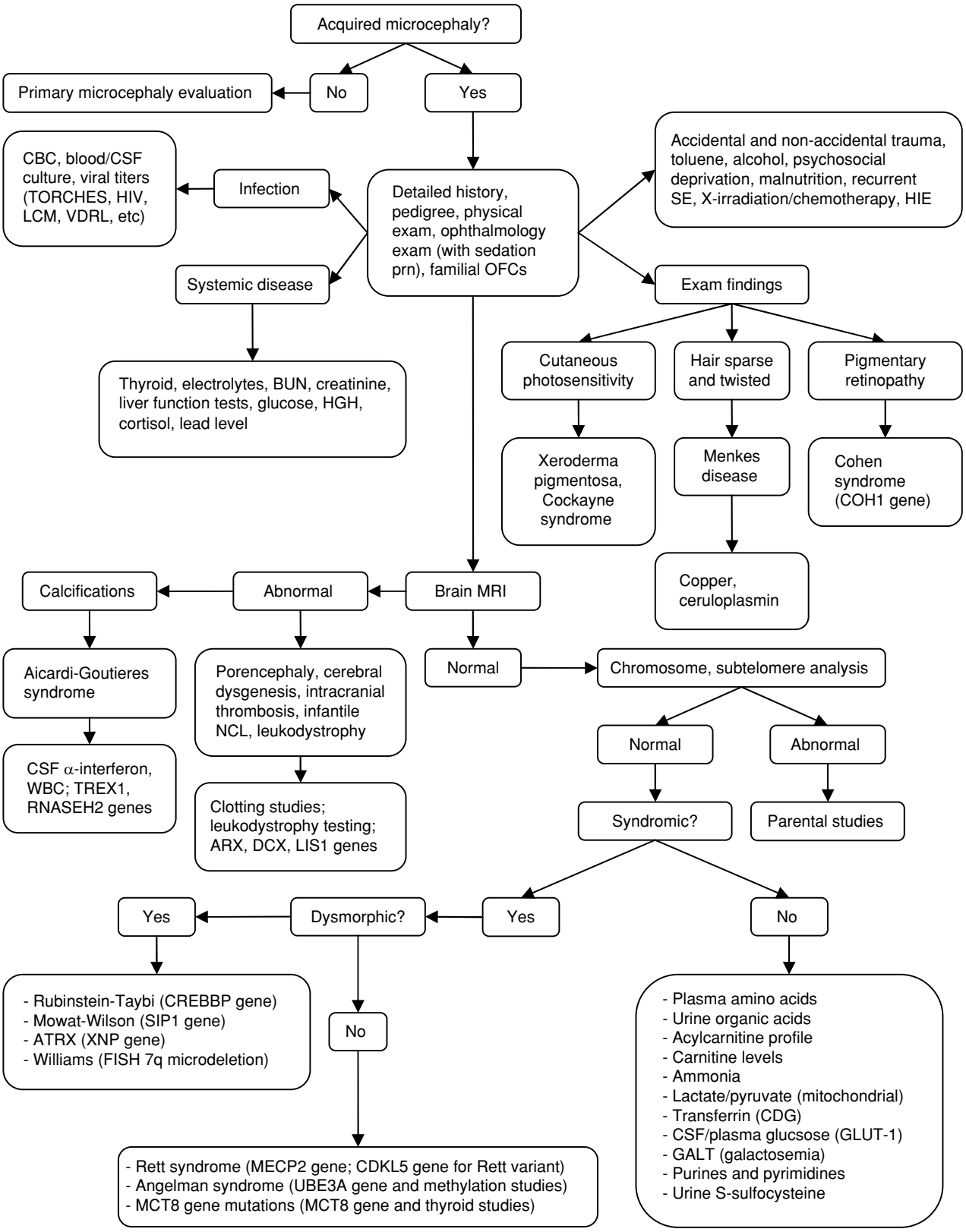

FIGURE 62-2. Algorithmic approach to the evaluation of acquired microcephaly.

1. OFC measurements are a valuable clinical sign and are not just for use in infancy. The discovery of an OFC > 2 SD below the mean for age and gender on physical exam is significant since microcephaly correlates with brain size. Brain growth in the first year of life significantly correlates with intelligence, and 70% of the final weight of the brain is present at 1 year of age.
2. Set 2 of the 2000 CDC OFC growth charts contains the preferred head circumference growth charts for ages from birth to 36 months. The Nellhaus curves are useful to evaluate OFC > 2 SD below the mean in the older (3–18 years old) pediatric age group.
3. Previous terminologies for microcephaly subtypes have become more meaningless and less helpful through the development of biochemical analyses, cytogenetics, molecular genetics, and neuroradiologic technologies. A strong recommendation has been made in this chapter to return to a nomenclature of "primary" microcephaly and "acquired" microcephaly to divide the microcephalic population into two groups. These two categories will facilitate cost-effective and meaningful evaluations, as well as expand our diagnostic and prognostic capabilities for these significant clinical findings over time.
4. Obtaining the newborn OFC is crucial to an evaluation of microcephaly. If a neonatal OFC is not available, any early head circumference in the first 1 to 2 months of life would help document whether the microcephaly was present as a neonate or developed after the neonatal period.
5. Acquired microcephaly is easily identified in most cases. Multiple etiologies and cost-effective workups are manageable after a standardized history, physical examination, thorough ophthalmologic examination (with or without sedation or anesthesia), and generally obtained investigational studies prior to elaborate neurogenetic evaluations. Part of this cost-effective workup would include measurement of first-degree relatives' OFCs and drawing a pedigree to search for familial microcephaly with and/or without neurodevelopmental disabilities.
6. Acquired microcephaly etiologies can exhibit characteristic presentations. A classic course or the time of development of microcephaly helps contribute to the cost-effective workup of this valuable clinical sign on routine pediatric examinations. Time will tell if the recently reported patterns of acquired microcephaly progression will also contribute to the successful identification of specific diagnoses.

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Practitioner and Patient Resources

CDC growth charts
http://www.cdc.gov/growthcharts/

Gene Reviews
<http://www.genetests.org>

Microcephaly Support Group
<http://www.microcephaly.co.uk/>

Online Mendelian Inheritance in Man
<http://www.ncbi.nlm.nih.gov/omim/>

CHAPTER 63

SLEEP DISTURBANCES

SURESH KOTAGAL, MD

Sleep-wake disorders impact close to a third of all children. This chapter will review salient aspects of sleep physiology, the clinical classification of sleep disorders, clinical assessment, and the impact of sleepiness on higher cortical functions. Commonly encountered sleep-wake disorders of infancy and childhood will then be discussed.

Sleep is a cyclic, physiologic state of decreased consciousness from which arousal is spontaneously accomplished. Sleep-wake disorders impact close to a third of all children. Attention to sleep during the history-taking and examination greatly enhances the ability of the physician to improve the quality of care and patient satisfaction. This chapter will review salient aspects of sleep physiology, the clinical classification of sleep disorders, clinical assessment, and the impact of sleepiness on higher cortical functions. Commonly encountered sleep-wake disorders of infancy and childhood will then be discussed.

Physiology

Ontogeny

Familiarity with sleep ontogeny and physiology is fundamental to understanding pediatric sleep disorders. Sleep can be easily differentiated from wakefulness by 26 to 28 weeks postconceptional age, at which time it is composed primarily of active (rapid eye movement or REM) sleep. By 32 weeks postconceptional age, active sleep can be clearly distinguished from quiet (nonrapid eye movement or NREM) sleep. At this age, active sleep constitutes approximately 80% of the total sleep. By 40 weeks postconceptional age, however, REM sleep decreases to approximately 50% of total sleep, with a corresponding increase in NREM sleep. By 3 to 4 years, REM sleep decreases to about 25% of the total sleep time. REM sleep is associated with higher levels of cerebral metabolic rate and blood flow than NREM sleep. NREM sleep differentiates into four stages, and this differentiation is completed by the age of six months. The characteristics of the various NREM stages are as follows:

Stage I or drowsiness mixed frequency (θ, α, and β) activity, isolated vertex sharp transients, slow rolling eye movements
Stage II prominent sleep spindles and K-complexes
Stage III delta (1 to 4 hertz range) slowing constitutes 20 to 50% of a 30-second epoch
Stage IV delta slowing constitutes 50% or more of a 30-second epoch

Table 63-1 lists the characteristics that help distinguish REM from NREM sleep. Up to the age of 3 months, the

TABLE 63-1. A Comparison Between REM and NREM Sleep

	REM Sleep	NREM Sleep
Prevalence	20–25% of total sleep time	75–80% of total sleep time
Electroencephalographic pattern	Low voltage, mixed frequency	Higher voltage, slower frequency; spindles and K-complexes in Stage II
Chin electromyographic pattern	Intermittent or phasic	Continuous or tonic
Muscle tone	Decreased (actively inhibited)	Increased
Eye movements	Abundant, rapid	Slow rolling in Stage I; otherwise generally absent
Twitching body movements	Prominent	Infrequent
Cerebral metabolism	Increased	Less than in REM sleep
Chemoresponsivity of brainstem respiratory neurons	Low	High

REM = rapid eye movement; NREM = nonrapid eye movement.

transition from wakefulness is normally into REM sleep, with NREM sleep appearing 45 to 60 minutes later. After the age of three months, however, the transition from wakefulness is directly in to NREM sleep, with REM sleep appearing 60 to 120 minutes later. Stage III and IV NREM sleep combined are also termed slow-wave sleep. The bulk of slow-wave sleep occupies the first third of the night's sleep. REM sleep is sparse in the first third of the night but becomes more abundant in the middle and final third of the night. The combination of one NREM sleep period with one REM sleep period is called a sleep cycle. Our night sleep is composed of a series of 5 to 6 sleep cycles.

Circadian Aspects

Normal newborns sleep 18 to 20 hours a day. *A circadian rhymicity* in sleep-wake function appears by 6 to 9 months, by which point the major 24-hour sleep episode occurs at night. The night sleep also becomes more continuous, and by 9 to 12 months, the majority of infants are sleeping through the night. The need for daytime naps diminishes progressively during infancy—two naps per day are common during infancy, and one nap per day in toddlers. Physiologic napping is uncommon beyond the age of 5 to 6 years. Around puberty, there is an increase in the need for sleep, combined with a shift in the time of sleep onset, which is now only around 10:00 or 10:30 p.m. Unfortunately, the lifestyle of most teenagers conflicts directly with their physiologic sleep needs. Questionnaire surveys have found that close to 45% of high school seniors admit to a need for more sleep.

Most of us tend to stay awake during the daytime and sleep at night. The tendency to cycle between sleep and wakefulness over time is termed circadian rhythmicity and is mediated by the *suprachiasmatic nucleus* of the hypothalamus, the activity of which is modified by illumination-dependent impulses received via the retinohypothalamic tract. Sleep-wake rhythms are also closely linked to body temperature; we tend to be most sleepy around the nadir of core body temperature, ie, 04:00 hours while a rise in body temperature during the mid and late morning coincides with awakening.

Neuroendocrine and Neurochemical Aspects

Melatonin, a pineal hormone, surges immediately prior to and during the first few hours of sleep. It helps in sleep induction and maintenance. Neurons of the suprachiasmatic nucleus express receptors for melatonin. The release of growth hormone at night is temporally linked to slow-wave sleep. Serotonin, delta sleep-inducing peptide, vasoactive intestinal peptide (high doses), somatostatin, enkephalins, β-endorphins, adenosine, and γ amino butyric acid mediate NREM sleep. Acetylcholine plays a role in mediating REM sleep. Wakefulness is mediated by dopamine, norepinephrine, histamine, glutamate, substance P, corticotrophin releasing factor, thyrotropin releasing factor, and the vasoactive intestinal peptide (low doses).

The International Classification of Sleep Disorders

This classification (Table 63-2), which was originally published in 1990 and subsequently modified, lists some 84 sleep disorders. It is clinically based. It provides a unique code for each disorder so that it can be efficiently tabulated for diagnostic, statistic, and research purposes. Diagnostic, severity, and duration criteria are presented, as well as an axial system, whereby clinicians can standardize the presentation of relevant clinical information. Axis A contains the primary sleep diagnosis. Axis B lists the procedures that are performed in the practice of sleep medicine, and Axis C comprises the medical and psychiatric disorders that are not primarily sleep disorders in of themselves. For example, narcolepsy may be recorded as follows:

Axis A: Narcolepsy, moderate, chronic, with excessive daytime sleepiness and cataplexy (347)
Axis B: Nocturnal polysomnogram (89.17)
Multiple sleep latency test (MSLT) (89.18)

Dyssomnias are associated with a primary sleep complaint of hypersomnia or insomnia and alterations in sleep architecture. *Parasomnias* are events that intrude onto sleep but do not lead to any visible alteration in sleep architecture.

TABLE 63-2. The International Classification of Sleep Disorders *(abbreviated by author)*

I. Dyssomnias
Intrinsic sleep disorders, eg, narcolepsy, obstructive sleep apnea
Extrinsic sleep disorders, eg, stimulant sleep disorder, sleep-onset association disorder, limit setting sleep disorder
Circadian rhythm disorder, eg, delayed sleep phase syndrome, jet lag
II. Parasomnias
Sleep-wake transition disorders, eg, sleep starts, head banging
Arousal disorders, eg, sleep walking, sleep terrors
Parasomnias associated with REM sleep, eg, nightmares, REM sleep behavior disorder
Other parasomnias, eg, bruxism
III. Sleep disorders associated with medical/psychiatric disorders
Associated with mental disorders, eg, psychosis
Associated with neurological disorders, eg, cerebral palsy, parkinsonism
Associated with other medical disorders, eg, asthma, arthritis
IV. Proposed sleep disorders, eg, sleep hyperhidrosis

REM = rapid eye movement.

Clinical Assessment

Sleep History

The sleep history is crucial in the planning of appropriate diagnostic procedures and arriving at a specific diagnosis. Questions relevant to infants and preschool age children include as follows:

a. sleeping environment, eg, crib, bassinet, parents room, etc.
b. sleeping position, eg, prone/supine, semiupright, etc.
c. need for sleep aids, eg, pacifier, rocking, patting, etc.
d. the time of bed onset, sleep onset, and the final morning awakening
e. presence of habitual snoring, mouth-breathing, restless sleep, sweating, gastro-esophageal reflux, abnormal behavior suggestive of seizures, parasomnias
f. behavior during the daytime (irritability, hyperactivity, sleepiness)
g. number of daytime naps and their duration
h. medications that may impact sleep-wake function
i. interventions to date that the parents have carried out to improve sleep

In school-age children, item *a* should be replaced by inquiring about events in the two to three hours prior to bedtime, eg, exercise, heavy meals, restless sleep, hypnagogic hallucinations, or sleep paralysis. The assessment of daytime function requires questions about involuntary naps in the classroom, as well as about cataplexy, hypnagogic hallucinations, and medications (prescription or over-the-counter) that may impact alertness.

Polysomnography

This technique of monitoring multiple physiologic parameters during sleep is useful in the evaluation of intrinsic sleep disorders, especially narcolepsy and obstructive sleep apnea (OSA). Generally, the electroencephalogram, eye movements, chin electromyogram, nasal airflow, thoracic and abdominal respiratory effort, electrocardiogram, end-tidal carbon dioxide, and oxygen saturation are sampled continuously during sleep. The data are recorded on a computerized system or paper. Standard criteria for the scoring of sleep stages and respiratory events have been established.

MSLT

The MSLT measures the speed with which one falls asleep, as well as the nature of the transition from wakefulness into sleep, ie, if it is into NREM or REM sleep. In order to determine whether daytime sleepiness is a consequence of a nocturnal sleep disturbance such as OSA, the MSLT should be preceded the night before by a polysomnogram. The MSLT consists of the provision of four or five daytime nap opportunities at two hourly intervals (usually 10:00, 12:00, 14:00, and 16:00 hours). During each nap opportunity, the time from "lights out" to sleep onset is measured while the EEG, eye movements, and chin EMG are being recorded. This time interval is termed "*sleep latency*." Mean sleep latency is then derived from all four or five naps. Normative values have been established for the mean sleep latency, which decreases progressively with increases in age and the Tanner stage of sexual development. It normally ranges between 12 and 18 minutes, whereas in narcolepsy, it is invariably less than eight minutes. The nature of the transition from wakefulness to sleep onset is also studied, ie, whether it is into NREM or REM sleep. In narcolepsy, it is often from wakefulness directly into REM sleep (Figure 63-1).

Actigraphy

This ambulatory procedure involves the recording and storing of skeletal muscle activity continuously for 1 to 2 weeks using a wrist watch-shaped microcomputer device. There is good correlation of periods of muscle activity with wakefulness and of the lack of muscle activity with sleep. There is good agreement between polysomnogram and actigraph determined sleep measures such as total sleep time, sleep latency, and sleep efficiency (percentage of time in bed spent sleeping). Wrist actigraphy is useful in the study of sleep initiation and maintenance difficulty. As an example, circadian rhythm disorders like the delayed sleep phase syndrome (DSPS) show nightly sleep onset in the early morning hours, uninterrupted sleep thereafter, with a final awakening in the mid to late morning hours (see Figure 63-1).

Common Pediatric Sleep-Wake Disorders

Narcolepsy

This is a chronic, lifelong disorder that is characterized by irresistible attacks of daytime sleepiness lasting 15 to 30 minutes, *cataplexy* (sudden loss of muscle tone in association with emotional stimuli like fright, surprise, or anger), *sleep paralysis* (an inability to move for a few seconds at sleep onset), and *hypnagogic hallucinations* (vivid dreams at sleep onset). Close to 100% of the patients possess the HLA DQB1*0602 antigen, which shows only a 25 to 30% prevalence in the general population. Canine narcolepsy is autosomal recessive and associated with mutations in the *hypocretin*-2 receptor gene. Human narcolepsy is, however, a multifactorial trait that is associated with a deficiency of hypocretin-1 ligand in the central nervous system. Hypocretin (synonymous

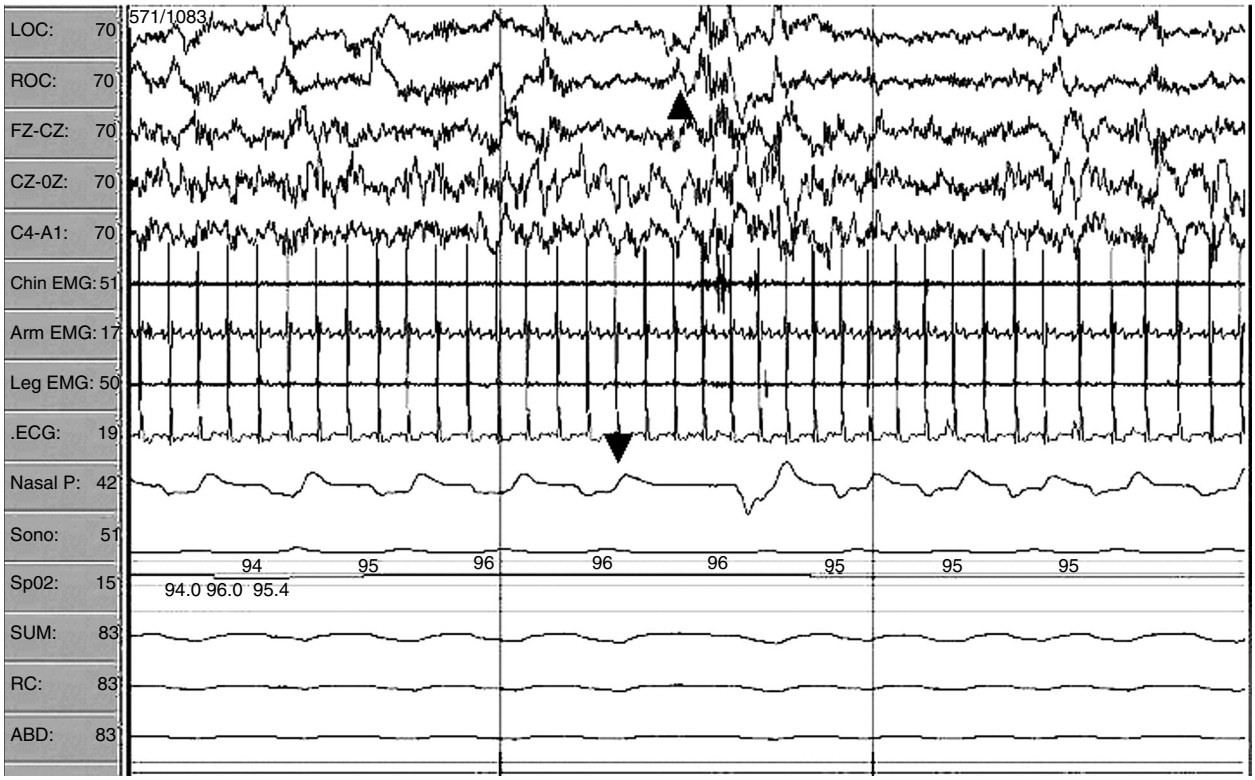

FIGURE 63-1. Wrist actigraphy over a two-week period in a child with a circadian rhythm disturbance, showing progressive delay in the time of sleep onset from one night to the next, along with a corresponding delay in the morning waking up time. The solid black areas represent muscle activity and correlate with wakefulness while the clear areas are associated with little or no wrist muscle activity and represent sleep. Each row corresponds to one day. Time across the 24-hour clock is shown over the top of the graph.

with orexin) is a peptide that is secreted by the dorsolateral hypothalamus. Hypocretin-containing neurons have widespread projections to the ventral forebrain and the brainstem and play a key role in the regulation of alertness, locomotor activity, and appetite. Patients with narcolepsy-cataplexy usually have low to absent cerebrospinal fluid hypocretin-1 (<100 pg/mL, with reference values in unaffected controls of 200–400 pg/mL). On the nocturnal polysomnogram, the diagnostic feature of narcolepsy is a short initial REM latency of <70 minutes and increased sleep fragmentation. On the daytime MSLT, children with narcolepsy show a short mean sleep latency of eight minutes or less (normal value is 12–18 minutes), together with two or more sleep-onset REM periods. Daytime sleepiness associated with narcolepsy is treated using stimulants like methylphenidate, dextroamphetamine, or modafinil. Cataplexy responds to anticholinergic agents such as protriptyline and clomimipramine or to selective serotonin reuptake inhibitors such as venlafaxine. One or two planned naps per day of 30 to 40 minutes duration may have a restorative impact on alertness. Emotional and behavioral problems are common in teenagers with narcolepsy and may necessitate psychological counseling. Owing to the increased risk of accidents, patients should be cautioned against driving or working near sharp, moving machinery.

Sleep-Related Airway Obstruction

OSA is characterized by the lack of oronasal airflow despite persistence of respiratory effort (Figure 63-2). It is commonly associated with adenotonsillar hypertrophy, obesity, Down syndrome, hypothyroidism, neuromuscular disorders, and craniofacial abnormalities like Pierre Robin and Crouzon syndromes. There is habitual snoring due to partial or complete upper airway occlusion during sleep, which in turn leads to repeated episodes of oxygen desaturation with consequent microarousals on the EEG. The sleep fragmentation is associated with rebound daytime sleepiness. *Nocturnal polysomnography* is helpful in establishing a diagnosis. The management includes tonsillectomy or adenoidectomy whenever these glands are enlarged and weight reduction (if obesity is present). The application of *continuous positive airway pressure* is helpful when there is no surgically correctable lesion.

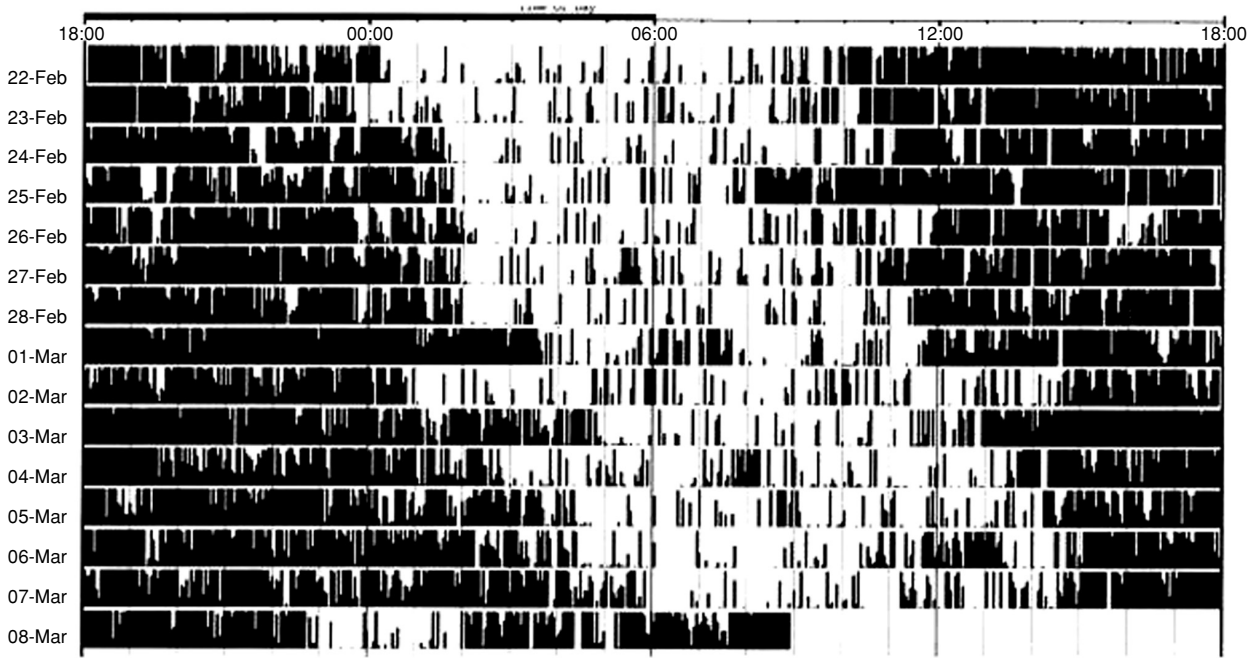

FIGURE 63-2. This is a 30-second segment of a nocturnal polysomnogram, illustrating the subtle nature of obstructive sleep apnea in children. The nasal pressure channel shows progressive flow limitation (down arrow), which leads to an electroencephalographic arousal (up arrow) and sympathetic activation in the form of heart rate acceleration. Sometimes, there is little or no oxygen desaturation. In contrast to adults who show complete cessation of oronasal airflow, children with obstructive sleep apnea manifest partial upper airway occlusion or as in this case, simply a respiratory event-related arousal.

Upper airway resistance syndrome (UARS) is a form of sleep-related upper airway obstruction in which the polysomnogram demonstrates no frank apnea, hypopneas, or oxygen desaturation, but the airway narrowing leads to recurrent arousals, fragmented sleep, and daytime sleepiness. UARS is actually twice as common as OSA in children. Some patients exhibit subtle posterior displacement of the mandible or a high-arched palate, but others may not show any craniofacial abnormalities at all. The polysomnogram may appear spuriously normal, with the exception of increased electroencephalographic microarousals of 3 or more seconds (normally less than 12 per hour of sleep). The simultaneously measured intraesophageal pressure using a balloon shows a marked increase in the intrathoracic negative pressure during the UARS episodes. The treatment is similar to that of OSA.

Central Alveolar Hypoventilation

The pathophysiology in these subjects is one of the defective automatic control of breathing, which leads to a failure to initiate and maintain respiration during sleep. The disorder may present during infancy (congenital form, ie, *Ondine's Curse*) or in later childhood. Developmental malformations of the brainstem, sometimes apparent only upon microscopic examination, are common in the congenital form. Head injury, bulbar poliomyelitis, syringobulbia, inborn errors of metabolism and Type II Arnold-Chiari malformation are other underlying disorders. The primary or idiopathic cases of congenital central hypoventilation syndrome (CCHS) may be linked to mutations in the homeobox gene, *PHOX2B*, which maps to chromosome 4p12. This gene encodes for a highly conserved transcription factor. About 20% of patients with CCHS have coexisting Hirschprung's disease, a disorder of bowel motility, which has defective development of autonomic ganglia in the wall of the large bowel. This combination of CCHS and Hirschprung's disease is called the *Haddad syndrome*. There is also an association between CCHS and neural crest tumors like ganglioglioma and neuroblastoma, which can coexist with CCHS in 5 to 10% of cases. It has been postulated that CCHS is a neural crest disorder in which there is defective fetal development because brainstem neurons that regulate chemosensitivity are actually derived from the neural crest.

In the early stages, the respiratory rate and depth are normal during wakefulness, but shallow and slow breathing, hypercarbia, and oxygen desaturation appear during sleep. Challenging breathing during NREM sleep using 5% inhaled carbon dioxide fails to induce the expected 3- to 5-fold increase in minute volume. There is no entirely satisfactory treatment, but acetazolamide and theophylline may enhance

the chemoreceptivity of the brainstem respiratory neurons. Home ventilation via a tracheostomy and diaphragmatic pacing are other treatment modalities. The disorder may prove to be fatal.

Restless Leg Syndrome and Periodic Limb Movement Disorder

Some children develop a peculiar urge to move their limbs in association with an uncomfortable sensory disturbance, which is frequently characterized as a creepy or crawling feeling. These symptoms, typically appear in the evening or at bed time, are made worse by keeping the limbs still and are relieved momentarily by moving the legs. They lead to disrupted and nonrestorative sleep as well as daytime sleepiness, inattentiveness, and fatigue. Restless leg syndrome (RLS) is transmitted as an autosomal dominant trait. Mild systemic iron deficiency is common, with serum levels of ferritin frequently being below 50 ug/dL. Excessive use of caffeine and tricyclic agents and deficiencies of vitamin B12 are other predisposing factors. The nocturnal polysomnogram shows sleep fragmentation. There may or may not be an associated periodic limb movement disorder (PLMD) that is defined as a series of 3 or more rhythmic, electromyographically recorded movements of the legs, each lasting 0.5 to 5 seconds that occur 5 to 20 seconds apart, generally in stages I or II of NREM sleep. RLS can be treated using oral iron supplementation or with bedtime gabapentin/clonazepam/dopamine receptor agonists like pramipexole and ropinorole.

Sleep Onset Association Disorder

Frequent nighttime awakenings are a problem in a third of all infants and toddlers. They generally disturb the sleep of the parents more than bothering the infant per se. Most healthy infants are able to "learn" to sleep uninterrupted for 4 to 6 hours at night by 4 to 6 months of age. Between 2 and 3, nighttime awakenings are physiologic in most infants, who will usually then "self-soothe" and fall back to sleep without parental involvement. The sleep-onset association disorder is characterized by frequent nighttime awakenings because the infant begins to associate sleep-onset with the obligatory presence of an external stimulus like rocking/patting/sucking a pacifier/exposure to music/sleeping in the parents' bed, etc. In the absence of these extraneous influences, the infant is unable to fall asleep. The management consists of firmly eliminating an association with the external object/action, placing the infant to sleep in his/her own crib, and encouraging the parent to leave the room prior to infant actually falling asleep. Eliminating the daytime nap and postponing bedtime by an hour may also make the child sleepier and thus liable to fall asleep without struggling.

Limit-Setting Sleep Disorder

This is a behavioral disorder in which the patient (usually a preschool age child) refuses to fall asleep at an age appropriate time. Nightly struggles between the child and the parent about going to sleep are common (the "another glass of milk" or "another bed-time story" scenario). The parents are often unable or unwilling to enforce bedtime rules even though the child is physiologically ready for bed. Lack of parental education about limit-setting, parental guilt, anxiety, depression, and alcoholism are common predisposing factors. The treatment consists of limiting the daytime nap to about one half hour, postponing the nightly bed onset by about 30 minutes to 1 hour (a sleepy child is less likely to engage in a struggle), and advising that the parent leave the room prior to the child actually falling asleep. If the child awakens, the parent should firmly return the child to his/her own room and keep the room door closed from the outside if necessary. Limit-setting also needs to be routinely enforced during daytime behavioral disturbances.

Insufficient Sleep Syndrome

Most adolescents require about 9.5 hours of sleep at night to ensure optimum daytime alertness. There is a physiological delay in the sleep-onset of time of most teenagers to about 10:30 p.m. High school students also have the pressures and distractions of homework, extracurricular activities, cell phones, friends, television, and the internet, etc, which tend to keep them up till late at night. They might also consume caffeine or drugs that might interfere with sleep onset. Most teenagers therefore receive substantially less sleep on weeknights than the recommended optimum. They are consequently sleepy in the daytime. Close to 45% of high school seniors have expressed a need for more sleep on questionnaire surveys. Sleep logs extending over 1 to 2 weeks, and actigraphy can be used to document sleep length. The management consists primarily of altering the daytime schedule in order to obtain more sleep at night.

DSPS

This is by far the most common circadian rhythm disorder, accounting for about 10% of all insomnia complaints. It is related to dysfunction of the suprachiasmatic nucleus, which is our circadian timekeeper. DSPS is associated with a constitutional inability to advance (prepone) sleep-onset prior to a given time. The patient is typically a teen-age "night owl" who is unable to fall asleep prior to 2:00 or 3:00 a.m despite the best of efforts at trying to fall asleep at an earlier hour. If allowed to sleep uninterrupted, eg, on weekends or holidays, the individual may sleep in till 11:00 a.m or 12:00 noon and feel very refreshed. There is no qualitative or quantitative abnormality in sleep, just that

sleep-onset and offset are at socially inappropriate times and lead to sleep-wake complaints. The treatment consists of keeping a rigid morning wake-up time and using 0.5 to 1 mg of melatonin about 5.5 hours prior to bedtime to try to advance the sleep-onset. Daily exposure to 8,000 to 10,000 lux of bright light for 20 to 30 minutes immediately upon awakening every morning, eg, while having breakfast, will also help to phase advance bedtime.

Night Terrors and Sleep Walking (NREM Dyssomnias)

These nonepileptiform events are characterized by 5 to 10 minutes of episodes of agitation, sweating, flushed face, kicking, jumping or aimless walking, typically during Stages III-IV of NREM sleep and for which the patient has no recollection the following day. These are transient disorders that generally resolve spontaneously over months to years and are considered *disorders of partial arousal* from sleep. The hallmark of both types of events is the time of occurrence relative to sleep onset—typically they occur during Stages III and IV of NREM sleep, which is mainly clustered into the first third of night sleep. Video-EEG studies are helpful in establishing the diagnosis. The EEG reveals high amplitude, rhythmic slowing in the 2 to 4 hertz range. Typically, the child is inconsolable but has no recollection of the event the following day. *Anticipatory awakening*, ie, awakening the child about 15 to 20 minutes prior to the usual time of occurrence of the events by wiping the face with a wet washcloth is helpful in some cases. In other instances, it may be important to exclude disorders like OSA that may trigger partial arousals and the resulting parasomnia. It is important to ensure adequate daytime naps. In refractory cases, a trial of low-dose clonazepam at bedtime generally proves effective.

Confusional Arousals

This parasomnia of stage III-IV NREM sleep typically occurs in 2- to 4-year-olds. The time of occurrence is once again in the first third of night sleep. The child wakes up crying and is inconsolable. In contrast to night terrors, however, sweating, flushing of face, and motor activity are minimal. The event usually subsides in 10 to 30 minutes. The management is identical to that of sleep terrors.

The Relationship Between Sleep and Epilepsy

Between 0.5 and 24% of epileptics have seizures during sleep. Janz, in a study of 2110 patients with generalized convulsive seizures, reported that 45% had seizures predominantly during sleep. Generalized epileptiform discharges are more likely to occur during stages I and II of NREM sleep, and focal discharges during REM and stages I and II of NREM sleep. Sleep deprivation is known to lower seizure threshold. *The syndrome of episodic nocturnal wanderings* is an epileptic disorder characterized by the presence of midline spikes in stages I and II of NREM sleep. It usually responds to carbamazepine or phenytoin. The *Landau Kleffner syndrome* is characterized by regression in language, inattentiveness, and behavioral problems generally between the ages of 3 and 10 years in association with focal or diffuse epileptiform discharges during both NREM and REM sleep that occur in over 80% of the night sleep epochs. An epoch is 30 seconds of nocturnal polysomnographic tracing. There may or may not be accompanying clinical seizures. Treatment with valproic acid/corticosteroids/intravenous immunoglobulin G may lead to a variable degree of improvement in language function. The syndrome of *electrical status epilepticus in sleep* is similar to the Landau Kleffner syndrome, with the distinction that epileptiform features remain restricted to NREM sleep. *Nocturnal frontal lobe epilepsy* can cause brief, 10- to 15-second periods of arousal from stages I and II of NREM sleep that may be accompanied by confusion, thrashing of the limbs, and vocalizations. These events mimic parasomnias like confusional arousals; video-polysomnography is the only definitive test for distinguishing nocturnal spells of epileptic and nonepileptic origin.

The Impact of Daytime Sleepiness on Higher Cortical Function

Acute, overnight sleep deprivation in children has been shown to decrease verbal fluency and creative thinking. Executive functions may also be impaired. In adults, sleepiness interferes with the transfer of information from the short-term to the long-term memory banks. A large number of adults with narcolepsy report symptoms of attention deficit disorder in childhood. A high proportion of children with OSA also experience symptoms of attention deficit disorder that reverse upon treatment of the sleep-disordered breathing. Behavioral disturbances like mood swings and irritability are also common in sleepy children, regardless of the etiology of the sleepiness. It has been hypothesized that sleepiness interferes with the "affect control" that is normally mediated by the prefrontal cortex.

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Practitioner and Patient Resources

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One Westbrook Corporate Center, Suite 920
Westchester, IL 60154
<http://www.aasmnet.org>
Phone: (708) 492-0930
Fax: (708) 492-0943

American Sleep Apnea Association
1424 K Street NW, Suite 302
Washington, DC 20005
Phone: (202) 293-3650
Fax: (202) 293-3656
E-mail: asaa@sleepapnea.org

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10421 Reed Hartman Highway
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Phone: (513) 891-3522
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E-mail: narnet@aol.com

CHAPTER 64

BREATH-HOLDING SPELLS

WILLIAM DEMYER, MD

Breath-holding spells consist of brief apneic episodes provoked by some acute emotional stimulus, such as anger or pain. The child then displays cyanosis or pallor, loss of consciousness, rigidity, and, sometimes, seizure-like twitching. Breath-holding spells usually begin spontaneously in otherwise normal children between the ages of 6 and 24 months and usually stop by the age of 5 years. Every primary-care physician will encounter patients with these common spells.

Pathophysiology

Breath-holding spells consist of a stereotypical sequence of pulmonary and cardiovascular responses to strong, usually adverse, emotions. The cyanotic type of breath-holding spells prevails over the pallid type in a ratio of about 3:1. Vagally mediated cardiac inhibition generally occurs in the pallid type of breath-holding spells, whereas reflex induced forceful and prolonged expiration causes the cyanotic type. Cerebral anoxia, whether produced by asystole or prolonged apnea, apparently causes the loss of consciousness. Some breath-holding spells may terminate with a true epileptic seizure.

Clinical Features

Breath-holding spells most commonly occur in children who appear physically and developmentally normal, but they can also affect retarded children. Breath-holding spells usually begin between the ages of 6 and 24 months, peaking in frequency by around 2 to 3 years. They may appear numerous times per day, but usually disappear by 5 to 6 years of age. Breath-holding spells affect boys more than girls in a ratio of about 1.3:1. Most children with breath holding spells seem to have urgent, demanding personalities, although studies have not shown a diagnostic personality profile.

Typically, breath-holding spells display four phases: (1) provocation, (2) expiratory apnea and cyanosis, (3) opisthotonic rigidity (backward arching), and (4) stupor. The provocation consists of some strong physical or emotional stimulus: a fall, anger, frustration, or pain. A breath-holding spell typically starts with crying, lasting 15 seconds or less. If crying lasts much longer, the breath holding spell may not occur. Abortive breath-holding spells occur, as well as the full tetrad. Sometimes the second phase occurs without the crying phase. The second phase consists of sustained, forced expiration, followed by progressive cyanosis in the majority of patients. The child remains aware during the first few seconds of this phase. During this interval, a counter-stimulus or diversion of the patient's attention may abort an attack. At the onset of the third stage, the rigid stage, the patient becomes restless and then opisthotonic, with strongly extended back, arms, and legs. Cyanosis has become prominent by this time, and the patient has lost consciousness. Some clonic twitches and, sometimes, incontinence may occur. The apneic stage of the attack ends with a gasp or the resumption of quiet breathing. The normal skin color promptly returns, and the patient lies motionless. The patient typically remains stuporous or drowsy for minutes to hours after an attack. Although the whole sequence to the stage of stupor lasts only a few minutes, anxious parents may estimate the time to be much longer, a matter to consider when eliciting the history. If in doubt, ask the parents to time an episode with a watch. A family history of breath-holding spells in 25 to 35% suggests an autosomal dominant pattern of inheritance with reduced penetrance. Whether this means a genetic predisposition to autonomic instability remains unknown. Because the child's parents often do not know whether they themselves have had breath-holding spells, questioning of the child's grandparents may lead to more accurate information.

Diagnosis and Differential Diagnosis

The diagnosis, as in migraine or any such episodic disorder, rests squarely on the quality of the history. In particular, the examiner has to determine that an emotional event has triggered each attack. Table 64-1 outlines the specific criteria for the diagnosis of breath-holding spells.

The common differential diagnoses include epilepsy, congenital heart disease, vasovagal syncope or hyperactive carotid sinus, prolonged QT interval, and posterior fossa or brainstem lesions. Breath-holding spells generally feature arrest of breathing after prolonged expiration, which distinguishes them from voluntary breath-holding, in which the person arrests breathing after inspiration. The fact that breath-holding spells rarely appear before 6 months of age serves to differentiate them from neonatal apnea and other apneic disorders of early infancy. The normal history and physical findings should readily differentiate congenital heart disease, with syncope or cyanosis precipitated by exercise. Syncopal attacks from ordinary causes in older patients rarely occur in the range of onset of breath-holding spells (6 to 24 months). Vasovagal syncope or carotid sinus hypersensitivity should be investigated by combined electroencephalographic-electrocardiographic monitoring, including eyeball compression and carotid sinus massage.

Exclusion of syncope leaves epilepsy as the major differential diagnosis. The typical full tetrad (provocation by emotion, expiratory apnea and cyanosis, opisthotonic rigidity, and stupor) readily differentiates breath-holding spells from typical epileptic attacks. Unfortunately, not all patients with epilepsy or breath-holding spells have typical attacks. The most difficulty arises with rigid or akinetic seizures, in which the patient may exhibit no overt convulsive movements. These attacks sometimes seem to follow provocations of the type that induce breath-holding spells. The correct diagnosis may require recording a spell by continuous video electroencephalogram (EEG) monitoring. Table 64-2 summarizes the differential diagnosis of breath-holding spells and epilepsy.

TABLE 64-1. Criteria for the Diagnosis of Breath-Holding Spells

1. The spells begin in a physically healthy patient between the ages of 6 and 24 months.
2. The spells follow an orderly tetrad of a provocative emotional stimulus, expiratory apnea and cyanosis, opisthotonic rigidity, and stupor.
3. The entire sequence of events up to the stupor phase lasts only a few minutes. The last stage, stupor, lasts a variable length of time.
4. The child may have many attacks per day or only a few at irregular intervals.
5. The family history often discloses breath-holding spells, particularly if the grandparents are questioned.
6. The physical examination, including careful cardiac evaluation, is normal.
7. The EEG, ECG, and MRI are normal, if obtained, but generally the history establishes the diagnosis without these tests.

ECG = electrocardiogram; EEG = electroencephalogram; MRI = magnetic resonance imaging.

Course and Prognosis

Patients 2 to 3 years of age usually display the most frequent breath-holding spells. The attacks then gradually grow fewer and usually disappear by 5 to 6 years of age. Despite having many cyanotic attacks per day for several years, the patients do not seem to suffer overt or cumulative brain damage. No specific, long-term psychiatric sequelae are known.

Management

During an attack, parents should place the patient in a lateral recumbent position but should generally avoid cardiopulmonary resuscitation. Usually the history suffices to secure the diagnosis, but some authors recommend routine electrocardiograms (ECGs) to check for a prolonged QT interval. Resolution of the diagnosis in a few patients may require combined ECG and video EEG monitoring, with ocular compression or other autonomic tests.

TABLE 64-2. Differentiation of Breath-Holding Spells from Epilepsy

Characteristic	Breath-Holding Spells	Epilepsy
Pregnancy, birth, and physical examination	Usually normal	Frequently abnormal, particularly with soft or hard neurologic signs
Family history	No history of epilepsy but may have history of breath-holding spells	Epilepsy common in near relatives
Triggering	Always triggered by an emotionally provocative event	May be triggered by fever, sound, or light or occur spontaneously
Evolution of events	Follows typical tetrad of provocation, apnea or cyanosis, opisthotonic rigidity, and stupor; cyanosis precedes loss of consciousness	Usually has an aura and early loss of consciousness; often shows clear tonic-clonic phase or other specific seizure pattern
Electroencephalogram	Nonepileptiform	Usually epileptiform
Response to antiepileptic medication	None	Frequent response

After having secured the diagnosis of breath-holding spells, the physician should thoroughly explain their benign nature to the parents. First of all, the physician should realize that the oft-recited advice merely to ignore the spells does not suffice. The spells frighten the parents, make them very anxious, and negatively affect their relationship with their child. The physician should educate the parents as to the involuntary, reflexive or autonomic nature of breath-holding spells, that the patient does not willfully and by malicious intent induce a spell to seek attention, and that the spells do not signify a flawed child with a serious physical or mental illness. After understanding the benign nature of breath-holding spells, the parents can usually cope with them and can learn to abort some spells by distracting the patient when provocative emotional stimuli arise. No known behavioral technique controls breath-holding spells, certainly not punishment.

Although the vast majority of children do not require any medication, severely affected patients may respond to piracetam. Antiepileptic drugs are not effective. Pallid breath-holding spells may respond to atropine when the ocular compression test shows significant asystole during ECG monitoring. Very rarely pacemaker implantation is indicated. Reduction of the breath-holding spells may follow correction of any underlying systemic illnesses. Evidence now suggests that iron-deficiency anemia occurs in greater frequency in patients with breath-holding spells than in normal control subjects, and correction may eliminate the breath-holding spells.

Suggested Readings

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CHAPTER 65

HIV-1/AIDS IN INFANTS AND CHILDREN

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This chapter briefly summarizes the features of pediatric human immunodeficiency virus type 1 (HIV-1) and/acquired immune deficiency syndrome (AIDS), describes associated neurologic disorders, and reviews changing epidemiology and current concepts of diagnosis and therapy.

Shortly after the clinical and immunologic features of pediatric AIDS were first described in the literature, neurologic involvement was recognized as a significant complication. Within the next 10 years, the numbers of children with HIV-1 or AIDS increased, reaching epidemic proportions. AIDS had become one of the leading causes of childhood morbidity and mortality in the United States and worldwide.

The etiologic agent of AIDS, isolated in 1983 and named *human immunodeficiency virus type 1* (HIV-1) in 1986, was found to be a retrovirus that replicated in and lysed activated human CD4+ T cells. The retrovirus was also found to belong to the Lentivirinae subfamily of nononcogenic cytopathic retroviruses. Lentiviruses are species-specific and have long periods of clinical latency and mechanisms to evade immune clearance. They target specific organs, cause persistent infection and multisystem disease in their natural hosts, and characteristically invade the central nervous system (CNS), resulting in chronic encephalitis. Morphologic and genetic similarities have been documented between HIV-1 and visna virus, an ovine retrovirus with well-known neurotropic properties. HIV-1, like all other lentiviruses, was also found to infect the CNS.

HIV-1 causes a wide spectrum of disease in infants and children. The most severe form of the disease results in AIDS. Neurologic complications are frequent, add significantly to the morbidity of the illness, and often have devastating consequences.

HIV-1 and AIDS neurologic disorders can be classified into two major categories: (1) HIV-1–associated CNS disease ("progressive encephalopathy"), a syndrome with cognitive, motor, and behavioral features related to primary HIV-1 CNS infection, and (2) secondary CNS complications (CNS neoplasms, CNS infections caused by pathogens other than HIV-1, and strokes) related to immunosuppression or to distinct AIDS-related conditions.

The CNS may also be adversely affected by complications related to systemic HIV-1 disease and its therapy, including metabolic and endocrinologic derangements associated with systemic HIV-1–related disorders, and by toxic or metabolic complications of antiretroviral and antimicrobial therapies. These conditions are not mutually exclusive, and coexisting pathologic conditions are common.

Neurodevelopmental status may also be affected by HIV-1–related and nonrelated comorbid conditions that occur with substantial frequency in this population (eg, those related to maternal high-risk factors during pregnancy, premature birth, and complications in the neonatal period, as well as innumerable postnatal psychosocial stressors).

During the past 2 decades, much has been learned about the biology of HIV-1 and the cells it infects. Major advances have led to a better understanding of factors pertaining to transmission. This has led to marked advances in prevention of maternal–infant viral transmission, more proficient diagnostic techniques (eg, polymerase chain reaction; measurements of HIV ribonucleic

acid [RNA] "viral load"), enabling early diagnosis and identification of HIV-1–infected infants during asymptomatic or mildly symptomatic disease stages, treatment of primary HIV-1 infection (highly active antriretroviral therapy [HAART] and immunomodulating therapy), successful prophylaxis for life-threatening opportunistic infections (OIs), and more aggressive and successful medical management of HIV-1/AIDS–associated conditions. As a result, in developed countries, the number of infants born with HIV-1 infection has declined, and the survival rate of infected children has improved. Children with HIV-1 infection are living longer. A significant and increasing percentage of children are surviving into adolescence and adulthood. Pediatric HIV-1/AIDS has become a chronic disease.

Natural History of Pediatric HIV-1/AIDS

The adverse effects of HIV-1 on the developing immune and nervous system often result in more rapid onset of clinical symptoms and progression to death. A bimodal evolution of symptomatic HIV-1 disease, with different rates of survival, has been observed. The first occurs in infancy and the second later in childhood. In actuality, a trimodal evolution exists, with the third "hump," albeit the smallest, occurring in the preadolescent and adolescent years. As in adults, latency to onset of moderately symptomatic disease in this group may be 10 years or more.

The first group constitutes infants who have high levels of detectable virus at birth. The disease progresses rapidly, and these children manifest severe clinical symptoms and immunologic abnormalities within the first years of life, including HIV encephalopathy, often the presenting condition that indicates AIDS. About 20% of infants develop this early severe form of the disease.

Children in the second and largest group have a form of HIV-1 disease that progresses more slowly. The factors underlying the difference between the two groups are unclear but may relate to the timing of HIV-1 infection (during gestation versus parturition), the stage of maternal HIV-1 disease during pregnancy and delivery (maternal viremia), the neonates' viral load, the virulence of the infecting virus, HLA class I sharing between mother and infant, CCR5 mutations, and other, undefined genetic and host-related factors as yet undefined.

Natural history studies (in the United States) prior to the antiretroviral era revealed that approximately 50% of children were symptomatic by age 5 years, with 75% surviving to that age. Mean time from birth to severe disease (stage C) was 6.6 years, with an estimated mean survival of 9.4 years. However, children with HIV-1/AIDS who live in developing countries are at greater risk for early death than are children in industrialized countries. African studies show about 50% of infected children die by age 2 years (Zambia) and 66% by age 3 years (Uganda).

Epidemiology

HIV-1 Transmission and Risk Factors

Mother-to-infant transmission occurs in utero, intrapartum, or postpartum via breast-feeding. At least 90% of infected children were infected via their mothers. It is believed that viral transmission occurs most frequently during or near the time of birth. A 25% rate (16–45%) of mother-to-infant transmission is estimated from studies conducted in the United States, Europe, Thailand, and Africa. Factors associated with increased transmission risk include low maternal CD4+ counts, high viral loads, advanced HIV-1 disease (AIDS), maternal-fetal HLA concordance, low levels of vitamin A, placental membrane inflammation, premature rupture of membranes, increased infant exposure to maternal blood, premature delivery, and breast-feeding.

Parenterally acquired HIV-1 infection through contaminated blood or blood products or contaminated injection equipment occurred prior to HIV-1 blood donor screening and is no longer considered a problem in developed countries. Virus transmission in medical settings also occurred (eg, in Romania) through the reuse of contaminated injection equipment.

Infection through sexual abuse takes two forms: (1) through sexual abuse in the home and community and (2) through commercial sexual exploitation of children (a multibillion-dollar worldwide industry). It is unknown how many child sex workers there are in the world because of the clandestine nature of the trade. Most children in the sex industry are girls aged 13 to 18 years.

Sexually transmitted HIV-1 infection and intravenous (IV) drug use in adolescents is of major concern. Over 50% of the 5 million new HIV-1 infections diagnosed in 2003 occurred in the 15- to 24-year-old age group. Sexual exposure and intravenous drug use are the most common risk factors. Approximately 65% of adolescents aged 13 to 19 years with AIDS were infected through these means.

The Changing Worldwide Epidemic

The World Health Organization (WHO-UNAIDS) reports about 40 million people worldwide were living with HIV/AIDS in 2006 (2.6 million more than in the year 2004!). Of these, 2.3 million were children aged 15 years or under, with the vast majority living in sub-Saharan Africa.

During the year 2006, 4.3 million persons were newly infected with HIV. Of these about one-half were women

and about 530,000 were children. An estimated 2.9 million people died of AIDS in 2006; 380,000 were children.

The number of people living with HIV/AIDS continues to increase in several regions. Although sub-Saharan and South Africa, continue to be the most affected regions, with about 25 million people infected, the steepest increases during the past several years have occurred in Eastern Europe, Central and East Asia.

An ever increasing proportion of people living with HIV infection are women and girls. In some regions of sub-Saharan Africa, of persons aged 15–24 years, 76% are female. Similar trends in female to male ratios are noted in other areas as well (Asia, Latin America, the Caribbean, and parts of Eastern Europe). As WHO/UNAIDS reports "…most women become infected through their partner's high risk behaviors (over which they have little control)."

The worldwide increase in the number of HIV-1 infected women of childbearing age is paralleled by the increased numbers of children with vertically acquired HIV infected. Although new vertically transmitted infection has now become rare in industrialized countries following the use of antiviral therapy, it continues to be rampant in some regions of resource poor nations.

AIDS Orphans

An increasing number of children (infected and uninfected) born to mothers with AIDS have or will become "AIDS orphans," a tragic sequelae of the epidemic. Since the beginning of the epidemic, more than 14 million children younger than 15 years of age are estimated to have lost their mother or both parents to AIDS. About 90% of these children live in a sub-Saharan African country. In the United States alone, there were an estimated 80,000 uninfected AIDS orphans in 1999.

Prevention of Vertically Acquired HIV-1 Infection

The most effective strategy for preventing mother-toinfant transmission is to prevent HIV-1 infection in the mother before pregnancy and, indeed, in all women of childbearing age. Short of that, the next most important strategy is to prevent HIV-1 transmission from the infected pregnant woman to her fetus.

In 1994, zidovudine (ZDV) given orally during pregnancy and intravenously during labor, with continued treatment of the newborn with 6 weeks of oral medication, was found to dramatically reduce the rate of perinatal transmission by 67%. Antiretroviral therapy was recommended for HIV-1–infected pregnant women. In developed countries, this resulted in a dramatically significant decline in the rate of mother-to-infant transmission (< 2%). Unfortunately, this is not the case in developing countries, where the epidemic predominates and where access to these medications is limited. Although not ideal, even short course ARV therapies have been shown to reduce transmission rates by approximately 40–50%. Yet fewer than 10 percent of pregnant women with H.I.V. in poor and middle-income countries are receiving the simple regimen of pills that can prevent the transmission of the AIDS virus to their newborns. (In contrast to rich countries which have virtually eliminated pediatric AIDS).

It is clear ARV in pregnancy substantially reduces the risk of HIV mother-to-child transmission, but the potential for teratogenic effects remains a concern. ARVs appear to be safe, with severe mitochondrial toxicity associated with NRTI use during pregnancy rare. However, possible long-term complications to the exposed fetus are as yet unknown. Studies in France identified children exposed to ARV *in utero* who have developed clinical and neuroimaging features of mitochondrial dysfunction. Follow up of these and other children with milder forms of possible ARV mitochondrial toxicity will be required to determine if ARV exposure has long-term deleterious effects. Monitoring of ARV exposed children for possible other adverse effects will also be essential in view of the increasing number of women on therapy at conception, during pregnancy as well as the likely continuing evolving diversity of drug regimens.

HIV-1 transmission infection through breast-feeding continues to be a significant problem since the rates of infection from breast-feeding may offset the benefits of treatment during pregnancy and the perinatal period, major concern in some developing countries, where safe alternatives to breast-feeding (access to formula milk powder, clean water, and sanitation) are lacking.

Clinical Manifestations of HIV-1/AIDS Neurologic Disorders

HIV-1–Associated CNS Disease Syndromes and Progressive Encephalopathy

Manifestations of HIV-1 CNS disease syndromes are described according to a classification scheme based on age of onset of clinically apparent disease and rate and pattern of disease progression. This information comes from clinical observations and studies conducted during the first decades of the HIV/AIDS epidemic, prior to HAART regimens.

Cognitive impairment, acquired microcephaly, and corticospinal tract (CST) signs are the most frequent manifestations. Movement disorders (usually superimposed upon spasticity) and cerebellar signs may also occur with advanced disease. Mood and behavioral problems are common. Rate and pattern of disease progression are variable. Neurologic deterioration is rapidly progressive in

some infants and young children. Within a few months they develop severe and progressive CNS dysfunction, resulting in quadriparesis and mental deficiency. In a subset of children, neurologic deterioration occurs over a period of months, followed by a relatively stable period and then by further deterioration. Cognitive and motor impairment can be discordant. Some children develop progressive and disabling motor deficits yet maintain relatively stable (albeit impaired) cognitive function. In contrast, in other children, cognitive function is more impaired than motor function. Finally, some children have more minor motor and cognitive deficiencies, with a stable course.

Neonates

HIV-1–infected newborns are usually well at birth, with no recognizable neurologic features of HIV-1 CNS disease. These neonates, however, can have or develop coexisting neurologic problems that often are related to maternal conditions during pregnancy. Preterm delivery is often interlinked with these "high-risk" conditions. In turn, the preterm HIV-1–infected infant (as the noninfected infant) is at risk for developing CNS complications.

Infants

The "severe infantile" form is the most severe, devastating, and clearly recognized syndrome. CNS signs usually appear within the first year of life but may begin in the second to third year and result in mental deficiency and spastic quadriparesis. Characteristic features are (1) decline in mental development or marked "delays" in cognitive development, (2) progressive CST signs and loss of previously acquired motor milestones or a markedly deviant rate of acquiring motor skills, and (3) acquired microcephaly. Neurologic deterioration may be rapid (over weeks to a few months), slowly progressive with an insidious decline, or episodic, with periods of deterioration interrupted by periods of relative neurologic stability.

A less severe neurologic syndrome may also occur within the first 2 years of life. Hypotonia with delays in attainment of motor milestones is characteristic. Mental development is often delayed, and deficiencies in language acquisition are common. Prognosis is guarded. Some children develop a diparesis-type syndrome in early childhood; others remain stable and continue to acquire new skills.

Toddlers and Young Children

A change of gait is often the first sign of HIV-1 CNS disease. Children begin to toe walk, are hyperreflexic, and develop increased muscle tone in the lower extremities.

TABLE 65-1. Diagnoses That Indicate AIDS*

Serious bacterial infections[c], multiple or recurrent
Candidiasis of the trachea, bronchi, or lungs[a]
Candidiasis of the esophagus[a, b]
Coccidioidomycosis, disseminated or extrapulmonary[c]
Cryptococcosis, extrapulmonary[a]
Cryptosporidiosis, chronic intestinal[a]
Cytomegalovirus (other than liver, spleen, nodes) onset at age > 1 month[a]
Cytomegalovirus retinitis (with loss of vision)[a, b]
HIV encephalopathy[c]
Chronic herpes simplex ulcer (> 1 month duration) or pneumonitis or esophagitis onset at > 1 month of age[a]
Histoplasmosis, disseminated or extrapulmonary[a]
Isosporiasis, chronic intestinal (> 1 month duration)[c]
Kaposi's sarcoma[a, b]
Lymphoid interstitial pneumonitis[a, b]
Lymphoma, primary brain[a]
Lymphoma (Burkitt's or immunoblastic sarcoma)[c]
Mycobacterium avium complex or *M. kansasii*, disseminated or extrapulmonary[a]
M. tuberculosis or acid-fast infection (species not identified), disseminated or extrapulmonary[c] or pulmonary[d]
Pneumonia, recurrent[d]
Pneumocystis carinii pneumonia[a, d]
Progressive multifocal leukoencephalopathy[a]
Toxoplasmosis of brain, onset at age > 1 month[a, b]
Wasting syndrome caused by HIV[c]

*Modified from 1993 CDC Revised Surveillance Definition for AIDS

[a]If indicator disease is diagnosed definitively (eg, biopsy, culture) and there is no other cause of immunodeficiency, laboratory documentation of HIV infection is not required.

[b]Presumptive diagnosis of indicator disease is accepted, if there is laboratory evidence of HIV infection (1987 addition).

[c]Requires laboratory evidence of HIV infection (1987 addition).

[d]Requires laboratory evidence of HIV infection (1993 addition; adults and adolescents).

The rate of progression varies. It may be rapid in some children, who become wheelchair bound within months; some will progress to quadriparesis. Cognitive decline becomes evident over time. The child may gain additional skills; however, the rate of acquisition of these new skills deviates not only from the norm but also from the child's previous rate of developmental progress. Poor brain growth is common.

In contrast, some children maintain independent ambulation for years, although their gait is spastic. Some children require orthotics for ambulation. Associated impairment of fine motor ability and dexterity is common. Cognitive deficits, although frequent, are not invariable. The degree of impairment ranges from low average or borderline intelligence to mild mental retardation. A subset of children will have a prolonged, stable course. Some, however, will ultimately go on to develop further neurologic involvement and progressive encephalopathy.

School-Aged Children

Loss of interest in school performance, cognitive decline, language-related problems, decreased vocalizations, decreased attention, psychomotor slowing, emotional lability and social withdrawal, and, more rarely, psychotic manifestations are reported. Hyperreflexia, clumsiness, and poor fine motor ability and dexterity are noted initially. Progressive long-tract signs, movement disorders, cerebellar signs, and myelopathy may develop in advanced stages of the disease. Cognitive decline occurs with advancing disease. At the end stage, the child is apathetic and abulic.

Epidemiology of HIV/AIDS-Associated CNS Disease and Progressive Encephalopathy

A 16 to 30 % incidence of HIV encephalopathy is reported. The frequency of HIV encephalopathy being the initial AIDS-defining illness is much higher in children (12–67%) than in adults (0.8–2.2%). In infants, encephalopathy may manifest prior to CD4+ T cell depletion and severe immunosuppression. In older children, HIV-1 CNS disease usually parallels progression and severity of immunodeficiency and systemic disease.

Neurodevelopmental Abnormalities

The prevalence of neurodevelopmental problems is high. About 50% of antiretroviral-naive symptomatic children in one study were reported to have abnormal neurodevelopmental findings, including abnormalities of motor function (23%), reflexes (21%), and behavior (13%). Nearly one-half the children in the youngest age groups had motor dysfunction. Cognitive deficiencies were present in approximately 21% of the cohort, again with the highest percentages in the youngest age groups: aged 3 to 12 months (33.7%); older than12 to 30 months (19%); and older than 30 months to 6 years (21%). "encephalopathy."

HIV-1–Associated Minor Motor and Cognitive Impairment

Minor motor impairment, with or without cognitive deficits, is a frequent finding in children, many of whom as infants had delays in motor and language development. As school-aged children, they are often mildly clumsy and have learning disabilities. Although composite IQ scores show average, low average, or borderline abilities, selective deficits in visual-spatial and organizational skills and cognitive flexibility are seen, suggesting that HIV-1 may compromise cognitive and motor development and result in a mild and stable encephalopathy.

Neuropsychiatric Problems

Mood, Affect, and Depression

Emotional lability, mood swings, agitation, new onset of extreme impulsiveness, and attentional problems are described. Flattened affect, lack of social responsiveness, withdrawal, and declining interest in the environment are also described. HIV-1–associated CNS disease can cause or contribute to be significantly associated with clinical or neuroimaging abnormalities and depressed CD4+ lymphocyte percentages, suggesting depressive disorders may be a clinical form of encephalopathy. "Organic" depression may be caused by primary HIV CNS infection (HIV-1-associated CNS disease), coexisting HIV-1/AIDS conditions, such as endocrinologic and metabolic disturbances.

The effects of chronic disease, frequent hospitalizations, illness and death of family members, changing caretakers, psychosocial stressors, and stigma attached to HIV disease may also affect mood and affect and lead to depression. A growing concern is the recently identified increased rate of mental health disorders and psychiatric hospitalizations of children and adolescents with perinatally-acquired HIV infection who have stable disease and are on HAART. The most common reasons for hospitalization were depression, anxiety and behavioral disorders.

Psychosis

Acute psychosis, confusion, agitation, delirium, mania, and catatonia have also been described in children with advanced disease. Changes in mental status may be due to HIV-1 CNS disease but also as a complication of nutritional deficiencies, CNS OIs (for example, cytomegalovirus [CMV] encephalitis), or toxic effects of antiretroviral and other therapies. For example abacavir, an ARV, can induce neuropsychiatric side effects in children that resolve rapidly when this medication is stopped.

Neuropathology of HIV-1/AIDS

Table 65-3 lists neuropathologic features. HIV-1 is localized primarily in blood-derived macrophages, intrinsic microglia (the resident mononuclear phagocytic system of the brain), and multinucleated giant cells (formed by the fusion of these cell types) found predominantly in the basal ganglia, subthalamic nucleus, substantia nigra, dentate nucleus, and white matter. These cells express both CD4+ and β-chemokine receptors (CCR5 and CXCR4), which permit HIV-1 entry, and it is these cells that support productive retroviral infection. More sensitive and specific viral detection techniques demonstrate HIV-1 in endothelial cells and glial cells (although glial cell infection is thought to be restricted [ie, nonproductive infection]).

TABLE 65-2. Pediatric HIV Classification: Clinical Categories*

Category N: Not Symptomatic
- Children who have no signs or symptoms considered to be the result of HIV infection or who only have **one** of the conditions listed in category A.

Category A: Mild Symptomatic
- Children with 2 of the following conditions but none of the conditions listed in categories B and C:
  - Lymphadenopathy (0.5 cm at more than two sites; bilateral = one site)
  - Hepatomegaly
  - Splenomegaly
  - Dermatitis
  - Parotitis
  - Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

Category B: Moderately Symptomatic
- Children who have symptomatic conditions other than those listed for categories A and C that are attributed to HIV infection. Conditions in clinical category B include but are not limited to:
  - Anemia (< 8 g/dL), neutropenia (< 1,000/mm), or thrombocytopenia (< 100,000/mm) persisting 30 days
  - Bacterial meningitis, pneumonia, or sepsis (single episode)
  - Candidiasis, oropharyngeal (ie, thrush) persisting for > 2 months
    Cardiomyopathy
  - Cytomegalovirus infection with onset before age 1 month
  - Diarrhea, recurrent or chronic
  - Hepatitis
  - Herpes simplex virus (HSV) stomatitis, recurrent (ie, > 2 episodes within 1 year)
  - HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month
  - Herpes zoster (ie, shingles) involving at least two distinct episodes or more than one dermatome
  - Leiomyosarcoma
  - Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
  - Nephropathy
  - Nocardiosis
  - Fever lasting > 1 month
  - Toxoplasmosis with onset before age 1 month
  - Varicella, disseminated (ie, complicated chickenpox)

Category C: Severely Symptomatic
- Children who have any condition listed in the 1987 surveillance case definition for AIDS, with the exception of the LIP (which is a category B condition; see Table 61-1).

*Modified from Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR Morb Mortal Wkly Rep 1994; 43 (RR-12);1–10.

TABLE 65-3. Neuropathologic Features and Findings

- Gross brain studies
  - Cerebral atrophy
    - Ventricular enlargement
    - Widening of sulci
    - Attenuation of deep cerebral white matter
- Microscopic studies
  - HIV-1 encephalitis
    - Foci of inflammatory cells, microglia, macrophages, multinucleated giant cells; one of the most impressive postmortem findings of CNS HIV-1 infection
    - More common in adults than in infants and young children
    - HIV-1 leukoencephalopathy
    - Diffuse staining pallor of myelin; diffuse damage to white matter
    - Myelin loss, reactive astrogliosis; multinucleated giant cells, macrophages
  - Calcific vasculopathy
    - Mineralization detected in walls of vessels in basal ganglia and white matter
    - Accompanying white matter changes and gliosis are common
    - Frequently seen with HIV encephalitis, BUT association not invariable
    - Many cases have basal ganglia calcification without inflammatory disease and little to no sign of acute infection
    - Calcific vasculopathy of the basal ganglia most characteristic and consistent neuropathologic finding in infants and children
- Spinal cord studies
  - Corticospinal tract pathology: striking myelin pallor restricted to the corticospinal tracts
    - "Axonopathy type"
    - "Myelinopathy type"
  - Myelitis
    - Vacuolar myelopathy: older children

Because direct neuronal HIV-1 infection and damage has not been identified, other neuropathophysiologic mechanisms are implied. Both virologic and neuroimmunologic processes are implicated, including toxicity of HIV proteins, macrophage factors, the role of cytokines produced by macrophages, microglia, and astrocytes, and blood-brain barrier changes. Neuropathogenetic mechanisms may involve factors related to (1) viral entry into the CNS, (2) the role of viral proteins and cellular products in neural tissue dysfunction or damage, and (3) the mechanisms of neuronal injury or death.

The emerging current consensus is that of a pathogenetic, cytokine-mediated cascade leading to neuronal dysfunction and to a neurodegenerative pathway. In adults, HIV-1/AIDS dementia develops in a mature and completely myelinated nervous system and a fully developed CNS immune system. In contrast, vertically transmitted HIV-1 infection occurs in an immature developing organism. Thus, the maturational stage (and vulnerability) of the nervous and immune systems when exposed to the effects of the virus (and a cytokine-mediated cascade) is of crucial importance.

Peripheral Nervous System Involvement

In general peripheral nervous system (PN) involvement appears to be a less common complication in children than in adults (perhaps because fewer children have underlying peripheral neuropathies which are exacerbated when HIV/ AIDS–related PN is superimposed). Reported complications include distal sensory or sensorimotor axonal neuropathy, demyelinating neuropathy, lumbosacral polyneuropathy, mononeuritis multiplex, inflammatory polyneuropathy, median nerve compression at the carpal tunnel, and neuropathy related to antiretroviral

therapy. Distal sensory neuropathy (described as pain and burning in the feet and legs) and CMV polyneuropathy are probably more common than previously thought and occur with increased frequency in children with advanced HIV-1 disease and CNS disease.

Secondary CNS Complications

CNS Infections

Bacterial meningitis caused by common childhood pathogens and OIs were described in immunosuppressed children (prior to HAART therapy). CMV encephalitis and *Candida albican*s meningitis and microabscesses are the most common OIs. Congenital CNS infections (toxoplasmosis, CMV, and syphilis) are reported, but infrequently. In adults, most CNS OIs are due to reactivation of previously acquired infection (eg, toxoplasmosis, CMV, herpes simplex virus [HSV], varicella zoster virus [VZV], and Jakob-Creutzfeldt virus infection). Therefore, reactivation of latent pathogens would not be expected to occur in infants and very young children but could be an anticipated complication in older immunosuppressed children with advanced disease. Now in the HAART era the incidence of CNS infections has dropped sharply. However in areas where HAART therapy is not available and where malaria and tuberculosis are endemic, cerebral malaria and *Mycobacterium tuberculosis* meningitis have become serious HIV related CNS complications.

Neoplasms

Primary CNS lymphoma (PCNSL) and systemic lymphoma metastatic to the CNS are the most common CNS neoplasms (PCNSL is the most frequent). Presenting signs include the new onset of focal neurologic deficits, seizures, or a change in mental status. At times, neurologic deterioration may be rapidly progressive and fulminant. Typically, PCNSL is an aggressive B-cell tumor considered to be part of the spectrum of B-cell proliferative disorders associated with pediatric HIV-1/AIDS and is thought to be related to Epstein-Barr virus.

PCNSL, the most frequent cause of mass lesions in children, may occur as a single mass lesion or as multicentric lesions. Computed tomography characteristics are variable: hyperdense or isodense mass lesions with variable contrast enhancement, diffusely infiltrating contrast enhancing lesions, or periventricular contrasting lesions. The most frequent locations are the basal ganglia, corpus callosum, and periventricular white matter. Definitive diagnosis is made by biopsy, although magnetic resonance spectroscopy may be able to differentiate lymphoma from other lesions. Reduction in tumor size can be achieved with radiation therapy; however, long-term survival rates are grim, due to both tumor recurrence as well as advancing HIV-1 disease. Patients most often succumb to other AIDS-related illnesses, OIs, or both.

Cerebrovascular Disorders

Intracerebral hemorrhage usually occurs in the setting of immune-mediated thrombocytopenia. Hemorrhage into tumor and subarachnoid hemorrhage associated with aneurysmal arteriopathy of major cerebral arteries are also reported. Clinical presentation includes the new onset of headache, mental status changes, and focal neurologic deficits (most commonly hemiparesis), with or without seizures. Presentation is variable, reflecting the severity and location of the hemorrhage. Strokes may be catastrophic and fatal or clinically silent.

Infarctions are associated with pathologic changes of cerebral blood vessels, meningeal infections, cardiomyopathy, or coagulopathies. Cerebral vascular ectasia and aneurysmal arteriopathy of major cerebral arteries and thrombosis of these arteries or of small cortical vessels are reported. Fusiform, aneurysmal dilation of the branch vessels of the circle of Willis (diffuse and fusiform or focal and saccular) is increasingly recognized. Immunohistochemical staining has demonstrated gp41-positive cells in arterial walls, also positive for a macrophage marker of leukocyte-common antigen but not with an endothelial marker, suggesting that HIV-1 may be directly involved in vascular pathology associated with pediatric HIV-1/AIDS.

The mechanism by which HIV-1 causes CNS arterial damage is unclear. Possibilities include direct HIV endothelial invasion and exposure to toxic cytokines. Others have hypothesized an association with VZV. A fibrosing inflammatory vasculopathy is also described and thought to be related to primary HIV-1 CNS infection. Pathologic examination shows sclerotic vessels with obliterated or markedly stenosed lumens. A subacute necrotizing encephalopathy with cystic encephalomalacia appears to be associated with dilated cardiomyopathy and may be related to an acquired mitochondrial cytopathy or hypoxic-ischemic damage. Multiple ischemic infarcts may also result from leptomeningitis associated with infectious etiologies, such as VZV, *Mycobacterium tuberculosis*, and *Treponema pallidum*.

Changing Neuroepidemiology

During the past decade, there has been a significant decrease in the incidence and prevalence of pediatric HIV-1/AIDS CNS disease and CNS complications in the United States and Europe. The decline is attributed to an overall reduced mother-to-infant transmission rate, resulting in a markedly reduced incidence rate of newly born HIV-1 infected infants; early identification of the infected child and more efficacious antiretroviral treatment regimens (HAART) on the basis of age, immune

status (CD4 cell count), and HIV RNA plasma levels has resulted in disease stabilization, immune reconstitution, and delay of progressive disease. In addition, prevalence of neurologic disease has decreased, because most of the children who had HIV CNS disease died early in the epidemic, prior to the availability of HAART therapy.

Diagnosis of HIV-1/AIDS Neurologic Disorders

The diagnosis of an HIV-1 neurologic disorder requires a careful medical and developmental history, HIV-1 systemic disease history, current immunologic and virologic status, medication history, neurologic examination, neuropsychological assessment, and neuroimaging studies.

The diagnosis of progressive encephalopathy is straightforward if the patient has been monitored prospectively. Serial assessments reveal progressive neurologic deficits (other causes excluded). The infant may stop vocalizing, lose head control, or develop axial hypotonia and upper motor neuron signs. The toddler or older child may have a change in gait, become hyperreflexic, refuse to walk, and, over time, develop progressive CST signs. The diagnosis is also straightforward if, on initial examination, the child is found to have motor impairment and the history reveals either the new onset or progression of these deficits.

Diagnostic difficulties arise when the youngster who has not been monitored prospectively is found to have neurologic deficits. Because the frequency of neurologic and developmental impairments in this population is high, it is often impossible for the clinician to ascribe these findings to HIV-1 CNS disease. A careful history is paramount:

- If no other risk factors are identified, the diagnosis is likely.
- Cerebrospinal fluid studies may be helpful, especially to rule out other infectious agents or to determine HIV-1 RNA levels (Table 65-4).
- Neuroimaging studies are crucial (Table 65-5). If calcification of basal ganglia is present (other causes excluded), the child's neurologic deficits probably are related to HIV-1 CNS disease. If cerebral atrophy is present in the absence of documented perinatal complications, corticosteroid use, or other known causes of atrophy, the diagnosis is also extremely likely.
- Head circumference measurements are invaluable. A review of medical records will usually show at least one or two past measurements, allowing serial measurements to be plotted. If acquired microcephaly is present, the diagnosis is likely.
- Neuroimaging evidence of atrophy accompanied by acquired microcephaly clearly strengthens the diagnosis. Follow-up neurologic, psychometric, and neuroimaging studies are required.

TABLE 65-4. Cerebrospinal Fluid Studies

± ⇑	white blood cells
± ⇑	protein content
±	HIV-1 antigen*
	Intrathecal production of anti-HIV-1 antibodies*
	Oligoclonal bands*
	Cytokines*
⇑	HIV-1 RNA levels**

*Prognostic significance uncertain (suggests HIV-1 CNS invasion has occurred in the early stage of infection).

**High HIV-1 RNA cerebrospinal fluid levels may correlate with cognitive impairment.

As the name of the disease implies, HIV-1/AIDS ultimately culminates in the development of profound immunosuppression. The patient becomes susceptible to various infections, neoplasms, and cerebrovascular complications. Secondary CNS complications should be considered in the differential diagnosis of the HIV-1-infected child who presents with the new onset of mental status changes, headache, seizures, or focal neurologic deficits.

CDC Pediatric HIV-1 Classification

The current Centers for Disease Control and Prevention (CDC) pediatric AIDS classification was revised in 1994 (Table 65-7), before the availability of uniform measurements of HIV-1 RNA plasma levels. It is based on three parameters: (1) infection status, (2) immunologic status, and (3) clinical status. This classification system reflects the child's disease stage and establishes mutually exclusive categories. Clinical conditions are specified (Tables 65-1 and 65-2), and pediatric age-related definitions of immune suppression are delineated.

HIV-1 RNA Plasma Levels

Assays that quantitate plasma HIV RNA copy number in infants and children are now considered a useful guide to initiating, monitoring, and changing therapy, especially when used in conjunction with a second marker, such as CD4+ T-lymphocyte count or percentage.

HIV-1 RNA levels in infants and young children differ from those of infected adults. Infants have a prolonged period of high HIV RNA copy numbers. This may be due to the lower efficiency of an immature but developing immune system in containing viral replication or, possibly, a greater number of HIV-susceptible cells, or both. RNA copy number slowly declines (even without therapy) during the first several years after birth, with the most rapid decline occurring during the first year of life. A slower decline continues until about 4 to 5 years of age. (Very high HIV RNA levels [> 299,000 copies/mL] in infants younger than 12 months of age appear to correlate with rapid disease progression and death.)

TABLE 65-5. Neuroimaging Features and Findings

Computed Tomography (CT)
- Cerebral Atrophy
  - Present in majority of patients
  - Serial studies often show progressive atrophy
- Basal Ganglia Calcification
  - More frequent in younger children with HIV-1 CNS disease than in older children
  - Serial studies may show progressive "calcification"
  - Frontal white matter calcification may be present
- White Matter
  - White matter changes [hypodensity-rarefaction]
  - Serial studies often show progressive changes

Magnetic resonance imaging
- Cerebral Atrophy
  - Present in majority of patients
  - Serial studies often show progressive atrophy
- Basal Ganglia
  - Abnormal high signal [T_2-weighted images] may be imaged at a time when CT is abnormal
  - May show abnormal low signal [T_2-weighted images] at time when CT shows calcification
- White Matter
  - Abnormal high signal [T_2-weighted images]

MR Spectroscopy

Noninvasive technique to assess the metabolic integrity and density of neurons and glial cells by examining metabolite concentrations and ratios of metabolites in different brain regions. Commonly studied brain metabolites include: *N*-acetylaspartate (NAA), a marker of neuron density and integrity; soluble choline compounds (CHO), an assessment of cell membrane turnover, gliosis, and myelination; myo-inositol (mI), a glial cell marker; and total creatine (CR), molecules involved in energy metabolism.

Decreased NAA; Increased cho and myo-inositol in the basal ganglia and centrum semi-ovale white matter in children with progressive encephalopathy

There appears to be a correlation between cerebral atrophy and severity of "encephalopathy," cognitive dysfunction, and behavioral changes.

TABLE 65-6. Antiretroviral Agents

Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTI)
- Zidovudine (ZVD) (AZT; Retrovir)
- Didanosine (ddI; Videx)
- Stavudine (d4T; Zerit)
- Lamivudine (3TC; Epivir)
- Zalcitabine (ddC; Hivid)
- Abacavir (ABC; Ziagen; Abacavir)
- Emtricitabine (FTC; Emtriva)

Non-nucleoside Reverse Transcriptase Inhibitors (NRTI)
- Nevirapine (NVP; Viramune)
- Delavirdine (DLV; Rescriptor)
- Efavirenz (EFV; Sustiva)

Protease Inhibitors (PI)
- Saquinavir (SQV; Zavirase, Fortovase, Invirase)
- Indinavir (IDV; Crixivan)
- Ritonavir (RTV; Norvir)
- Nelfinavir (NFV; Viracept)
- Amprenavir (VIX478; Agenerase)
- Lopinavir (Kaletra)

Fusion Inhibitors
- Enfuvirtide (Fuzeon,T-20)

Management and Therapy of HIV-1/AIDS

The mainstays of HIV-1 management include antiretroviral (ARV) therapy targeted to the retrovirus (Table 65-6), prophylaxis and treatment of OIs, and management of HIV/AIDS-related conditions. As of October 2006, 22 antiretroviral drugs were approved for use in HIV-infected adults and adolescents. Of these, 13 have an approved pediatric treatment indication and 11 are available in pediatric formulation. ARV agents include fusion inhibitors which prevent viral entry; nucleoside/nucleotide reverse transcriptase inhibitors; non-nucleoside reverse transcriptase inhibitors, which act at the early stage of replication, prior to viral integration into the host genome and protease inhibitors which effect later stage of replication, after viral integration. New ARV agents are under investigation and include CCR5 inhibitors, maturation inhibitors and integrase inhibitors.

Currently, highly active combination regimens including at least 3 drugs are recommended. These regimens have shown enhanced survival, reduction of IOs, and other HIV complications, impaired growth and neurodevelopmental function.

Children with HIV infection are now surviving into adolescence and young adulthood. HIV infection is now a chronic disease. The management and therapy of HIV infection.

Treatment of HIV-1/AIDS–Associated Neurologic Disorders

HIV-1–Associated Progressive Encephalopathy

Treatment is recommended with at least one antiretroviral agent with substantial CNS penetration having CSF/plasma ratios > 0.2 (eg, ZDV or NVD). HAART has been shown to reverse or arrest progressive encephalopathy, in some cases, when treated in the early stage.

Neurobehavioral Complications

- Psychotherapy
  - Short-term psychotherapy to help children cope with issues, such as death in the family
  - A children's group (longer-term therapy) to help children deal with issues of chronic illness, death, and social stigmas associated with HIV infection
  - Psychotherapy should be included in treatment of depression and psychosis

TABLE 65-7. CDC Pediatric HIV Classification (1994)

Immunologic	Clinical			
	Signs/Symptoms			
	N: No	A: Mild	B: Moderate	C: Severe
No evidence of suppression	N1	A1	B1	C1
Evidence of moderate suppression	N2	A2	B2	C2
Severe suppression	N3	A3	B3	C3

CDC = Centers for Disease Control and Prevention.

WHO Clinical Staging of HIV/AIDS for Children with Confirmed HIV Infection

The clinical staging and case definition of HIV for resource-constrained settings were developed by the WHO in 1990 and revised in 2006. Staging is based on clinical findings that guide the diagnosis, evaluation, and management of HIV/AIDS, and does not require a CD4 cell count. This staging system is used in many countries to determine eligibility for antiretroviral therapy. Clinical stages are categorized as 1 through 4, progressing from primary HIV infection to advanced HIV/AIDS. These stages are defined by specific clinical conditions or symptoms. For the purpose of the WHO staging system, adolescents and adults are defined as individuals aged ≥15 years.

Clinical Stage 1

Asymptomatic
Persistent generalized lymphadenopathy

Clinical Stage 2

Unexplained persistent hepatosplenomegaly
Papular pruitic eruptions
Extensive wart virus infection
Extensive molluscum contagiosum
Fungal nail infections
Recurrent oral ulcerations
Unexplained persistent parotid enlargement
Lineal gingival erythema
Herpes zoster
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis or tonsillitis)

Clinical Stage 3

Unexplained[a] moderate malnutrition not adequately responding to standard therapy
Unexplained persistent diarrhea (14 days or more)
Unexplained persistent fever (above 37.5° C intermittent or constant, for longer than 1 month)
Persistent oral candidiasis (after first 6-8 weeks of life)
Oral hairy leukoplakia
Acute necrotizing ulcerative gingivitis or periodontitis
Lymph node tuberculosis
Pulmonary tuberculosis
Severe recurrent bacterial pneumonia
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including bronchiectasis
Unexplained anemia ($<0.5x10^9$ per liter) and/or chronic thrombocytopenia ($<50x10^9$ per liter)

Clinical Stage 4

Unexplained severe wasting, stunting or severe malnutrition nor responding to standard therapy
Pneumocystis pneumonia
Recurrent severe bacterial infection (such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia)
Extrapulmonary tuberculosis
Kaposi sarcoma
Espophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Central nervous system toxoplasmosis (after one month of life)
HIV encephalopathy
Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month
Extrapulmonary cryptococcosis (including meningitis)
Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
Chronic isosporiasis
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated non-tuberculous mycobacterial infection
Cerebral or B-cell non-Hodgkin lymphoma
Progressive multifocal leukoencephalopathy
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

- Neuroleptics
  - Treatment for acute psychotic episodes
  - Children with HIV-1 CNS disease may require lower-than-normal doses
- Antidepressants
  - Treatment of depression
  - The clinician needs to be aware of potential drug interactions
- Psychostimulants
  - Methylphenidate may benefit the child with attention-deficit disorder or ADHD
  - Behavioral modification techniques are recommended and, when possible, should be instituted prior to and in conjunction with a medication trial
  - Appetite suppression with stimulants can be an undesirable side effect in HIV-1-infected children and should be monitored

Pain

- Painful medical procedures are frequent
- Children may also have pain related to HIV-1–related conditions
- A combination of pharmacologic and nonpharmacologic therapies is recommended, as is an aggressive approach to pain management, including management of painful procedures
- Analgesic therapy should be initiated after a thorough clinical assessment, which includes assessment of pain severity and identification and treatment of the underlying cause of pain
- The WHO's analgesic ladder provides a useful guideline for treatment strategies

Habilitation and Rehabilitation

Habilitation and rehabilitation programs, including (when indicated) therapeutic nursery schools and special

education classes and physical and occupational programs, should be an integral part of the clinical regimen and should be individualized to the needs of the child.

Suggested Readings

Centers for Disease Control and Prevention.1998 USPHS/IDSA Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection Morb Mortal Wkly Rep MMWR 47(RR-4); 1-31 (This site is being maintained for historical purposes, but has had no new entriess since October 1998. The most recent updates can be found in the above reference.

http://www.aidsinfo.nih.gov/guidelines

"**Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**" Use of antiretroviral agents in pediatric patients is evolving rapidly. These guidelines from the U.S. Department of Health and Human Services (DHSSC) site are updated regularly to provide the most current information. The "Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection" includes: diagnosis of HIV infection in infants; laboratory monitoring of pediatric HIV infection; treatment recommendations; monitoring of children on antriretroviral therapy; specific issues in antiretroviral therapy for HIV-infected adolescents; adherence to antiretroviral therapy for HIV-infected children and adolescents; management of the treatment-experienced child; antiretroviral drug resistance testing; managing complications of HIV infection and new supplements on nutrition and pain management.

Supplement I: Pediatric Antiretroviral Drug Information–October 26, 2006

Supplement II: "Managing Complications of HIV Infection in HIV-Infected Children on Antiretroviral Therapy–October 26, 2006

Supplement III: Adverse Drug Effects–October 26, 2006

Joint United Nations Program on HIV/AIDS World Health Organization (UNAIDS/WHO) Report of the Global HIV/AIDS Epidemic. Geneva, Switzerland, December 2006. http://www. unaids.org/epidemic_update/report.htm HIV/AIDS in infants, children, and adolescents. Pediatr Clin North Am 2000;February:47. Mann JM, Tarantola DJM, editors. The Global AIDS Policy Coalition. AIDS in the World II. Global dimensions, social roots, and responses. New York: Oxford University Press; l996.

Practitioner and Patient Resources

Women, Children, and HIV
http://www.womenchildrenhiv.org
This site contains a library of practically applicable materials on mother and child HIV infection including preventing mother-to child HIV transmission, infant feeding, clinical care of women and children living with HIV infection, and the support of orphans. The goal of this site is to contribute to an improvement in the scale and quality of international HIV/AIDS prevention, care, and treatment programs for women and children by increasing access to authoritative HIV/AIDS information.

Library of Clinical HIV images
http://womenchildrenhiv.org/wchiv?page=im-00-00).
The library is a comprehensive collection of over 250 images related to the clinical symptoms of HIV infection in adults and children. Created in partnership with the VA National HIV/AIDS Program (www.hiv.va.gov), the library aims to facilitate training in HIV care worldwide. Images in the library can be downloaded, printed, archived, and distributed, free of charge, so long as appropriate credit is given to the original image contributors.

http://www.hivinsite.ucsf.edu
This HIV In Site Knowledge Base chapter reviews the association between HIV and malaria, response to treatment and drug interactions, public health implications of coinfection, and implications for clinical and public health management

The Orphan Project: Families and Children in the HIV Epidemic
http://www.aidsinfonyc.org/orphan
The Orphan Project was established in 1991 by its executive director, Carol Levine, to explore policy options to meet the needs of the entire spectrum of affected children—from dying infants to healthy adolescents. In carrying out its work, The Orphan Project convenes meetings, publishes articles and reports, and develops collaborative work with direct service providers and family members.

Elizabeth Glaser Pediatric AIDS Foundation
1140 Connecticut Avenue NW, Suite 200
Washington, DC 20036
Phone: (202) 296-9165
Fax: (202) 296-9185
http://www.pedaids.org/
The Foundation creates a future of hope for children and families worldwide by eradicating pediatric AIDS, providing care and treatment to people with HIV/AIDS, and accelerating the discovery of new treatments for other serious and life-threatening pediatric illnesses.

CHAPTER 66

BELL'S PALSY

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This chapter reviews current diagnostic and management strategies for children presenting with facial palsy and describes the associated clinical and anatomic pathology.

Bell's palsy is an acute idiopathic paralysis of the muscles of facial expression. It accounts for 60% of cases of facial palsy in children. In most cases, the etiology is unknown, although several viruses have been implicated. The annual incidence of Bell's palsy in the first decade of life is about 3 per 100,000 and increases to 10 per 100,000 in the second decade, without predilection for a particular gender or race. Eight percent of affected patients have a positive family history of Bell's palsy. Although most children recover partially or completely, they can suffer substantial functional and psychological disability. This has prompted extensive research to determine the etiology and treatment of this disorder as well as rehabilitative measures to minimize residual motor deficits.

Anatomy

The facial nerve is primarily a motor nerve that controls voluntary movement of the muscles of facial expression. It also includes a smaller sensory component. The sensory fibers mediate taste sensation from the anterior two thirds of the tongue. Other fibers relay sensation from a portion of the external auditory canal. Autonomic fibers control secretions of the mandibular, sublingual, and lacrimal glands.

The central nervous system pathways involved in facial movement begin in the cortex of both hemispheres and descend along the pyramidal fibers to form synapses in the brainstem facial nucleus. The facial nerve emerges from the nucleus at the base of the pons in the brainstem. It then passes through the internal auditory meatus into the facial canal of the petrous temporal bone along with the acoustic nerve (Figure 66-1). As the facial nerve passes through the petrous temporal bone, it turns posteriorly to give off a branch, the greater petrosal nerve, which controls lacrimal gland function. It then travels posteriorly and laterally around the vestibule of the inner ear and sends a branch to the stapedius muscle mediating the stapedial reflex. Damage to the facial nerve proximal to this branch causes hyperacusis (painful hypersensitivity to loud noise). The facial nerve has branches that supply the chorda tympani,

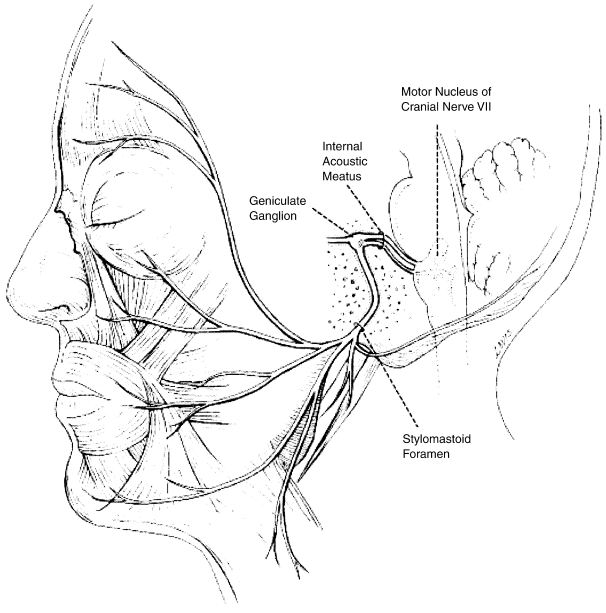

FIGURE 66-1. Anatomic course of the facial nerve. Weakness in Bell's palsy results from edema of the nerve and associated compression, ischemia, and degeneration as it courses through the temporal bone.

which controls secretions from the submandibular and sublingual glands and taste sensation to the anterior two thirds of the tongue. The facial nerve exits the skull through the stylomastoid foramen and then courses through the parotid gland, where it terminates in the temporal, zygomatic, buccal, mandibular, and cervical branches to supply the muscles of facial expression and eyelid closure.

The forehead receives innervation from both cerebral hemispheres. A unilateral lesion in the central nervous system above the facial nerve nucleus involving the cell bodies or fibers that connect with the facial nucleus causes paralysis of the lower half of the face only. In contrast, a lesion of the brainstem facial nucleus or nerve itself will cause paralysis of the lower half of the face and forehead.

Pathogenesis

Unilateral facial weakness in Bell's palsy is thought to result from edema within the facial canal and associated compression, ischemia, and degeneration of the facial nerve.

Viruses have long been suspected as etiologic agents. Specifically, the herpes group of viruses has been heavily implicated. In Ramsay Hunt syndrome, there is facial palsy and loss of taste over the anterior two-thirds of the tongue; varicella is readily isolated from the vesicles on the tympanum, ear, anterior pillar of the fauces, and the zone between the ear and the mastoid. Acyclovir is effective treatment. Whether varicella is associated with facial nerve palsy in the absence of vesicular eruption is controversial. The appearance of vesicles has been reported to occur several days after the initial signs of facial paresis in a small percentage of patients. Herpes simplex virus type 1 (HSV-1) has been linked to Bell's palsy; antigens have been detected in the facial nerve, ganglia, and brainstem nucleus. Through polymerase chain reaction, HSV-1 deoxyribonucleic acid (DNA) has been detected in the facial nerve endoneurial fluid and in the posterior auricular muscle. Other viruses, including Epstein-Barr, mumps, and rubella, also have been linked to Bell's palsy.

Geographic differences in the etiology of facial paralysis in children have been described. A study of Bell's palsy among patients living in the mid-Atlantic states in the United States showed Lyme disease to be the most common cause (50% of cases). A history of tick bite, erythema chronicum migrans, and radiculoneuropathy may be elicited. Acute idiopathic polyneuritis may present with a peripheral facial palsy, but additional abnormalities, such as weakness and hyporeflexia, are typically present. *Mycoplasma pneumoniae* has also been implicated as a causative agent of Bell's palsy. Central nervous system demyelinating diseases, such as multiple sclerosis, can present with facial paresis, though this is rare. More typically, a lesion to the facial nerve associated with multiple sclerosis is accompanied by other cranial nerve or central nervous system abnormalities.

Neoplasm is a rare cause of isolated facial palsy in children. Primary or metastatic tumors of the parotid gland, cholesteatoma, meningioma, acoustic neuroma, facial neuroma, and primary or metastatic sarcoma are examples of tumors causing facial paralysis in adults. Neuropathies of the facial nerve are often seen in central nervous system leukemia as well. Although extremely rare, there has been documentation of facial palsy as the initial presenting symptom of childhood leukemia. Congenital facial weakness may be traumatic or developmental. Developmental abnormality of brainstem structures may result in Möbius' syndrome, characterized by bilateral facial paresis and weakness of horizontal eye movement due to involvement of the abducens nuclei. Familial Bell's palsy, although uncommon, may present during childhood and carries a low recurrence risk. Melkersson-Rosenthal syndrome presents as recurrent facial paresis associated with lip swelling and furrowing of the tongue. With recurrent episodes, return of facial nerve function may be incomplete. The etiology of this disorder is currently unknown.

Clinical Presentation and Diagnosis

Typically, Bell's palsy is characterized by a sudden onset of unilateral facial paresis that progresses over 1 to 5 days and may result in complete facial paralysis. It frequently occurs following an upper respiratory tract infection. Postauricular pain may precede the symptoms of weakness by 24 to 48 hours. Clinical symptoms associated with the facial paresis vary according to the location of nerve inflammation and entrapment. A lesion distal to the chorda tympani produces weakness or heaviness only.

Sensory loss should not be elicited by physical examination, even though the patient may complain of numbness. Entrapment between the chorda tympani and the geniculate ganglion produces additional loss of taste on the anterior two-thirds of the tongue. A lesion involving the nerve to the stapedius produces hyperacusis. Damage to the geniculate ganglion or the motor nerve proximal to the ganglion causes additional loss of lacrimation. A slight impairment in trigeminal or vestibular function may accompany a Bell's palsy. Alternatively, concomitant palsy of the facial nerve and of the abducens nerve, which controls function of horizontal eye movement or hearing loss with or without vertigo, is suggestive of a brainstem process. Facial palsy associated with loss of sensation to the ipsilateral face and ipsilateral hearing loss implicates a lesion at the petrous apex of the temporal bone. Therefore, the presence of additional cranial nerve abnormalities warrants further investigation with magnetic resonance

imaging (MRI) or high-resolution computed tomography (HRCT) and neurologic consultation. Paralysis lasting longer than 4 months should be evaluated radiographically to rule out a neoplastic process.

As facial nerve function recovers, evidence of aberrant regeneration may be apparent. For example, the patient may demonstrate "crocodile tears," described as excessive lacrimation on eating or smelling food. Synkinesis, an unintentional movement accompanying a voluntary movement, also may be demonstrated. For example, smiling may be associated with eyelid closure.

Diagnostic Studies

Physical examination demonstrates unilateral weakness or paralysis of the entire face. The patient should be asked to demonstrate each component of facial movement, such as to raise eyebrows, close eyes, and show teeth. Normal or near normal movement of the forehead suggests a central nervous system process incompatible with Bell's palsy. Paresis of only one peripheral branch suggests tumor or trauma as etiology. Evidence of synkinesis or crocodile tears should be noted. Complete facial paralysis is usually accompanied by loss of the stapedial reflex and associated hyperacusis. Lacrimation is infrequently diminished. Significant improvement in nerve function within 3 weeks following the onset of Bell's palsy is a good prognostic sign for eventual full recovery.

Examination should include the external ear canal and tympanic membrane. The presence of vesicles suggests the diagnosis of Ramsay Hunt syndrome. Subjective unilateral hearing loss must be evaluated by otolaryngology. In the absence of otitis media, a retrocochlear lesion should be considered. Palpation of the parotid gland is necessary to evaluate for parotid tumor.

In the presence of complete facial paralysis, nerve function can be further assessed with electroneurography or electromyography. Electroneurography entails electrical stimulation of the facial nerve and recording of the surface muscle compound action potential. This is typically performed at 3 days and 3 weeks after the onset of weakness. Percentage of nerve fiber degeneration is calculated on the basis of compound muscle potentials on the normal and affected sides. Less than 90% nerve fiber degeneration at 3 weeks is associated with a good prognosis for recovery. Degeneration between 90 and 95% is associated with a 50% recovery. Greater than 95% degeneration has a poor prognosis for recovery. Electroneurography is nondiagnostic beyond 3 weeks from onset of facial weakness. Electromyography can be performed at this time. Lack of muscle response to attempts at voluntary contraction and the presence of fibrillation potentials beyond 3 weeks from onset of palsy carry a poor prognosis for recovery. Transcranial magnetic stimulation (TMS) offers a noninvasive technique to assess the intracranial portion of the facial nerve and localize lesions. Strength of motor responses has also been correlated with recovery time in adult studies.

Radiologic studies should be reserved for atypical cases of facial weakness, such as those presenting with a subacute and slowly progressive paresis, persistence of paralysis beyond 4 months, prominent vestibular symptoms, hearing loss, tinnitus, otorrhea, or involvement of multiple cranial nerves. MRI with gadolinium is preferred for evaluating soft tissue and differentiating between neoplastic and inflammatory processes. Studies done on adults suggest that the use of MRI has potential as a valuable prognostic indicator at an early stage in acute facial paresis before electroneurography is useful. Enhancement of the facial nerve detected by MRI implies a prolonged recovery, though it is not clear how MRI studies might aid in the prognosis of children with Bell's palsy. HRCT is superior for evaluation of processes involving bony structures.

Treatment

Facial palsy in children has an excellent recovery rate, approaching 100%, regardless of treatment. Eye care in patients with reduced blink reflex is critical to prevent drying of the cornea and associated abrasions or ulcerations. The use of artificial tears and skin tape during the day and ocular patches with ophthalmic ointment at night is mandatory. However, massage of weakened muscles, heat, exercises, sympathetic blockade, and electrical stimulation are of no benefit.

The use of steroids is controversial. Inamura and colleagues (1994) showed no difference in the time to recovery or completeness of recovery in children treated with or without steroids. In another study, children between the ages of 24 and 74 months were randomized into two groups within 3 days of onset of facial paresis. One group was treated conservatively with eye protection only; the other group received 1 mg/kg oral Solu-Medrol® daily for 10 days in addition to the conservative treatment. Recovery was evaluated at several intervals during the following year. No statistically significant difference was found between the two groups, either in the time to recovery or in completeness of recovery. All children recovered completely by 12 months.

A systematic review completed in 2004 concluded that treatment of pediatric Bell's palsy with steroids is not recommended. Based on the findings reporting no positive evidence from the effects of corticosteroids in Bell's palsy and the benign natural history of the disease in the pediatric population a large multicenter randomized control trial is needed to prove the benefit from the use of steroid treatment.

The efficacy of acyclovir in the treatment of childhood Bell's palsy has not been investigated. Adult patients treated with prednisolone and acyclovir had a statistically improved recovery rate, compared with those treated with prednisone alone. Several recent publications suggest that early diagnosis and treatment with steroids and antiviral medication is crucial to its efficacy. The dose of acyclovir used in that study was 400 mg five times daily for 10 days 40 mg/kg/d). Until a randomized study in children is performed, we recommend treatment with oral Solu-Medrol® (1 mg/kg/d) and acyclovir (40 mg/kg/d) if the Bell's palsy has been present for less than 3 days.

Surgical decompression in cases of idiopathic Bell's palsy has failed to demonstrate improved recovery, compared with medical management. Surgical management should be limited to cases of facial weakness caused by structural lesions or acute trauma with nerve impingement.

Rehabilitation

A minority of children with facial nerve paralysis do not recover completely. Various methods of surgical rehabilitation have been tried, with some success. Upper eyelid gold-weighted implants are widely used as treatment for residual weakness of eye closure. This treatment provides corneal protection and is easily reversible. A lower-lid tightening procedure may be necessary in individuals with residual orbicularis paralysis.

Facial nerve grafting is sometimes used to restore facial expression. Facial–hypoglossal nerve anastomosis has the least donor site morbidity and the most reliable reinnervation patterns. Recovery can take up to 12 months. After 2 years of facial paralysis, extensive muscle and neural degeneration precludes successful nerve grafting and reinnervation. An alternative for these patients is transfer of the temporalis muscle. This procedure provides suspension of the lower face and corner of the mouth. Temporalis muscle transfer should not be performed until the child has achieved full growth.

Summary

The etiology of Bell's palsy remains controversial but may be related to viral infection. The diagnosis is one of exclusion and is most frequently characterized by unilateral paresis of the muscles of facial expression. Associated neurologic abnormalities should raise concerns about central nervous system disease. Patients with facial palsy should be provided with moisturizing eye drops, and the eye should be lubricated and patched at night. By extrapolating results from studies in adults, we recommend that children with new-onset Bell's palsy be treated with oral Solu-Medrol® and acyclovir for 10 days. Complete recovery is expected within 6 months of onset. Surgical intervention is rarely required in the acute setting or in follow-up.

Suggested Readings

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Practitioner and Patient Resources

Bell's Palsy Research Foundation
9121 E. Tanque Verde, Suite 105-286
Tucson, AZ 85749
Phone: (877) 412-5335
E-mail: BellsPalsy@aol.com
http://www.bellspalsyresearch.com
An organization providing online information and support to those diagnosed with facial paralysis.

National Institute of Neurological Disorders and Stroke (NINDS)
NIH Neurological Institute
P.O. Box 5801
Bethesda, MD 20824
Phone: (800) 352-9424
http://www.ninds.nih.gov/health_and_medical/disorders/bells_doc.htm
An information fact sheet on Bell's palsy compiled by the NINDS.

Bell's Palsy Information Site
http://www.bellspalsy.ws
The Bell's Palsy Information Site is a comprehensive, up-to-date source of facial paralysis information with online discussion and support forums. Although Bell's palsy is the primary focus, it includes information that applies to facial palsy regardless of what precipitated the condition.

CHAPTER 67

MANAGEMENT OF DIZZINESS IN CHILDREN

LYDIA EVIATAR, MD

Dizziness is a fairly common complaint in children, who often use the term indiscriminately to describe vertigo, lightheadedness, balance difficulties, anxiety, or even headaches. As it is a nonspecific complaint, it may be caused by a variety of systemic disorders or visual disturbances. The more specific complaint of true vertigo, best described as a spinning sensation (either of self or of the environment), is more likely the result of a true vestibular dysfunction.

Obtaining a detailed and accurate history of the patients' symptoms is essential. The circumstances associated with the occurrence of vertigo and the duration, frequency, and presence of related problems such as dysequilibrium, loss of postural control, confusion, nausea, or vomiting need to be assessed to reach an accurate diagnosis. Precipitating factors may be head trauma, infection, exposure to ototoxic drugs, or abrupt changes in position. In young children, congenital anomalies of the inner ear, such as a Mondini's malformation or large vestibular aqueduct, may be predisposing factors. A family history of progressive hearing loss suggests a genetically transmitted disorder that may be associated with vestibular dysfunction. Systemic illnesses such as diabetes, endocrine disorders, or severe anemia should be considered. Progressive degenerative neurologic disorders, such as Friedreich's ataxia, Huntington's disease, multiple sclerosis, or Refsum's disease, Ca channelopathies, and mithochondrial disorders are associated with vestibular neuropathy and may present with dizziness. Arnold-Chiari malformation and vertebrobasilar insufficiency with or without pontomedullary or cerebellar infarcts are also associated with dizziness or vertigo.

Neurovestibular Examination

The neurovestibular examination (Table 67-1) should test the integrity of the equilibrium system. Maintenance of equilibrium depends on appropriate information from the visual, proprioceptive, and vestibular systems regarding the position of the body in space and the normal function of the pyramidal and extrapyramidal systems that enable the body to correct its position in response to a change in the center of gravity. The appropriate central integration of sensory input is essential for adequate postural control and, according to more recent investigations, is not fully developed until 15 years of age. An acute visual, vestibular, or proprioceptive disturbance will cause a mismatch to previously stored sensory information and present as dizziness and problems with postural control.

The neurologic evaluation should be adapted to the patient's age and level of maturation. In infants younger than 6 months of age, head tilt, delayed head control, and delayed postural control may be due to vestibular dysfunction. By 6 months, head control should be well established and good symmetric righting reflexes indicate a functional vestibular system. An asymmetric reflex suggests a unilateral lesion when no motor deficit is present. By 4 years, the child's brain is mature enough to have established equilibrium responses that can be tested clinically or by posturography (Foudriat et al, 1993).

TABLE 67-1. Clinical Neurovestibular Testing

Neurologic examination adapted to child's age
Righting and equilibrium responses
Reinforced Romberg test
Stepping test
Tandem gait, eyes closed
Dix-Hallpike maneuver
Orthostatic hypotension test

The neurologic evaluation should assess the presence of cranial nerve deficits, the integrity of extraocular movements, and the presence of spontaneous, gaze-induced (30° lateral, upward, and downward gaze), or positional nystagmus. The Dix-Hallpike maneuver involves looking for nystagmus induced by abruptly changing the patient's position from sitting with a lateral head deviation of 45° to reclining with the head hanging off the examining table and maintained in the same lateral position. This maneuver is repeated with the head to the right, to the left, and hyperextended in the midline position. It will elicit positional-induced nystagmus and is positive in paroxysmal positional nystagmus and other peripheral labyrinthine disorders (ie, labyrinthitis, neuronitis, Meniere's disease, and perilymphatic fistula). This positional-induced nystagmus has a brief latency (< 10 s), fatigues with repeated maneuvers, and is most intense when the affected ear is down. The patient will also complain of being most uncomfortable with the affected ear down, which is a typical symptom of a peripheral vestibular lesion (Table 67-2). Nystagmus due to peripheral lesions may be inhibited by fixation. The use of Frenzel goggles (10+ diopters) during this test eliminates fixation and facilitates eye observation by the examiner. It is important to look for latency and duration of response as well as habituation with repeated positioning, as these features help differentiate between central and peripheral lesions (Table 67-3).

A central nystagmus is not inhibited by fixation, is not positional, and does not fatigue. Dizziness due to central vestibular disorders, such as cerebellopontine lesions, is usually associated with hearing loss and often with other cranial nerves deficits. With posterior fossa lesions, cerebellar signs and pyramidal signs may be present, affecting gait and coordination.

With vestibular disorders, tandem gait with eyes closed may elicit swaying and veering toward the affected side. A reinforced Romberg test is more sensitive than the regular version and helps elicit subtle vestibular findings. The stepping test, introduced by Fukuda, requires the patient to step in place with eyes closed at the intersection of two perpendicular lines while counting to 60. With unilateral vestibular lesions, this maneuver will elicit veering toward the affected side by more than 45°. With bilateral vestibular dysfunction, a significant forward displacement of more than 20 inches may be seen.

TABLE 67-2. Peripheral Vestibular Disorder

Acute onset vertigo
Head tilt or swaying toward affected side
Autonomic dysfunction
Nystagmus toward unaffected side
Positive Dix-Hallpike maneuver
Preferred position: supine, affected ear up
Improves over time

TABLE 67-3. Central Vestibular Disorder

Unremitting dizziness or vertigo
Nystagmus is constant and not positional; does not habituate and is not inhibited by fixation
Dix-Hallpike maneuver noncontributory
Cranial nerve deficits may be present
Pyramidal or cerebellar deficits may coexist
Imaging studies recommended

Differential Diagnosis (Table IV)

It is helpful to approach the differential diagnosis by separating dizziness from vertigo and by separating vertigo with hearing loss from vertigo without hearing loss. Proceeding with a specific line of questioning that addresses the nature and constellation of symptoms will lead to the correct diagnosis. A comprehensive "pediatric dizziness questionnaire" was designed by the author and tested on 62 patients. The sensitivity of the questionnaire in reaching the correct diagnosis was calculated at 92% (3).

Dizziness

Dizziness may be a symptom superimposed on a preexisting condition or as a seemingly isolated complaint (Figure 67-1). Visual disturbances causing distortion of images often are associated with dizziness. This is especially common when the wrong glasses are prescribed. Systemic disorders, such as diabetes, endocrine disorders, longstanding renal insufficiency with uremia, demyelinating disorders (eg, multiple sclerosis), and degenerative disorders, may be associated with low-grade constant dizziness, fluctuating in intensity, as a result of a chronic vestibular neuropathy. Long-standing use of aminoglycosides, quinine, acetylsalicylic acid, chemotherapeutic drugs, loop diuretics, non steroidal anti-inflammatory drugs and diphenylhydantoin may damage the vestibular nerve or the labyrinth and cause unremitting dizziness. Unremitting dizziness may occur in acoustic neuroma, other cerebellopontine (CP) angle lesions, and posterior fossa tumors. There is usually progressive hearing loss and progressive involvement of other cranial nerves, pyramidal tract signs, and cerebellar dysfunction.

Magnetic resonance imaging (MRI) of the brain with contrast and thin cuts through the CP angle will obviate the diagnosis. In the absence of neurologic findings, endocrine abnormalities, or exposure to ototoxic drugs, the possibility of anxiety or panic attacks or psychosocial stress needs to be considered. These patients will admit upon questioning to hyperventilation, excessive palm sweating, palpitations, and even chest pressure during the attacks. Many patients complaining of constant dizziness with mild variations in intensity also have

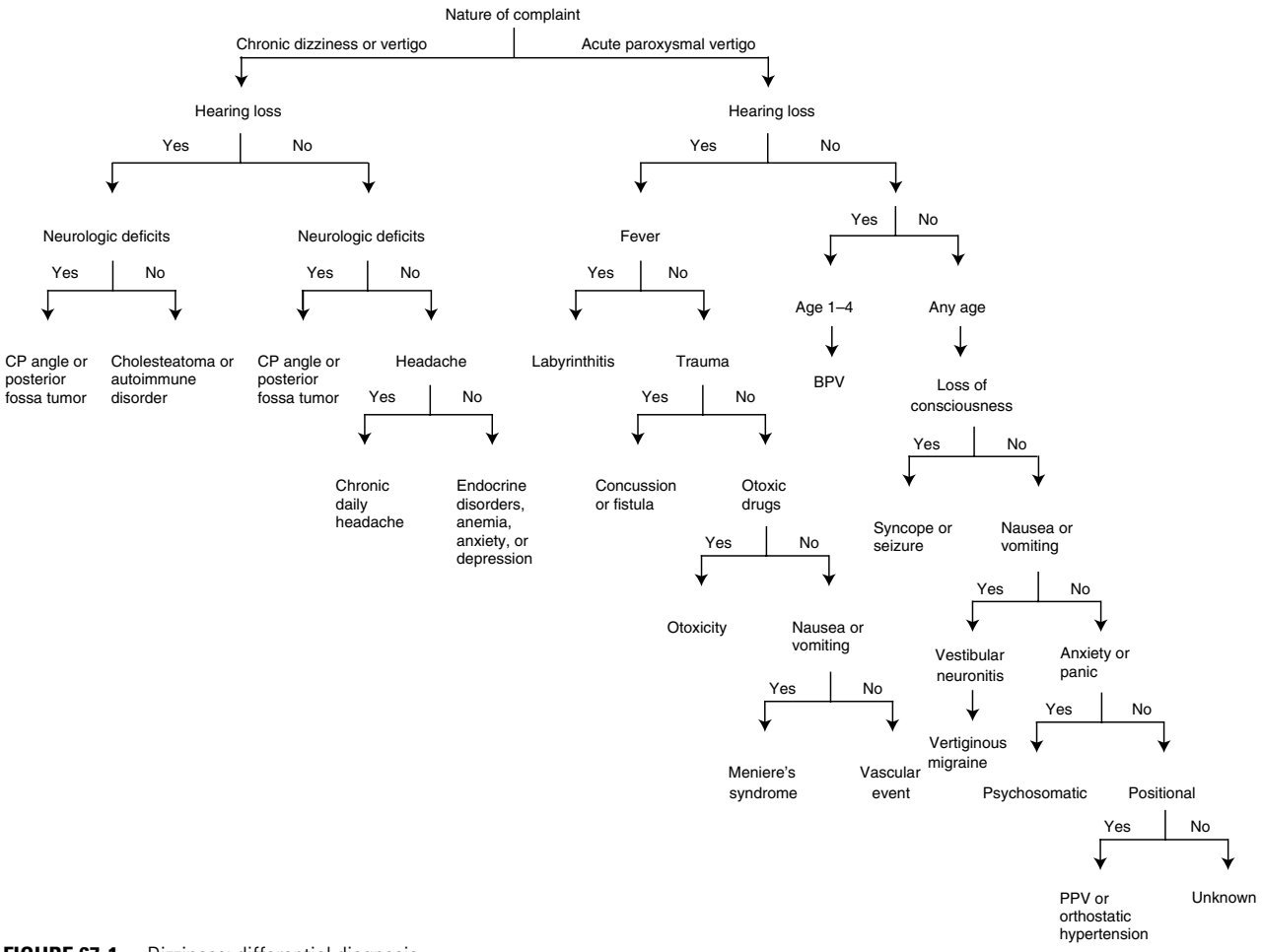

FIGURE 67-1. Dizziness: differential diagnosis.
BPV = benign paroxysmal vertigo; CP = cerebellopontine; PPV = paroxysmal positional vertigo.

frequent headaches. This combination of symptoms may be the manifestation of underlying stress, anxiety, or depression. When headaches are associated with recurrent dizziness, one should consider vertiginous migraines. Autonomic features are often present in vertiginous migraine.

The difference between dizziness and vertigo is very important indeed. Whereas dizziness is a less-specific symptom associated with systemic ailments, space-occupying lesions, or psychosocial stresses, vertigo is more likely associated with a true vestibular disorder that can be due to a vascular, inflammatory, or degenerative process.

It is helpful to approach the diagnosis of vertigo by separating vertigo with hearing loss from vertigo without hearing loss and to proceed with a specific line of questioning that will lead to the correct diagnosis. A comprehensive pediatric "dizziness" questionnaire was designed by the author and tested on 62 patients with dizziness. The sensitivity of the questionnaire in reaching the correct diagnosis was calculated at 92%.

Acute Paroxysmal Vertigo with Hearing Loss

Labyrinthitis

The acute onset of vertigo, nausea, and vomiting, aggravated by head motion and associated with fever and hearing loss, is typical of an acute labyrinthitis. The attacks may last several days and are associated with severe equilibrium disturbances and autonomic disturbances. Acute labyrinthitis is probably the most common etiology of vertigo and hearing loss in young children who present with fever and bacterial or viral otitis media. Immediate, aggressive treatment of the otitis is required. Meclizine, diphenhydramine, or a scopolamine patch will alleviate the vertigo. Intravenous fluids may be required to overcome dehydration resulting from vomiting and antiemetics are helpful in stopping vomiting.

Meniere's Disease

Meniere's disease presents in a similar fashion to labyrinthitis but without fever. It is accompanied by tinnitus, ear

pressure, and fluctuating hearing loss. The attacks are recurrent and associated with progressive hearing loss. Fortunately, the condition is very rare in children. Treatment consists of diuretics for the alleged labyrinthine hydrops and symptomatic treatment for vertigo with meclizine, diphenhydramine, or scopolamine patch.

Perilymphatic Fistula

Head trauma, barotrauma, and exertion may cause a rupture of the round or oval window, leading to a perilymphatic fistula presenting with episodes of vertigo and progressive sensorineural hearing loss (SNHL). As in the previously described peripheral vestibular disorders, the vertigo is usually positional and the attacks may be associated with nystagmus. Nystagmus can often be elicited by increasing pressure in the ear canal with a pneumatic otoscope. It can be observed with the naked eye or recorded by electronystagmography. Exploratory ear surgery may be required to identify and correct the leak, localized at the oval or the round window. Early corrective surgery may salvage hearing and control the vertigo. Congenital anomalies of the inner ear may be predisposing factors and high-resolution computed tomography (CT) of the temporal bone may establish the diagnosis.

Head Trauma

Head trauma can cause temporal bone fracture resulting in SNHL and vestibular damage, or it may cause a labyrinthine concussion without hearing loss. Auditory brainstem evoked potentials are helpful in detecting brainstem involvement. Steroids have been advocated for reduction of immediate posttraumatic swelling and promoting healing of the cochlear and vestibular nerves. Subsequent vestibular rehabilitation is helpful in promoting adaptation to the acute vestibular trauma.

Vascular Occlusion

Vascular occlusion of the labyrinthine artery may occur in hypercoagulable states, such as sickle cell disease. Treatment focuses on the underlying condition. Traumatic vertebral artery aneurysmal dissection may cause embolization of brainstem and cerebellum, and acute vertigo. Initial treatment with heparin is indicated to prevent further embolization, followed, in time, by surgical correction of the aneurysm.

Autoimmune Disorders

Autoimmune disorders, such as Cogan's syndrome, may cause hearing loss and acute labyrinthine dysfunction. The mechanism is an autoimmune process affecting the cochlea and labyrinth, resulting in elevated anticochlear antibodies. Checking for presence of anticochlear antibodies is recommended. The recommended treatment is intravenous immunoglobulin G or steroids, which are reported to substantially ameliorate the symptoms.

Paroxysmal Vertigo without Hearing Loss

Paroxysmal vertigo without hearing loss should be evaluated according to the patient's age.

Benign Paroxysmal Vertigo

Infants and children younger than the age of 5 years may experience a sudden spinning sensation and loss of equilibrium and hold on to the nearest support, usually their mother, until the vertigo subsides. The attack may last minutes to hours, during which the child appears diaphoretic and pale, with nystagmus often present. Head tilt nausea and vomiting are occasionally present. There is no confusion or automatism during the episode and no confusion or sleepiness after it, as observed with partial complex seizures. Equilibrium is definitely impaired during the attack and the child refuses to move. The neurologic examination between attacks is entirely normal. The condition is called *benign paroxysmal vertigo* (BPV). There is usually a strong family history of migraine and 50% of these children develop migraine attacks in adolescence. Because the episodes are usually brief, treatment is not indicated, but reassuring the child and the family regarding the benign nature of the condition is very helpful. Children should have a brain MRI and electroencephalogram (EEG) at the time of the first attack to exclude a space-occupying lesion or partial complex seizures.

Paroxysmal Torticollis or Tortipelvis

Paroxysmal torticollis and paroxysmal tortipelvis also are manifestations of acute vestibular dysfunction in young children. The etiology of these conditions is not fully understood. They are considered migraine equivalents because of the strong association with migraine later in life. Because of the brief duration of the episodes, treatment is usually futile. Children who exhibit poor balance between attacks benefit from physiotherapy.

Vestibular Neuronitis

In older children and in adolescents, an acute episode of vertigo, often preceded by an upper respiratory infection and associated with nausea, vomiting, and dysequilibrium, is termed *vestibular neuronitis*. The condition lasts from a few days to several weeks, with decreasing duration and intensity over time. Episodes may recur months and even years later, usually with decreased severity and duration. Acute treatment consists of hydration, bed rest, and symptomatic treatment of the vertigo with meclizine,

scopolamine, or diphenhydramine, and antiemetics (Table 67-4). A prospective longitudinal study of 21 children with vestibular neuronitis provides data on the natural history of the condition. It shows progressive decline of symptoms. Complete recovery was documented in all the children studied after 5 years (Taborelli et al, 2000). Symptoms that persist beyond 2 or 3 weeks of treatment with antivertigo medication are helped with physiotherapy aimed at correcting the sensory mismatch and promoting habituation. This is achieved by encouraging the patient to repeatedly assume the most uncomfortable position (affected ear down) while using visual and proprioceptive cues during the procedure. This maneuver helps the patient to compensate for the vestibular loss and promotes central reorganization of postural control, leading to progressive resolution of the dizziness.

Migraine Variants

Vertigo may precede or accompany a headache and may be associated with nausea or vomiting. Phonophobia and sonophobia, characteristic of migraine, may or may not be present. This constellation of symptoms is characteristic of the migraine variant known as vertiginous migraine, which respond to the same medications used to treat classic migraine.

TABLE 67-4. Treatment of Dizziness

Acute vertigo and autonomic symptoms
Intravenous hydration
Diazepam IV 0.05–0.15 mg/kg/dose or PO 0.12–0.8 mg/kg/dose
Meclizine PO 25–100 mg/dose/d
Prochlorperazine IM 0.05–0.15 mg/kg/dose or PO 0.4 mg/kg /dose in 3–4 doses
Diphenhydramine IV or IM 5 mg/kg/d in 3–4 doses; adolescents: transdermal scopolamine 1.5 mg
Hydrops or Meniere's disease: diuretics (diazides or Diamox®)
Bacterial labyrinthitis: antibiotics
Autoimmune disorders: steroids
Subacute or chronic vertigo
Meclizine 25–100 mg/d
Treat underlying disorder:
Migraine: nonsteroidal anti-inflammatory drugs for subacute episode
Chronic migraine: amitriptyline 10–75 mg/d, propanolol 10–20 mg bid, or divalproex sodium (Depakote®) 1 or 2 capsules of 125 mg bid or ER 250 mg bid
Vertiginous seizures: carbamazepine 25 mg/kg/d or as per EEG
CP angle or posterior fossa tumor: surgery
Cholesteatoma: surgery
Perilymphatic fistula: surgery
Orthostatic hypotension: increase fluid and salt intake or mineralcorticoids
Paroxysmal positional vertigo: physiotherapy, ie, positioning maneuvers
Panic or anxiety attacks: psychiatric counseling; alprazolam 2–4 mg/d or paroxetine 10–40 mg/d

bid = twice daily; CP = cerebello-pontine; EEG = electroencephalogram; ER = extended release; IM = intramuscularly; IV = intravenously; PO = orally.

Basilar Artery Migraine

Acute paroxysmal vertigo associated with tinnitus, acroparesthesias, perioral paresthesia, and visual obscuration was initially described by Bickerstaf in prepubescent girls and labeled *basilar artery migraine* (BAM) because the symptoms are consistent with vasoconstriction in the vertebrobasilar territory. The condition is recognized in all age groups and in both genders and can be a frightening experience for patients and parents alike. It may be associated with loss of consciousness when the decreased perfusion of the reticular activating system in the brainstem is of long duration. Both brain MRI and EEG are indicated to rule out a vascular malformation of the brainstem or a seizure disorder. For suspected vascular malformations, magnetic resonance angiography (MRA) or CT angiography may be necessary to confirm the diagnosis. Treatment of the acute episode is primarily with nonsteroidal anti-inflammatory agents. Ergot preparations are contraindicated for fear of causing severe vasoconstriction in the vertebrobasilar distribution, causing stroke. Calcium channel blockers may be effective as preventive therapy but should be used with extreme caution.

Cyclic Vertigo

We described a group of children with cyclic vertigo. The vertigo occurred at very predictable intervals, starting early in the morning with severe photophobia, nausea, and vomiting. After many years of cyclic vertigo, the children developed classic headaches. Three of nine children were subsequently diagnosed with bipolar disorder. This presentation is most likely another migraine variant associated with a functional disturbance of the internal biologic clock. The treatment is symptomatic during the episode. When attacks are frequent, migraine prophylaxis with propranolol, valproate, or topiramate can be effective.

Motion Sickness

Most children with migraines suffer from motion sickness and are prone to vertigo, nausea, and vomiting during passive locomotion (car rides) or motion in the surrounding environment while they remain still. They may be especially oversensitive to optokinetic stimulation. The explanation for this disorder is not clear but may be due to the patient's inability to tolerate an abrupt sensory mismatch. Habituation may be achieved by gradually increasing exposure to longer rides and by ensuring a wide-open visual field during rides. The use of meclizine during prolonged trips may be helpful for symptom control.

Vertiginous Seizures

Loss of consciousness or altered consciousness immediately preceded by vertigo suggests a vertiginous partial complex seizure. Vertiginous seizures are very rare; however, dizziness

may be experienced in various seizure types. The diagnosis should rely on EEG abnormalities best elicited after sleep deprivation or, better yet, recorded during the event itself. Treatment should be selected on the basis of the nature of the underlying seizure disorder.

Panic Attacks

Severe panic attacks, agoraphobias, and claustrophobias have presented as episodic vertigo. A carefully directed line of questioning (as suggested in the "dizziness questionnaire") will elicit the episodes of hyperventilation, palpitation, and autonomic instability that characterize these conditions and eliminate the need for extensive and costly work-up. Management of the condition preferably should be assigned to a psychiatrist. Antidepressant and antianxiety medication, such as paroxetine or benzodiazepines, can be very helpful in controlling symptoms (see Table 67-4).

Orthostatic Hypotension

Vertigo associated with abrupt changes in position from supine to sitting or standing is most likely the result of orthostatic hypotension. This diagnosis can be easily established during the general physical examination by measuring blood pressure in the supine and standing positions and documenting a significant drop of > 20 mm Hg of the systolic pressure during standing. Tilt testing in a neurophysiology laboratory may provide additional confirmatory evidence. Increasing fluid and salt intake may eliminate the orthostatic hypotension; however, corticosteroids (eg, Florinef®) need to be added in severe cases.

Paroxysmal Positional Vertigo

Paroxysmal positional vertigo occurs during abrupt changes of head position while turning over abruptly in bed or causing other abrupt changes in head position. The sensation of vertigo often is associated with a brief bout of torsional nystagmus elicited when the affected ear is undermost. This can be reproduced in the office by using the Dix-Hallpike maneuver. The etiology is attributed to calcium debris broken off the otololiths and lodging in the posterior semicircular canal. The condition is very rare in children but may occur as the result of head trauma. Treatment consists of head positioning exercises that will induce habituation and may even reposition the debris in some cases. The field of vestibular therapy using multisensory integration modalities is rapidly expanding on the basis of extensive experiments on vestibular compensation in adults and in children. It is a very useful, safe, and effective treatment that is receiving progressively more recognition in clinical practice as an adjunct or a substitute to medication.

Laboratory Testing

The therapeutic and technology assessment subcommittee of the American Academy of Neurology recently reviewed the vestibular testing techniques used in adults and children (Table 67-5). Most laboratory testing relies on evaluation of the vestibulo-ocular reflex (VOR). This is a short latency reflex that generates compensatory eye movements in response to head movements in order to maintain visual fixation. The VOR can be evaluated during the application of stimuli such as rotation and caloric irrigation. The most common method of testing the VOR is electro-oculography, also referred to as electronystagmography. The technique measures changes in corneoretinal potential using electrodes placed around the inner and outer canthi of the eyes. It permits recording of the direction, amplitude, and velocity of eye movements in different head positions and in response to different types of vestibular stimulation. Infrared video nystagmography uses infrared cameras positioned in eye goggles that detect movements of the eyes. Most commercially available techniques record horizontal eye movements. Two methods are used for stimulation of the vestibular apparatus: rotation and caloric irrigation of the ear canals by air or water.

Caloric testing should be performed with the head positioned in such manner that the horizontal semicircular canal is vertically placed. The caloric irrigation produces a convection current, causing the endolymph to rise when warmed and sink when cooled. The nystagmus during cool irrigation is away from the ear and during warm irrigation toward the irrigated ear. A pitfall of the technique is that a narrow or an obstructed ear canal may reduce the intensity of the stimulus, causing a reduced response. Using a formula developed by Yonkees, it is possible to determine the presence of a hypoactive labyrinth (less nystagmus generated by hot and cold stimulation in one ear compared with the other ear) or directional preponderance (the nystagmus elicited by the caloric irrigations beats primarily in one direction). The presence of a hypoactive labyrinth suggests damage to the peripheral organ, as in vestibular neuronitis or labyrinthitis.

TABLE 67-5. Laboratory Testing

Electronystagmography
Hearing test adapted to patient's age
Auditory brainstem potentials in suspected brainstem involvement
Brain MRI with contrast in suspected central disorders
MRA or CT angiogram in vascular disorders
CBC, FBS, TFT, electrolytes, and coagulation studies

CBC = complete blood count; CT = computed tomography; FBS = fasting blood sugar; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; TFT = thyroid function tests.

Directional preponderance is more likely associated with a central lesion or an old peripheral lesion.

Children older than 3 years of age usually are able to tolerate a bithermal caloric irrigation, even though the procedure requires about half an hour and may cause vertigo, especially when performed after an acute labyrinthine insult. Rotational testing using a sinusoidal stimulation with a computerized rotational chair that delivers frequencies of rotation from 0.01 Hz to 0.16 Hz is more suitable for pediatric testing. Unfortunately, the equipment is expensive and not universally available. Rotational testing allows precise application of multiple frequencies of rotational stimuli, whereas caloric testing is equivalent to a single very low frequency (0.003 Hz). The disadvantage is that it tests both ears simultaneously and is not as reliable in detecting unilateral lesions. The test is suitable for very young children who can be tested while sitting in a parent's lap. Measurement of the VOR in rotational testing is expressed in terms of gain (eye velocity relative to head velocity) and phase (timing of eye motion relative to head motion). A perfect VOR function will present a gain of 1 and a phase shift of 180°. The VOR is less efficient during very low frequencies of head movement and is best at rotations of 1 to 6 Hz, which closely simulate head motion during locomotion. The VOR may show asymmetry in cases of substantial unilateral labyrinth hypofunction. The rotational test is best suited for assessment of ototoxicity.

Posturography uses a computerized moving platform to elicit postural reactions to abrupt changes in the center of gravity with and without visual and proprioceptive clues. The computer analyzes body sway and compensatory postural reactions. The test requires special equipment and has had limited practical use because of its high cost, difficulty administering it in young children, and limited standardization in children. Several studies on posturography from Japan and the United States are available and describe a delay in acquiring mature integrated postural reactions in children younger than 15 years of age. However the studies were performed with equipment designed and used for adults, which may account for some of the alleged delays. The limited number of children studied and the discrepancies between the results published from various centers underlie the difficulty in using these tests for routine diagnostic purposes.

Indications for Vestibular Testing

Vestibular testing is especially helpful in disorders of the peripheral organ (ie, labyrinthitis, vestibular neuronitis, posttraumatic vertigo, perilymphatic fistula, Meniere's disease, or vestibular schwannoma). A hypoactive labyrinth will confirm damage to the peripheral organ. Repeated testing may provide a measure of the degree of recovery over time. Drug ototoxicity can be carefully assessed and monitored with rotational testing. Testing also is indicated in balance disorders when it is important to differentiate between poor balance resulting from visual, vestibular, or proprioceptive disorders. Although the history and clinical testing will give a definite clue concerning the disorder's etiology, vestibular testing helps confirm the diagnosis.

Children with acquired or congenital hearing loss also will benefit from testing, as the cochlea and labyrinth are in close proximity and may be affected by the same noxious agents. A child with poor bilateral labyrinthine function may become very disoriented in the dark or while diving into a pool, as visual cues are missing in the dark and proprioceptive clues missing when one is immersed in water. Testing the VOR during smooth pursuit or generation of saccades provides information on cerebellar control of eye motions, and suppression of nystagmus with fixation will indicate that the lesion is peripheral and not central.

Hearing testing is essential in all suspected peripheral lesions and suspected posterior fossa lesions, especially vestibular schwannoma.

EEG should be performed in cases of vertigo with loss of consciousness or loss of postural control to exclude the possibility of seizures versus basilar artery migraine or vertiginous migraine.

MRI of the brain is the method of choice to rule out posterior fossa tumors, including CP angle lesions. When vascular anomalies are suspected, MRA is recommended.

CT of the head with thin cuts through the temporal bone is especially helpful to demonstrate congenital anomalies of the inner ear.

Determining the etiology for and the management of dizziness and dysequilibrium are very difficult diagnostic dilemmas. Using a comprehensive standardized "dizziness questionnaire" and a step-by-step diagnostic algorithm approach will greatly facilitate finding the etiology and instituting appropriate treatment.

Suggested Readings

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Practitioner and Patient Resource

Vestibular Disorders Association (VEDA)
P.O. Box 4467
Portland, OR 97208-4467
Phone: (503) 229-7705
Fax: (503) 229-8064
E-mail: veda@vestibular.org
http://www.vestibular.org
VEDA is a nonprofit organization that provides information to the public and health professionals about inner-ear balance disorders such as Meniere's disease, benign paroxysmal positional vertigo, and labyrinthitis.

CHAPTER 68

FAINTING AND SYNCOPE

JOHN B.P. STEPHENSON, MA, DM, FRCP, HON. FRCPCH

Although syncope is relatively common, few texts describe the entity in any detail. Those texts that do may dismiss the subject in a few lines, referring to it as "only a simple faint." Such supposed reassurance is as helpful as saying to someone who has epilepsy that "it's only a simple fit." This chapter aims to remedy such deficiencies. It will show that syncope is important and that the correct diagnosis may prevent years of misery and drug toxicity. It will show that syncopes may present as highly convulsive events—true seizures, anoxic seizures, but not epileptic seizures—accompanied by extremely unpleasant feelings.

Recognizing syncope usually only requires the best of one's skills in history taking. Simply making the correct diagnosis, transmitting it to the family, and understanding their feelings may be of major help, not least because it allows the family to contact a parent support group. When difficulties arise, the dearth of evidence-based treatment options argues for a generally conservative approach.

What Is Syncope?

Syncope happens when the brain is abruptly deprived of energy. This occurs either because blood flow ceases, the brain's oxygen supply fails, or some combination of the two. Not surprisingly, it is commonly a dramatic event, not in the sense of a histrionic swoon but owing to the appearance of the syncopal convulsion. It is important to realize that although some faints are syncopes, syncopes do not resemble the popular conception of fainting. The stereotype—in which the patient sighs, sinks to the floor, lies motionless with eyes closed, and finally recovers and says "Where am I?"—is wrong in every particular way. Knowing this gives the pediatrician a good start in arriving at the correct diagnosis.

Terminology

Using words with precision is central to making the correct diagnosis, especially in patients whose symptoms are complex. This particularly applies to those words used to label paroxysmal events. If this seems to be an attack on North American speech, it is not. The problem addressed here is universal, at least among the English-speaking peoples.

Seizure

In an epileptic seizure, changes in behavior—objective or subjective—are associated with a sudden change in the electrical activity of the brain, commonly as a hypersynchronous discharge of many neurons, usually neurons in the cerebral cortex. Nonepileptic seizures are sudden changes in objective or subjective behavior that do not have at their root a sudden cerebral discharge.

There are two main varieties of nonepileptic seizure. The most important is the anoxic seizure, which results from syncope. In an anoxic seizure, cerebral activity is extinguished. In contrast to both epileptic and anoxic seizures, there is no massive change in cerebral activity in the psychological type of nonepileptic seizure. Pediatricians who believe that they confine the term "seizure" to epileptic seizure may reflect for a moment on febrile seizures. Although most febrile seizures are epileptic in mechanism (albeit the child usually does not have epilepsy), it is certain that some febrile seizures are anoxic seizures.

Convulsion

What has just been said about seizure applies equally to the term "convulsion," except that in a convulsive seizure the child convulses—that is, has some combination of jerks, spasms, and stiffenings. In contrast to epileptic seizures (eg, absence seizure), anoxic seizures are generally convulsive.

The term "convulsive syncope" implies, first, that there is a peculiar variety of syncope with clonic or tonic muscle activity and, second, that there may be an epileptic mechanism involved. Both of these presumptions are wrong: nonepileptic syncope is naturally convulsive.

Fit

"Fit" may not be a popular term for a convulsion in North America, but in Scotland, this author has found it a useful one, particularly in discussing with families the difference between a fainting fit (anoxic seizure) and an epileptic fit.

Attack, Event, Episode, Turn, Blackout, and Transient Loss of Consciousness

Attack, event, episode, and *turn* are nonspecific terms for something paroxysmal. *Blackout* and *transient loss of consciousness* (TLOC) have been used for episodes involving a loss of awareness whose cause is not clear.

Seizure Disorder and Convulsive Disorder

Some use these terms as if they were synonymous with epilepsy. Such use is hazardous, for it allows the difference between syncopal disorders and epileptic disorders to become blurred. Insofar as clarity of thought leads to better patient management, these terms should be jettisoned for good.

Words Used for Syncopes

Typing syncope into the search window of PubMed or Ovid will retrieve articles on pallid, neurally mediated, neurocardiogenic, and vasovagal syncope but not breath holding, reflex anoxic seizures, or most of the items discussed below under "Dangerous, Rare, but Treatable Syncopes."

How to Take a History

It is sometimes possible to arrive at a diagnosis of syncope in a minute or two, but beware the knee-jerk diagnosis of epilepsy or psychological attacks. When the diagnosis is difficult, there are many steps to the conclusion.

Prolonged Interrogation

In the world of paroxysmal events, the diagnosis is as good as the history. The objective is to build a moving picture of the event from before it started until after it ended. The result will be better than a video recording because it will also include the mental experiences of the patient before and after the loss of consciousness that led to the consultation.

History from Both Patient and Witness

Obviously, there is a lower age limit for eliciting anything useful, but even a young child may reveal information not yet known to the parents. Not surprisingly, it is necessary to track down the witness who was present at the onset. Because of the situational context of most syncopes, they are likely to occur at the nursery or at school. Reflex anoxic seizure or reflex asystolic syncope (RAS) is an exception: episodes tend to occur when the child is "off guard" at home. When the story is of a seizure, convulsion, or fit just in school, vasovagal syncope is the likely diagnosis (the child was probably standing and reading to the class), but one needs to check details with the teacher directly.

History from a Second Witness

When syncope in an infant always occurs in the mother's presence but is witnessed by others, it is necessary to check whether those witnesses saw the actual onset.

Mime, Video, and That's It!

The use of mime by the physician and by the parent is an extension of the verbal history in the diagnosis of motor seizures, including syncope. Showing parents a variety of video recorded events in other children and asking which, if any, resemble the episodes in their own child is also helpful. "That's it!" indicates a hit. This technique is becoming easier now that CDs showing multiple examples of seizures and syncope are more widely available (see for example the episodes on the CD associated with Stephenson, 2001, and Stephenson et al, 2004).

Camcorder in the Home

The capturing of a natural event on film extends the clinical history to its limits. A difficulty is the time it takes from the onset until the camcorder is running, but the diagnosis of longer events, such as anoxic-epileptic seizures, may be confirmed in this way (see the CD with Stephenson et al, 2004).

Recognizing Syncope

Settings, Provocations, Precipitants, Stimuli, and Triggers

No part of the history is more important than this. Syncopes occur in particular settings—in church, when reading in class, when blood is being drawn, in pregnancy—and are provoked by stimuli. Not every syncope has a discernible provocation, but good history taking will unearth provocations in some, maybe 90%, certainly some of the time. For the practitioner, the safest rule is to assume that if some events have typical precipitants, then all the events are syncopes. In toddlers, a common precipitant is an unexpected blow to the head; in adolescents, it is more likely to be the sight of blood. How provocations may change with age is illustrated in the following example.

Case 1

This girl suffered her first episode of syncope at the age of 10 months after a slight bump to her head. The presentation was similar from then on, except that the episodes became more "severe" as she got older. When she was old enough to talk, she would say "Oh Mum, I've hurt myself" and look pale. After 10 or 20 seconds, she would fall rigidly, making a gurgling noise, her hands and feet turning in and her back arching. Her arms might jerk a little and her legs move as if she were pedaling a bike, but sometimes this motor activity was more violent. She would then "look like death" and not know what had happened for a couple of minutes before wanting to lie down and sleep.

From the age of 7 years she began to describe an aura. She would hear a noise, like a high-pitched screaming and something like a voice, though without words. Sometimes she would see red, a color she does not like, and sometimes she would have hallucinations, such as a train rushing toward her.

Her mother described how the triggers that would precipitate a syncope changed over the years. After the first episode after the head bump, all the syncopes in early childhood followed slight but unexpected pains, such as her finger being bent back. Later, she began to experience the same reaction on seeing a minor injury, such as a scab that had come off a wound. Then she developed inevitable syncope at the sight of blood. Finally, even the thought of self-injury was enough to bring on an attack. On the day before this author saw her in consultation at the age of 13 years, she was warned—wrongly!—that her eyeballs would be pressed into her head, and within 2 minutes she was in a violent syncope, stiff and snorting.

In this girl, virtually every syncope had a recognizable provocation, but even if only a proportion of her convulsive attacks had been provoked, the diagnosis of (vasovagal) syncope would have been entirely secure. The range of unpleasant syncopagenic stimuli is enormous, but, to an extent, each affected individual has "preferred" stimuli. Whether there are important differences in the syncopes induced by different precipitants, such as pain and disgust, is not known.

Some precipitants, such as hair grooming, are not, as far as one can see, unpleasant. Fortunately for the pediatrician, the story that the convulsion began during a haircutting or blow-drying session immediately secures the diagnosis of syncope.

An unusual trigger is flickering light as from the television: when such reflex syncopes are convulsive, confusion with photosensitive epilepsy is easy.

The question of exercise as a trigger will be discussed under "Dangerous, Rare, but Treatable Syncopes."

Aura, Warning, or Prodrome

Many neurologists and pediatricians imagine that an aura means an epileptic seizure. However, subjective premonitory symptoms occur before most syncopes. The same rule applies as with provocations: if some events, attacks, seizures, convulsions, or fits begin with a typical presyncopal experience, then all these events are likely to be syncopal. The best-known symptoms are blurring of vision with blacking out, together with an alteration in hearing with fading of sounds and some sort of tinnitus, followed by loss of consciousness. This combination always implies syncope. Other symptoms, such as a sensation of dread, may be less specific, but clinical studies are unable to adequately test this point. In some individuals, abdominal pain is a common precursor. Clearly, there is a lower age limit for recognizing a syncopal aura.

Complex Aura

Although hallucinations, misperceptions, and out-of-body experiences (see below) commonly occur at the end of a syncope during the recovery phase, sometimes something of the sort is experienced at the onset, as described in Case 1 above.

Falls

One might imagine that falling is an inevitable component of syncope, but, of course, that is not so in the very young nor in those who are unable to walk for other reasons. It used to be thought and taught that in syncope, the fall was limp and flaccid. It is now clear this is not necessarily so: a stiff (tonic) fall occurs just as often.

Injury

It should come as no surprise that the abrupt falls of syncope may injure the patient.

Convulsions

Some sort of convulsion is the rule rather than the exception in "pure" syncope. The movements involved include myoclonus, varying from subtle twitches to a storm of violent jerks involving the whole body, together with spasms and tonic extensions. The spasms have some resemblance to the better-known epileptic infantile spasms. The tonic extensions may be severe enough to induce opisthotonus but may also be subtle. Asymmetry of all these features may be prominent, with an appearance akin to the asymmetrical tonic reflex of young infants. Although these syncopal convulsions may be dramatic, they do not include prolonged regular rhythmic clonic activity.

Eye Movements

Eye movements in syncope include upward deviation, downbeat nystagmus, and brief conjugate lateral deviation.

Vocalizations

The emitting of some sort of noise is common during the unconscious phase of a syncope. These sounds have been described as growling, moaning, cackling, barking, grunting, snorting, and gurgling (see Case 1). Often, there is a single brief inspiratory groan, particularly near the end of the syncope in a breath-holding spell.

Tongue Biting

Although very rare, the presence of some tongue biting does not exclude syncope.

Urinary Incontinence

This is common in syncope and of no diagnostic value. Obviously, it is extremely embarrassing for the sufferer, long before adolescence.

Automatisms

Complex movements during a syncope are not unusual but are usually very brief. Even if they are prolonged for minutes, the diagnosis of syncope should not be discarded as long as the other characteristic features of syncope—precipitants and prodrome—are present.

Hallucinations and Out-of-Body Experiences

If the child is old enough, it is likely that hallucinations are the rule rather than the exception, but such symptoms, including out-of-body experiences, will not be volunteered without sensitive questioning. These symptoms commonly occur as the individual is beginning to regain consciousness. Descriptions include visual and auditory experiences but not formed speech. One patient of this author described a dream in which firemen with a fire engine were spraying blood out of a hose.

Out-of-body experiences are also not rare, even though the feeling of floating up to the ceiling and looking down on one's body is unusual. More commonly, there is a feeling of passing into a dark tunnel and being hurtled through space toward a bright light. A child who is coming round from a syncope in the school classroom may imagine that he is at home in bed and dreaming that he is at school. There may be no sense of personal identity, including not being aware of the existence of one's body or limbs, even if recovery is associated (as it sometimes is) with excruciating unlocalized pain.

Postictal Phenomena

It is said that confusion after syncope lasts less than 30 seconds, but this is not always so (see Case 1). Once again, one must accept that if the onset was as in syncope, then syncope is the diagnosis. Great fatigue, intense desire to sleep, pains, difficulty speaking, and wanting to remain on the ground may last a long time. An experience that everyone else is rushing about and talking too fast and too loudly is common and may last for days. In young children, nighttime sleep disturbance is upsetting for families.

Syncope versus Epilepsy

In the previous section, it was discussed how the pediatrician will know when a patient has syncope because most of management comes from getting the diagnosis right. The major importance of this is to avoid the erroneous diagnosis of epilepsy. Such an error is extremely common. Such an error leads to inappropriate alterations in lifestyle with unnecessary restrictions, completely unnecessary side effects from antiepileptic drugs, and, when a female patient grows older and becomes pregnant, inexcusable hazard to the fetus. Bear in mind that a "family history of epilepsy" is frequently wrong, maybe in 50% of cases.

Epileptic tonic-clonic seizures differ from syncopes in these ways:

- They are never precipitated, provoked, or triggered, or, at any rate, never provoked by the stimuli that provoke syncope.
- The convulsion is always long—one minute or more.
- The convulsion is always rhythmic—fast generalized twitching that slows down.

If there is doubt, it is syncope!

A good example of the erroneous diagnosis of epilepsy follows, in this case by a neurologist who was not a pediatric specialist.

Case 2

The consultant neurologist wrote to the general practitioner: "Thank you for asking me to see this 7-year-old young man. As a toddler, he began to have attacks of loss of awareness, rigidity, and eye rolling, which would be induced by minor knocks. This has continued, and recently, he had an undoubted tonic-clonic seizure with incontinence of urine. Curiously, as far as I can tell from the mother's account, every attack has been triggered by a minor bump on the head, and he has never had an attack out of the blue…It seems to me that this boy is having some sort of reflex epileptic seizure [and should continue] with sodium valproate…Even though two [electroencephalograms] EEGs have been normal…he should be on treatment for at least a couple of years free from attacks."

The neurologist failed to recognize that a triggered seizure is a syncope, in this case RAS, as discussed in the next section.

Vasovagal and Similar Syncopes

The major problem—recognizing syncope—has now been solved by the clinical history alone. It remains to establish

the underlying "cause." Most childhood syncopes are likely variants of vasovagal syncope, otherwise called neurally mediated or neurocardiogenic syncope. Various other labels have been applied, including breath-holding spells (see Chapter 64, "Breath-Holding Spells").

Vasovagal Syncope

This is the name given to the most frequent syncope of the older child, adolescent, and adult. It involves acute changes in the sympathetic and vagal outflows, but critical analysis indicates that the pathogenesis is still not understood. When such syncopes are severe, the mechanism is likely to include prolonged cardiac asystole (20 to 30 seconds or more).

Reflex Asystolic Syncope

The term *RAS* has come to be used for the short-latency dramatic syncopes of younger children, as illustrated in Case 2. There may be nothing fundamentally different between this syncope and vasovagal syncope (see Case 1). Although there are superficial resemblances between RAS and (cyanotic) breath-holding spells—such that they have been called pallid breath-holding spells—the mechanism of RAS is vagal-mediated asystole. Hence, some now use the term RAS to mean reflex asystolic syncope.

Induced Syncopes

Sometimes syncopes are self-induced and sometimes induced by others.

Compulsive Valsalva

Some children with learning difficulties, particularly those with autism, seem to enjoy hyperventilating and then undertaking a powerful Valsalva's maneuver. In this context, it is easy to mistake the resultant anoxic seizure for an epileptic seizure; sometimes, anoxic-epileptic seizures occur in this situation (see end of chapter).

Stretch Syncope

Healthy adolescents may unintentionally induce syncope by stretching, with neck extended.

Imposed Upper Airway Obstruction

In this dangerous manifestation of Munchausen syndrome (or factitious disorder) by proxy, the syncopes always begin in the presence of the mother, but she shows the syncopal infant to another adult—a relative or hospital staff—before recovery. Episodes cease immediately if the mother is no longer allowed unsupervised access.

Poisoning

The list is limitless, but a confusing situation arises as a manifestation of Munchausen syndrome by proxy when a mother feeds her child a tricyclic antidepressant. Such a drug may induce syncopes secondary to acquired long QT syndrome and independent epileptic seizures.

Dangerous, Rare, but Treatable Syncopes

The apparently life-threatening events induced by imposed upper airway obstruction in Munchausen syndrome by proxy, described above, are dangerous, rare, but treatable syncopes. More "organic" examples are described below.

Long QT and Other Cardiac Syncopes

This is an increasingly difficult area. One is taught—and one teaches—that syncope occurring during exercise may be cardiac, as in long QT syndrome. Difficulties include the facts that (1) all those carrying a long QT-associated ion channel mutation do not have long QT on a standard electrocardiogram (ECG) and (2) most of those who have exercise-related syncope may have vasovagal syncope with no cardiac disorder. However, if a patient experiences emotionally charged exercise that induces syncope (such as being chased by a dog) or syncope induced by a sudden sound or syncope during sleep (in which one has neither the obvious trigger nor the prodrome), then a long QT syndrome or similar tendency to ventricular tachyarrhythmia is highly likely. If there is doubt, an ECG should be ordered and the patient referred to a cardiologist. Recently, short QT syndrome has been described, associated with a high rate of familial mortality.

Hyperekplexia

In the neonatal variety of startle disease, slight stimuli induce a nonepileptic convulsion that may be tonic or clonic or a mixture of the two. A quivering vocalization precedes the silence when a profound syncope ensues, with subsequent anoxic seizure. The clinical diagnosis is made by the nose-tap test: percussion of the tip of the nose induces an obvious startle. Ictal treatment is by repeatedly flexing the baby (face to knee); further episodes are prevented by clonazepam or clobazam.

Familial Rectal Pain

In this rare disorder, episodes begin in the neonatal period. Stimuli include perineal cleansing and defecation. The presyncopal appearance has resemblances to hyperekplexia, but the clinical clue is harlequin color change of the face or of the trunk. Although this disorder is not a form of epilepsy, carbamazepine is usually helpful.

"Fainting" and Cerebral Syncope

The Hollywood stereotype of the swooning faint is likely to be a psychological (psychiatric) disorder. Head-up tilt test

studies (see below) have shown that these "pseudosyncopes" may be easily induced. There have been recent descriptions of apparent syncopes without change in heart rate or blood pressure but with isolated reductions in cerebral blood flow shown by transcranial Doppler or near-infrared spectroscopy. Such findings have prompted the label *cerebral syncope*. But the possibility of concurrent hyperventilation with consequent hypocapnia has not been excluded in these studies. In any such cases, the pediatrician must think deeply and choose a referral physician with much care. Postural orthostatic tachycardia syndrome is predominantly a feature of women of childbearing age; see http://www.potsplace.com for more information.

Useless and Useful Investigations

This author does not favor unnecessary tests. Seemingly innocent investigations may have adverse consequences.

Electroencephalography

It is difficult to think of any good reason for ordering a standard EEG in a child with a history of syncope. The main danger is that an irrelevant abnormality may lead to serious mismanagement. The next case illustrates this.

Case 3

A schoolboy began to have convulsions. The pediatrician thought that these must be syncopal because they were provoked—as when running—and there was an aura of dizziness, but he ordered an EEG nonetheless. Numerous centrotemporal spike discharges were seen, and because another episode had occurred in sleep, the diagnosis was changed to benign rolandic epilepsy. The boy had no episodes while on sodium valproate. At the age of 12 years, he collapsed and could not be resuscitated from his ventricular tachyarrhythmia. Review of the ECG strip on the original EEG record showed unequivocal prolongation of the QT interval. He had inherited long QT syndrome from one of his parents.

This case also illustrates the danger of the use of the "therapeutic trial" (here sodium valproate) in deciding if the diagnosis is epilepsy or syncope.

Electrocardiography

It is perhaps reasonable to ask for a standard ECG in any child with syncope, but if the history includes episodes during emotionally laden exercise and in sleep, cardiac consultation is mandatory. Missing the diagnosis of cardiogenic syncope is far more dangerous than missing the diagnosis of epilepsy.

Ocular Compression

Before the days of cardiac event monitors, this was a useful test when it was important to the parents for the doctor to see the RAS that resulted from prolonged asystole. Almost the only remaining indication now is when a young child with RAS is suspected of having absence status (and perhaps other types of epileptic seizure) induced by the syncope (see "Anoxic-Epileptic Seizures").

Head-Up Tilt

There is a huge amount of literature on head-up tilt testing, much of it empiric. We now know that falsepositives—syncopes in control volunteers—are frequent. If tilting is used, the end point must be the exact reproduction of the natural attack, whether that is a syncope, a syncope with hyperventilation, or a psychological pseudosyncope. This is technically complex, in that is it may involve continuous pCO_2 and EEG monitoring, and should inhibit unnecessary tilt testing. It is now evident that what happens when tilt provokes a syncope is not necessarily the same as what happens in that patient's 'natural' syncopes (as shown by prolonged home monitoring), a further argument against tilt testing without compelling reason.

Home Event Monitoring

The advent of small, lightweight ECG recorders that may be worn for weeks and the more recent introduction of implantable cardiac event recorders have simplified the diagnosis of the type of syncope and the confirmation of asystole in RAS in particular.

Prolactin

Prolactin levels increase after syncopes as readily as after epileptic seizures and so are of no value in that differential diagnosis.

Management

Diagnostic Imperative

In the management of syncopes, making the correct diagnosis is of such overwhelming importance that guidance on honing one's diagnostic skills dominates this chapter. Just imagine a patient—a female child with seizures who grows up and by the time of her first pregnancy is taking two antiepileptic drugs because the first drug did not help—presenting with her mentally retarded, malformed offspring and asking why she had been prescribed these antiepileptic drugs, as she has discovered that she has had vasovagal syncope all along? It is just as important not to misdiagnose syncopes as psychological or hysterical.

High-quality randomized, placebo-controlled, double-blind trials do not feature highly in any category of management. Some treatments may seem helpful only because many syncopes tend to improve.

Appreciation of Patients' and Parents' Perceptions

Severe syncopes are highly unpleasant convulsive events. To dismiss concerns by saying "It's only a simple faint" is as heartless as saying "It's only a simple fit" at the onset of epilepsy. The feelings of the individual who suffers syncopes need to be sensitively explored. Having a severe syncope is unpleasant, both immediately before and for a long time afterward. Then there is the problem of how to deal with onlookers, friends, and family, not to mention unsympathetic emergency room staff.

Chapter 64, "Breath-Holding Spells," deals with breath-holding spells, but parents of children with RAS do not like that label. They translate breath holding into temper tantrums due to bad parenting, although they know their child cannot help it and is not in control. It is a reflex—a reflex arrest of the heart, beyond the child's control.

Advice on Posture

Those who have already had a syncope will be on the ground and will not want to be moved. Those who have postural hypotension might like an alternative to lying down during the aura, that is, raising the arms above the head. Squatting on the spot is an excellent emergency measure. It was previously known that crossing the legs combined with muscle tensing was effective in aborting vasovagal syncope in the laboratory. It is now known that such techniques, known as physical counter-pressure maneuvers, are effective in preventing syncope in the everyday situation (see van Dijk et al in Suggested Readings). This is the first therapy whose efficacy has been established by randomized trial.

Dietary Advice

Adequate salt and plenty of fluid (water) are advocated. Ingesting a mug of water may be helpful when a syncope is expected, if that is not a contradiction in terms.

Medical Therapy

Many pharmacologic agents have been employed for vasovagal syncopes and for RAS, including beta-blockers, atropine, mineralcorticoids, iron, and piracetam. There is not a strong evidence base for the use of any of them.

Psychological Approaches

Although syncopes are "organic" disorders in the same sense that epileptic seizures are "organic," psychological methods may help syncopes, as in the case of epilepsies. Two examples may suffice.

The psychological term for the basis of vasovagal syncope triggered by "blood and gore" is blood-illness-injury phobia. One reportedly successful psychological approach is to teach the use of anger directed at the triggering stimulus.

One study reported the abolition of anoxic-epileptic seizures (in the form of clonic status epilepticus triggered by breath-holding spells) after "psychotherapy for the mother and daughter," once it was found that a severely disturbed mother-daughter relationship was the trigger for the spells.

Cardiac Pacing

One double-blind study has shown that cardiac pacing may prevent RAS. This trial was undertaken, with ethical approval and informed consent, on children who had frequent severe syncopes with RAS and prolonged asystole recorded on cardiac event monitors. Thus, it is known that pacing is effective in preventing RAS (Stephenson and McLeod, 2000), but the possible long-term harm of a pacing system in a growing child means that this should only be considered in very exceptional circumstances, such as when frequent severe attacks disrupt family, social, and educational life or when anoxic-epileptic seizures are frequent, and antiepileptic medication is not acceptable. Asystole of at least 10 seconds (probably at least 20 seconds) should have been demonstrated in at least two natural attacks. If possible, it should be demonstrated by ictal EEG or ECG recordings that the duration of isoelectric EEG is entirely accounted for by the duration of cardiac asystole.

Patient Support Groups

Several years ago, the author persuaded a mother from England to start a family support group to help those afflicted with RAS. Her organization (Syncope Trust And Reflex anoxic Seizures) now covers the whole range of syncopes, and families around the world find such contacts extremely helpful. Severe syncopes may be so strange that sufferers find it reassuring to contact others with the same experiences.

Anoxic-Epileptic Seizures

In childhood particularly, syncopes—RAS, prolonged expiratory apnea, or compulsive Valsalva's maneuvers—may be followed not only by the usual anoxic seizure but also by "true" epileptic seizures. The epileptic component is usually clonic—often running into epilepticus status—or an absence seizure, also often long. The epileptic component may also resemble a myoclonic absence. Most such children do not have epilepsy in the usual sense of recurrent unprovoked epileptic seizures: the epileptic seizures occur only after the syncope. The existence of anoxic-epileptic seizures should inhibit the casual use of the term "seizure disorder."

Conclusion

Inevitably, only the surface of the vast subject of syncope has been skimmed. However, if this chapter has whetted

an appetite for more knowledge and helped to make the diagnosis and management of syncope easier and more sympathetic, then it will have served its purpose.

Acknowledgments

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Practitioner and Patient Resources

Syncope Trust And Reflex anoxic Seizures (STARS)
P.O. Box 175
Stratford Upon Avon
Warwickshire, UK CV37 8YD
http://www.stars.org.uk
Patient and family support group for all types of syncope.

Dysautonomia Information Network
PO Box 55
Brooklyn MI 49230
http://www.potsplace.com

National Institute of Neurological Disorders and Stroke
http://www.ninds.nih.gov/health_and_medical/disorders/syncope_doc.htm
Syncope information page.

CHAPTER 69

SPINAL MUSCULAR ATROPHY

KATHRYN J. SWOBODA, MD, FACMG

"Spinal muscular atrophy (SMA)" broadly refers to a group of inherited disorders characterized by loss of α motor neurons in the spinal cord, resulting in muscular weakness and atrophy. However, SMA used specifically refers to the most common of these disorders, 5q SMA, a recessive motor neuron disease caused by mutation of the survival motor neuron (SMN) gene. This chapter provides an overview of clinical phenotypes, diagnostic approaches, and guidelines for clinical management of frequently associated problems in the most common form of the disorder.

The spinal muscular atrophies (SMAs) encompass an increasingly broad spectrum of disorders. These disorders are distinguished by their variable age of onset, inheritance patterns, distribution of muscular weakness, presence or absence of respiratory and bulbar involvement, and associated systemic and neurologic features. Table 69-1 provides a summary of these disorders, key features, associated genetic loci, allelic disorders, and causative genes if known. While both SMA and amyotrophic lateral sclerosis (ALS) phenotypes demonstrate degeneration of α motor neurons in the spinal cord, SMA phenotypes are generally distinguished from familial and sporadic forms of ALS by a more chronic and slowly progressive course, lack of upper motor neuron signs consistent with spinal cord involvement, and predominantly symmetric pattern of muscular weakness. In most forms of SMA, cognition and peripheral sensation are preserved and typical features of motor neuron disease are present including fasciculation, muscular atrophy, tremor, and diminished or absent tendon reflexes. In most of the SMA variants in Table 69-1, motor neuron disease is the predominant phenotype. However, sometimes a SMA phenotype is observed as part of a more complex disease phenotype; a good example is pontocerebellar hypoplasia type I. In addition, SMA phenotypes have also been reported in the mitochondrial depletion syndrome associated with thymidine kinase mutations and in variant late-onset GM2 gangliosidosis (Tay-Sach's Disease).

Werdnig provided the first written description of infantile SMA, in 1890, describing it as a "neurogenic dystrophy." In 1891, Hoffmann appropriately recognized it as a disorder of spinal origin. The severe infantile proximal SMA variant, SMA type I, thus carries the eponym Werdnig-Hoffman disease. Kugelberg and Welander described the later-onset, more benign forms of SMA in 1956. Clinicians subsequently began to divide patients with SMA into subgroups based on severity of disease, whether weakness was predominantly proximal or distal, age of onset, and level of motor function. The group of disorders now known as 5q SMA clearly represents the most common form of SMA. Because of the incredibly broad spectrum of phenotypic severity, and for ease of clinical classification, these have been divided as follows (Figure 69-1): SMA type I (the severe infantile variant), SMA type II (intermediate childhood variant), SMA type III (Kugelburg-Welander, ambulatory childhood variant), and SMA type IV (adult-onset variant). Dubowitz and colleagues have emphasized the continuous spectrum of the 5q SMA phenotypes, an observation further strengthened by the discovery that homozygous deletion of the survival motor neuron 1 (SMN1) gene is causative in the large majority of patients regardless of disease subtype. The incidence of 5q SMA is approximately 1 in 8,000 births and is a leading cause of infant mortality.

TABLE 69-1. Spinal Muscular Atrophies

Disorder	Defining Features	Locus/Allelic Disorders/Inheritance	Gene
Proximal SMA phenotypes			
SMA type I, Werdnig Hoffman, SMA1	proximal > distal weakness; bell-shaped chest; respiratory and bulbar insufficiency; prenatal to infantile onset	5q12.2-q13.3; SMA types II–IV	SMN1
SMA type II, SMA2	proximal > distal weakness; respiratory ± bulbar insufficiency; infantile to early childhood onset	5q12.2-q13.3; SMA types I, III, IV; recessive	SMN1
SMA type III, Kugelberg-Welander, SMA3	proximal > distal weakness; lower limb predominance; tremor; early to late childhood onset	5q12.2-q13.3; SMA types I, II, IV; recessive	SMN1
SMA type IV, SMA4	proximal > distal weakness; adult onset	5q; SMA types I–III; recessive	SMN1
SBMA, SMAX1, Kennedy disease	proximal > distal weakness; early bulbar involvement; tremor; androgen insensitivity; childhood to adult onset	Xq11-q12; benign SMA with calf hypertrophy; X-linked recessive	AR
SMA, Finkel-type	proximal > distal weakness; late adult onset	20q13.3	VAPB
Distal SMA phenotypes			
SMARD1	distal > proximal weakness; upper limb pre-dominance, infantile onset; diaphragm paralysis	11q13.2-13.4; recessive	IGHMBP2
X-linked distal SMA; SMAX2	arthrogryposis multiplex congenital; distal predominance, respiratory failure	Xp11.3-q11.2; X-linked recessive	?
X-linked distal SMA, SMAX3	distal > proximal weakness; childhood onset, pes cavus	Xq13.1-q21; X-linked recessive	?
SMAL	distal > proximal weakness; congenital benign contractures, lower extremity; early childhood onset	12q23-q24; dominant	?
Distal SMA type II, dHMN2, dSMA2	distal motor neuropathy type II childhood to adult onset	12q24	HSPB8
Distal SMA, recessive, SMAR, DSM4	distal > proximal weakness, upper limb predominance; childhood onset	11q13	?
Distal SMA type V, DSMAV	distal > proximal weakness; amyotrophy hands and feet, upper limb predominance adolescent to adult onset	11q13; SPG17; 7p15; CMT2D; dominant	GARS, BSCL2
Other SMA variants			
Scapuloperoneal SMA, SPSMA	progressive scapuloperoneal wasting; distal weakness; laryngeal palsy; childhood onset	12q24.1-q24.31; dominant	?
OPCA with SMA, PCH1	proximal infantile SMA phenotype; progressive microcephaly with pontocerebellar hypoplasia; prenatal to infantile onset	Recessive	?

AR = androgen receptor; dSMA = distal spinal muscular atrophy; OPCA = olivopontocerebellar atrophy; PCH1 = pontocerebellar hypoplasia; SBMA = spinal and bulbar muscular atrophy; SMA = spinal muscular atrophy; SMARD1 = spinal muscular atrophy with respiratory distress; SMN1 = survival motor neuron 1; SPSMA = scapuloperoneal spinal muscular atrophy; VAPB = vesicle-associated membrane protein B.

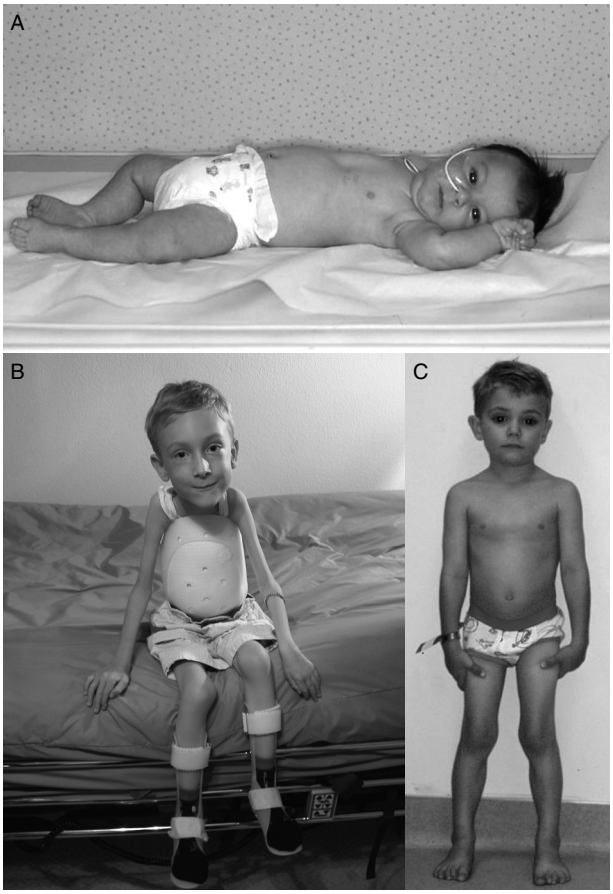

FIGURE 69-1. (A) Infant with SMA type I, (B) SMA type II, and (C) SMA type III.

The preponderance of cases demonstrates the severe infantile and intermediate childhood forms of the disease, making this one of the most common neuromuscular disorders in children.

The dominantly inherited distal forms of SMA most commonly present with symptom onset in adolescence or adulthood. An example of the expanding phenotypes and increasing complexity of the nomenclature in this group of disorders is exemplified by hereditary distal SMA type V (DSMAV, OMIM 600794). DSMAV is associated with distal amyotrophy of the hands and feet with predominate involvement of the upper limbs. However, DSMAV is now known to be allelic with Charcot-Marie-Tooth Type 2D (CMT2D, OMIM 601472), a sensorimotor polyneuropathy, for mutations in the gene encoding GARS, a glycyl-tRNA synthetase. DSMAV has also been demonstrated to be allelic with Spastic Paraplegia 17 (SPG17, OMIM 270685), a spastic paraparesis with associated motor neuronopathy, for mutations in the BSCL2 gene. Infantile-onset distal forms include SMA with respiratory distress (SMARD1), characterized by early respiratory insufficiency due to diaphragmatic paralysis, and X-linked forms with and without arthrogryposis. The remainder of this chapter will focus on identification, diagnosis, and management of children with the most common disorder, 5q SMA.

Clinical Features

Degeneration of anterior horn cells in the spinal cord and lower brainstem results in a lower motor neuron pattern of weakness and muscular atrophy of the limbs and, in more severe variants, the tongue. The pattern of weakness in the limbs is symmetric, more proximal than distal, and most severe in the lower extremities. A "piano-playing" tremor is often present but is most prominent in individuals with milder forms of the disease (SMA types II–IV). More severely affected infants and children have significant involvement of trunk muscles as well as intercostal muscle weakness and bulbar involvement. Deep tendon reflexes are decreased or absent, while plantar reflexes, if present, are normal. Intellectual capacity is normal, and sensory loss and sphincter disturbance are absent. Extraocular muscle weakness, ptosis, cardiac involvement, and loss of hearing or vision are not associated with 5q SMA. Facial muscles are typically spared until late in the disease in severely affected children.

Subclassification

Childhood-onset SMA is classified into three types on the basis of age of onset and clinical severity. The acute infantile form (Werdnig-Hoffmann or type I) is present before 6 months of age. Many infants are normal to examination within the first few weeks or months of life, although some are noted to be hypotonic at birth or to have exhibited decreased fetal movements. Children with SMA type I never attain the ability to sit, due to severe involvement of trunk muscles. Bulbar insufficiency as evidenced by poor feeding or aspiration is often an early sign, and tongue fasciculation and wasting can be an important diagnostic clue. Progression to generalized severe paresis of the limbs and trunk is often rapid, and both proximal and distal muscles are severely affected. Polyminimyoclonus (small, brief, tremulous finger movements) can be seen in infants when the forearm is supported. Intercostal weakness is most severe in this group, often resulting in the development of the classic bell-shaped chest deformity within a few weeks or months postbirth. Typically, the diaphragm is spared until late in the disease, and the respiratory pattern is characterized by paradoxical chest and abdominal movement. There is no primary involvement of cardiac muscle. The infant is visually alert, and intellectual capacity should be normal unless the child has sustained a hypoxic injury associated with a respiratory crisis. Gastrointestinal

problems including reflux, delayed gastric emptying, and constipation are frequent. Feeding difficulties, aspiration, recurrent respiratory infection, and restrictive lung disease result in death by 2 years of age in most infants in the absence of extensive respiratory and nutritional support and intervention.

Children with the intermediate form of SMA (type II or "chronic" Werdnig-Hoffmann disease) typically have onset of weakness between 6 and 18 months of age. These children may be assessed as normal during the first 6 to 9 months of life and attain the ability to sit without support. Subsequent motor development is arrested, and although they are sometimes able to cruise, they are unable to achieve the ability to walk independently. Tremor of the fingers is typical, and tongue fasciculation is present in most cases. Facial weakness is variable and is seen in the more severely affected. Bulbar dysfunction is less marked than in type I but often becomes evident as the disease progresses in later childhood. Sensory examination and cognitive function are typically unimpaired. Muscle stretch reflexes are either markedly diminished or absent. Although many have described the muscle weakness as nonprogressive or static, most patients experience increasingly severe muscle weakness, contractures, and loss of motor function over time. Impaired respiratory function occurs in the large majority of patients: restrictive lung disease manifests itself by diminished forced vital capacity, weak cough, and dependence on abdominal breathing due to intercostal muscle weakness. The diaphragm is the least severely affected muscle. Scoliosis eventually develops in virtually all children.

Survival, as in type I, is linked primarily to respiratory function, and death is usually secondary to respiratory infection or progressive restrictive pulmonary disease. Prolonged survival into the third or fourth decade and beyond with or without the need for ventilatory support may occur in this group of patients, although many still die in childhood or young adulthood as a result of respiratory complications.

Children with SMA type III (Kugelberg-Welander) most frequently present between 18 months and 17 years of age with proximal symmetric muscle weakness predominantly affecting the legs. These patients walk independently early on in the course of their disease and in many cases retain this ability well into adulthood. However, joint contractures, scoliosis and falls resulting in fracture, or excessive weight gain may result in the loss of this ability, particularly in those with onset of disease as toddlers or young children. Bulbar function is usually preserved, and respiratory failure is uncommon. Fatigue is a much more evident symptom when ambulatory capacity is preserved. This form of SMA is the most difficult to differentiate clinically from the limb-girdle muscular dystrophies, as SMA type III children often demonstrate a Gower's sign, and their creatinine kinase levels may be modestly elevated. However, tremor is usually present and can be a helpful distinguishing feature.

Since genetic testing for SMN gene deletion has become readily available, an even broader spectrum of phenotypes has been defined for 5q-linked SMA, including a severe infantile form with congenital arthrogryposis referred to as SMA type 0 and a milder adult onset form referred to as SMA type IV. Although the incidence of SMA type I is highest, accounting for an estimated 60 to 70% of cases, SMA types II and III are more prevalent in light of the limited lifespan of most children with SMA type I.

Diagnosis

SMA is inherited in an autosomal recessive pattern. Genetic testing is now readily available using a polymerase chain reaction assay that detects homozygous deletions of the SMN1 gene. However, since a small proportion of affected patients demonstrate one deletion and one point mutation, carrier testing is indicated if the clinical picture is compelling. In the event of negative carrier testing, 5q SMA is excluded with a high degree of certainty, but this should not exclude consideration of other, non-5q SMA phenotypes. If the clinical phenotype is highly suggestive of SMA, electromyographic (EMG) testing is very helpful in confirming a suspected clinical diagnosis of motor neuron disease. Typical features of EMG include preserved sensory responses, normal or diminished amplitude of compound muscle action potentials, and features characteristic of ongoing denervation and reinnervation on the needle examination. Such findings include abnormal spontaneous activity with positive sharp waves and fibrillation potentials. Motor unit recruitment is significantly decreased, and the individual motor units demonstrate increased duration, amplitude, and complexity consistent with reinnervation. The EMG varies considerably with severity of disease in that CMAP amplitudes are often preserved in the stronger type II and III subjects, while they can be markedly diminished in amplitude in type I and in weaker type II subjects. The capacity for reinnervation is clearly reduced in weaker, more severely affected subjects, while giant potentials are not infrequently seen in type III subjects. CMAP amplitudes demonstrate a correlation with motor function and, if the age of the child is taken into account, can provide some prognostic information. Muscle biopsy, now infrequently performed in the era of molecular testing, demonstrates characteristic neurogenic features including fiber type grouping and atrophy, as well as some relatively unique features often considered suggestive of myopathy. Atrophied fibers are typically grouped and consist of a mixture of small, rounded type I and type II fibers. Large grouped hypertrophied fibers are predominantly type I. Carriers are

normal clinically and on laboratory testing, unless a test for carrier status is specifically requested. Analysis of 5q SMA families supports the view that with certain exceptions, there is little phenotypic intrafamilial variability, although occasional sibling pairs may have divergent courses and different survival characteristics, especially in families with children with SMA II and III phenotypes. Prenatal molecular diagnosis for 5q-linked SMA is routinely available via chorionic villus sampling or amniocentesis. When mapping with polymorphic markers close to the SMA locus, more than 99% of 5q-linked families are informative. Appropriate allowances must be made in genetic counseling for sporadic cases due to noninherited causes and for linkage heterogeneity or misdiagnosis.

The chromosomal region including the SMN genes is complex, characterized by a 500 kb inverted duplicated region containing several nearly identical genes, present in 0 to 4 copies per chromosome. The instability of this region leads to a higher probability of gene deletion and conversion events. SMN1 is the more telomeric of the genes and varies from its centromeric copy, SMN2, by a critical base pair change in exon 7. This critical change results in alternative splicing and an altered protein product. Variable size deletions can cause de novo mutations via unequal crossing over during paternal meiosis. This appears to be the most common mechanism in SMA type I. Alternatively, unequal crossing over can result in hybrid genes whose origin initiates within SMN2, effectively converting an SMN1 to an SMN2 copy on that chromosome. Between 94 and 98% of SMA types I to III have homozygous deletions of the telomeric copy of the SMN gene SMN1. Compound heterozygotes, having a deletion and a point mutation, account for about 2 to 4% of cases. The remaining 2 to 4% of cases are unlinked to 5q. The protein is widely expressed and plays a role in premessenger RNA processing and spliceosomal ribonuclear protein biogenesis and assembly. The precise mechanisms leading to the specificity of lower motor neuron involvement and cell death in SMA remain unknown. The number of SMN2 gene copies correlates inversely with disease severity. However, although an SMN2 copy number of 2 or less is more likely to be associated with a severe infantile phenotype, predicting phenotypes on the basis of SMN2 copy number in the absence of clinical information is not advisable. Overexpression of SMN2 genes in a knock out transgenic mouse model of SMA rescues the animals from nerve cell death. The neuronal apoptosis inhibitory protein gene plays a role in motor neuron apoptosis and maps close to but outside the critical SMA region. However, parts of this gene are deleted in approximately 67% of type I SMA chromosomes, suggesting that this gene may also contribute to the SMA phenotype, although the role it plays, if any, remains uncertain.

Genetic counseling is valuable in light of the complexities of gene duplication resulting in variable SMN1 and SMN2 copy number at this locus. Formal genetic counseling provides an opportunity for parents both to discuss potential concerns regarding the risk of recurrence in future pregnancies and to become familiar with carrier and prenatal testing as well as alternative options for future pregnancies. An increasing number of adult patients with SMA are considering pregnancies of their own. Pregnancy can be a significant challenge in this setting, as it can further compromise respiratory and nutritional status, and pelvic variation may prevent vaginal delivery. SMA III subjects have an increased risk of falls, and fatigue during and after the pregnancy can greatly impact functional motor abilities. Finally, patients with SMA may also fail to recognize the risk of having an affected child of their own, given the relatively high frequency of carriers in the general population.

Management and Treatment

While there are as yet no specific pharmaceutical therapies proven to extend lifespan or increase strength in SMA subjects, the identification of compounds that can increase SMN protein in cell culture and genetic animal models of SMA is promising. Moreover, proactive management strategies to optimize respiratory function, physical mobility, and nutritional status can help preserve motor function, improve quality of life, and extend survival, particularly in more severely affected SMA infants and young children. Before and after confirmatory genetic testing is completed in an obviously severely affected infant, it is essential to work closely with parents to ensure that they understand what they may face in the months following the diagnosis, fully reviewing their options regarding supportive nutritional and respiratory interventions. This is particularly important to address early since these infants are often diagnosed in the setting of an initial respiratory event and may already have bulbar insufficiency and respiratory insufficiency. It is important that families be presented with a range of options and that quality of life for the entire family be preserved as much as possible. Many parents, when presented with options, choose to forgo invasive diagnostic and therapeutic procedures. However, others are anxious and willing to embrace a very proactive care plan if it means extending the life of their child. It is vital to maintain open communication so that all caregivers are aware of choices already made as well as areas of continuing uncertainty regarding interventions to be considered.

Proper positioning, daily passive range of motion, and use of alternative mattress systems or seating devices can enhance quality life. A flat car bed rather than a car seat is advisable for infants who rely primarily on abdominal breathing. If bulbar insufficiency is mild, thickening the

formula and positioning the infant properly can help avoid aspiration, but families of Type I infants will almost certainly need to consider some alternative means of providing nutrition. A nasogastric or nasojejunal tube is often sufficient for prolonged periods of time, allowing the family time to consider the range of options. More permanent options include gastrostomy or a combined Nissan/gastrostomy procedure. While surgery and general anesthesia clearly carry some potential risks, laparoscopic techniques are available that allow a more rapid recovery. In severely weak infants in whom general anesthesia is contraindicated, percutaneous gastrostomy with local anesthesia is an option. Given the SMA child's need to eat regularly, limiting fasting prior to such procedures, and providing nutritional support immediately afterward will help enhance recovery.

Respiratory management is a challenge, presenting the greatest risk of morbidity and mortality in severely weak infants and children. The most aggressive approach, including tracheostomy and mechanical ventilation, does nothing to prevent disease progression, and complications such as tracheitis, sepsis, and ongoing respiratory complications can compromise quality of life. Families may be pressured to make quick long-term decisions without adequate preparation when infants are intubated emergently due to respiratory crisis. However, the increasing availability of noninvasive ventilation techniques including bi-level positive pressure support (BiPaP), inexsufflator treatments (cough assist machine), percussion, postural drainage, and suction can help allow such infants to be extubated more readily than in the past, providing an intermediary between tracheostomy and withdrawal of support. Perhaps more important, however, it offers families additional options for ongoing respiratory support on a daily basis at home, thus minimizing emergency room and hospital visits, and potentially extending lifespan in more moderately affected infants. An individualized approach to respiratory infection or compromise should be developed with the child's family and updated regularly with regard to choices surrounding a need for intubation. If the family chooses palliative care, hospice provides compassionate support for such families. The use of narcotic medication in this setting to reduce discomfort, along with proper positioning and a less aggressive respiratory support regimen, in concert with the family wishes can minimize discomfort for the infant. It may be beneficial to have the family communicate with others who have experienced the loss of an infant with SMA type I during this difficult period.

Upon confirmation of a diagnosis in children with milder forms of SMA, including the infant with an as yet uncertain prognosis, it is important to work closely with parents in order to anticipate problems and pursue management aggressively to optimize outcomes. Because of the tremendous variability in phenotypes, an individualized approach is often necessary. Far too often, respiratory, nutritional, and even physical rehabilitation interventions are reactive rather than proactive. Since respiratory management can impact lifespan considerably, physicians should support families in implementing a proactive approach. While pulmonary management is often demanding, it is also the therapeutic modality that will most likely enhance quality of life and prolong lifespan. To maintain ventilatory capacity, breathing exercises and supplementary aids may be helpful. Incentive inspirometry and "breath-stacking" can be implemented at an early age but requires discipline to perform on a daily basis. Aerosol therapy with nebulizers may be helpful in some settings and can be initiated at the onset of respiratory symptoms. Benefit from the routine use of mucolytics, bronchodilators, or steroid treatments is unclear and should be dictated by individual circumstances. Cough assist devices such as the Emerson In-Exsufflator, along with postural drainage and percussion, are essential when ineffective cough inhibits adequate removal of bronchial secretions in the lower airways. Regular use of such therapies can help prevent a mild upper respiratory infection from evolving into pneumonia or a collapsed lung resulting in respiratory crisis. Even when children are well, daily use of such a regimen can help minimize atelectasis and chest wall contractures and deformity. In many children and young adults, nocturnal hypoventilation with and without obstructive apnea necessitates assisted ventilation. BiPAP can be initiated when the vital capacity falls to <40%. Recurrent nocturnal awakenings are often an indication that patients may benefit from institution of nocturnal BiPAP, and a sleep study may prove helpful in determining whether or not there is an obstructive component or whether nocturnal hypoventilation is present. BiPAP is often instituted for use only at night but can be invaluable whenever an upper respiratory infection or other illness resulting in increased fatigue is present.

Flu prophylaxis is recommended annually. In younger infants and children with significant intercostal weakness (all type I and weak type II subjects), prophylaxis for respiratory syncytial virus is also recommended. Pulmonary medicine consultation is recommended to assist in making decisions regarding long-term respiratory management. Aggressive treatment of respiratory infection is essential. Antibiotic use is of value when symptoms arising from a presumed viral upper respiratory infection persist longer than expected or new fever or altered secretions appear in the midst of an apparent viral illness. Since recurrent or prolonged antibiotic treatment can predispose patients to yeast infections or even enterocolitis, a balanced approach is needed. In the severely compromised infant or child, a lower threshold for administering antibiotics may be warranted. If illness results in persistent hypoxemia below 93%, the need for hospitalization and potential intubation should

be discussed, although many such patients can be managed effectively in hospital using a noninvasive respiratory protocol. Oxygen therapy should only be used in conjunction with assisted ventilation in such patients as it can suppress respiratory drive, resulting in atelectasis and hypercarbia.

Maintenance of appropriate nutrition is critical during illness. SMA subjects have diminished lean body mass and a secondary defect in fatty acid oxidation that limits their reserve in the setting of prolonged fasting. Thus, when concerns regarding the ability to safely administer oral feeds develop, alternative forms of nutrition should be considered. Options include temporary nasogastric or nasojejunal feeds or peripheral or total parenteral nutrition.

Treatment for the intermediate or milder forms of SMA should be focused on preserving mobility and minimizing respiratory complications, particularly restrictive pulmonary disease or respiratory compromise due to progressive scoliosis. Specific interventions can be helpful in optimizing the individual's health and helping to maintain motor function. Physical therapy on a daily basis, performed by parents with appropriate direction from a physical therapist, can help minimize joint contractures and maintain mobility. The use of standing devices, appropriate orthotics, bracing, and facilitated ambulation can help significantly in this regard. Weight bearing on a daily basis, instituted as early as possible in nonambulatory children for a minimum of 2 hours per day, can help delay onset of scoliosis, limit contractures, and improve circulation and gastrointestinal motility. Daily exercise should be encouraged, to include the upper extremities in those children with severely impaired lower extremity function, to help maintain motor function and promote cardiovascular health. A daily exercise program could include part-time use of manually propelled mobility devices. The major orthopedic problems these children face include scoliosis, hip dislocation, and an increased risk of fracture due to decreased bone density and propensity for falls. The age of onset and rate of progression of such complications are directly related to the severity of muscle weakness, but early intervention can minimize the impact and severity of such problems. Contractures can develop quite rapidly in the setting of illness, excessive time spent in a wheelchair, decreased activity, or recovery after scoliosis surgery or other orthopedic procedures. Daily range of motion and early return to supported weightbearing can help maintain function in these children.

Scoliosis almost invariably begins in the first decade of life in SMA type II and in a substantial proportion of children with SMA type III. The curves progress over time, sometimes quite rapidly during transition to increased wheelchair use or in conjunction with a growth spurt. In nonambulatory patients, spinal bracing may improve sitting stability, as long as care is taken not to compromise abdominal movement in those with intercostal muscle weakness. However, continuous use of such bracing should be limited if possible in order to maintain trunk strength and mobility. Periodic pulmonary function studies help establish a profile for the individual patient, allowing design of the most appropriate care plan surrounding respiratory care in the postsurgical period. Since worsening is invariable, once the curve reaches 40° a decision to intervene early may be warranted. When very young patients develop scoliosis, bracing can sometimes help defer surgery for variable periods of time, and "growth rods" or other means of accommodating growth may be indicated.

Proximal muscle weakness predisposes patients to progressive subluxation and dislocation of the hip. Subsequent hip degeneration can result in significant chronic pain. In nonambulatory patients, it is important to prevent the hips from dislocating for reasons of comfort, good sitting balance, and maintenance of pelvic alignment. To achieve an optimal result, operative intervention may be required in some cases. Patients who have type III SMA and are still able to walk present a difficult management problem. These patients are also prone to subluxation of the hip due to significant proximal muscle weakness. However, because surgical intervention with proximal femoral varus osteotomy may result in additional weakening of the abductor muscles, the physician should be cautious in recommending such surgical procedures in an ambulatory patient. Since these patients rely to a great extent on lumbar lordosis and a side-to-side waddle to walk, bracing or spinal arthrodesis may worsen their gait. It is not uncommon for SMA type III patients to become nonambulatory following spinal surgery, particularly if a rehabilitation plan is not instituted immediately in the postoperative period. Joint contractures can progress quite rapidly in this setting without dedicated prevention. In a subset of cases in which ambulatory status is considered at risk, postponement of surgery may be the best choice.

Truly effective treatments for SMA may soon become a reality as we gain a better understanding of disease pathogenesis. Clinical trials to assess compounds that increase SMN protein levels in cell and animal models have begun. In the meantime, a proactive management strategy can help limit disease progression and optimize outcome. Undoubtedly, intervening as early as possible in the disease process will prove most effective as additional therapeutic strategies are identified.

Summary

SMA should be considered in any infant or child who presents with muscle weakness, diminished or absent reflexes, normal sensory examination, and preserved cognition. The SMAs are distinguished by their variable age of onset, inheritance patterns, distribution of muscular weakness, presence or absence of respiratory and bulbar involvement, and associated systemic and neurologic features. The most

common form of SMA is the autosomal recessive disease linked to 5q, associated with deletions of the SMN1 gene in >95% of cases. Confirmatory diagnostic, prenatal, and carrier testing is widely available via molecular testing. If such testing proves negative, consideration of alternative SMA phenotypes and additional electrodiagnostic and pathologic assessment to confirm a motor neuron disease may be warranted. The therapeutic approach is defined by the type of SMA and its associated features and anticipated complications. A proactive management approach is invaluable in optimizing outcomes as increasingly effective therapies are developed.

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Practitioner and Patient Resources

Families of Spinal Muscular Atrophy
<http://www.fsma.org>

FightSMA
<http://www.fightsma.com>

Genetests
<http://www.genetests.org>

Muscular Dystrophy Association
<http://mdausa.org>

Online Mendelian Inheritance in Man
<http://ncbi.nlm.nih.gov/omim>

SMA Foundation
<http://www.smafoundation.org>

SMA Support
<http://www.smasupport.com>

CHAPTER 70

HEREDITARY NEUROPATHY

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In this chapter, we review current knowledge regarding inherited peripheral neuropathies, emphasizing the clinical examination, electrodiagnostic testing, and genetic evaluation. Correlation between genotype and phenotype will facilitate an understanding of the pathogenesis of these disorders.

This chapter reviews current ideas regarding clinical evaluation, genetics, and molecular pathogenesis of hereditary neuropathies. Acquired neuropathies (mostly immune mediated), neuropathies secondary to systemic disease (diabetes and vasculitides), primary motor neuron degenerations (spinal muscular atrophies), and disorders in which neuropathy is part of a more widespread neurologic disorder (leukodystrophies, mitochondrial disorders, lipoprotein deficiencies, Fabry's disease, porphyrias, and hereditary ataxias) are considered elsewhere. The genetic defects underlying many of the hereditary neuropathies have been determined and others are under investigation, accounting for the continually changing classification of the inherited neuropathies.

Early classification schemes were based on clinical features (age of onset, inheritance pattern, and presence of hypertrophic nerves), results of electrodiagnostic tests (separating demyelinating from axonal processes), and pathological features on nerve biopsy. This led to a classification into clinical subtypes: hereditary motor and sensory neuropathies (HMSNs), hereditary motor neuropathies (HMNs), and hereditary sensory and autonomic neuropathies (HSANs). The best-recognized clinical HMSN syndromes are Charcot-Marie-Tooth (CMT) disease (demyelinating and axonal types), Dejerine-Sottas disease (DSD), hereditary neuropathy with susceptibility to pressure palsies (HNPP), and congenital hypomyelinating neuropathy. There is a more-or-less parallel genetic classification into CMT subtypes (Table 70-1), but one needs a fairly complex table to see the correspondence between the clinical and genetic classification schemes. Clinical and genetic heterogeneity confound the classification problem. For instance, several genes (*PMP22, MPZ*, *EGR*) can result in the demyelinating HMSN I phenotype, and different mutations in a given gene can cause distinct clinical syndromes (either HMSN I, DSD, or HNPP). Ultimately, the classification scheme will be based entirely on the underlying genetic defect, which attempts to correlate genotype with phenotype, and relates the gene defect to pathogenesis. Because of the multitude of genes that have been discovered, it has become even more important for the clinician to formulate an optimal and cost-effective diagnostic plan on the basis of clinical features.

Clinical Syndromes

CMT is the most common inherited peripheral neuropathy, with a prevalence of 1/10,000 to 4/10,000. Clinical symptoms appear in the first or second decade, with slowly progressive distal weakness and atrophy, particularly of the small muscles of the foot and peroneal muscles. This is responsible for the typical foot drop and the high-step gait characteristic of these patients. Atrophy due to wasting of the peroneal muscles results in the inverted "champagne bottle" appearance of the leg. Progression can lead to hand and forearm atrophy, often with a "claw-hand" deformity. These features are accompanied by distal sensory deficits and loss of deep tendon reflexes.

The autosomal dominant forms of CMT can be divided into two groups on the basis of results from electrophysiologic studies: (1) *CMT1*, with features suggesting demyelination as the primary pathology and symptom

TABLE 70-1. Gene Mutations and Clinical Syndromes in Hereditary Neuropathies

Clinical Subtype	Inheritance	Gene	Locus	Clinical Features
Demyelinating Neuropathies				
CMT1				
CMT1A	AD	*PMP22*	17p11	Onset in 1st to 2nd decade; distal weakness, atrophy, and sensory loss, gene duplication
HNPP	AD	*PMP22*	17p11	Focal neuropathies, entrapment syndromes tomacula, gene deletion
CMT1B	AD	*MPZ*	1q22	More severe than CMT1A; 30% primary axonal pathology
CMT1C	AD	*LITAF/SIMPLE*	16p13	Marked reduction in mNCV, temporal dispersion, and conduction block
CMT1D	AD	*EGR2*	10q21	Variable severity
CMT-X	XR/XD	*GJB1/Cx32*	Xq	Distal atrophy, males more severe than females
CMT3				
DSD	AD	*PMP22, MPZ GJB1, EGR2, NEFL*		Delayed motor development by age three. Severe distal motor disease with severe large Fiber sensory loss
	AR	*MTMR2, PRX*		
CHN	AD	*PMP22, MPZ, EGR2*		Hypotonia at birth, delayed motor development
	AR	*EGR2*		
CMT4				
CMT4A	AR	*GDAP1*	8q21.1	Early childhood onset, loss of mobility over time
CMT4B1	AR	*MTMR2*	11q23	Milder than CMT4A, focally folded myelin
CMT4B2	AR	*MTMR13/SBF2*	11p15	Childhood onset, glaucoma, focally folded myelin
CMT4C	AR	*SH3TC2*	5q23-q33	
CMT4C4	AR	*GDAP1*	8q21.1	
CMT4DLom	AR	*NDRG1*	8q24	In gypsies, hearing loss, dysmorphic severe disability by age 50–60
CMT4E	AR	*EGR2*	10q21	Infantile onset, early loss of mobility
CMT4F	AR	*PRX*	19q13	Infantile onset, progression to wheelchair dependency
CMT4R	AR	??	10q23	
Axonal Neuropathies				
CMT2				
CMT2A1	AD	*KIF1B*	1p35-p36	Onset by age 10, motor greater than sensory, feet
CMT2A2	AD	*MFN2*		Early onset, severe disease, optic atrophy
CMT2B	AD	*RAB7*	3q13-q22	Onset in 2nd to 3rd decade, severe sensory symptoms with ulcers
CMT2C	AD	*HSPB8*	12q24	
CMT2D	AD	*GARS*	7p15	Onset in 2nd decade, atrophy and weakness in hands with sensory and leg symptoms occasionally
CMT2E	AD	*NEFL*	8p21	Variable onset and severity
CMT2-P0	AD	*MPZ*	1q22	Onset in 3rd decade, pain hearing loss, and abnormal pupil reaction
AR-CMT2A	AR	*LMN-A/C*	1q21	Onset in 2nd decade, eventual severe distal weakness
GAN	AR	*Gigaxonin*	16q24	Onset in 1st decade, giant axons with neurofilament CNS involvement
Sensory/Autonomic Neuropathies				
HSAN 1	AD	*SPTLC-1*	9q22	Onset in 2nd to 3rd decade, ulceration distally, lancinating pain, sensory loss, and distal weakness
HSAN 3	AR	*IKBKAP*	9q31	Riley-Day syndrome, neonatal onset, autonomic
HSAN 4	AR	*NTRK-1*	1q22-q23	Congenital insensitivity to pain, anhidrosis and mental retardation

AD = autosomal dominant; AR = autosomal recessive; CMT = Charcot-Marie-Tooth; CNS = central nervous system; GAN = giant axonal neuropathy; HNPP = hereditary neuropathy with susceptibility to pressure palsies; HSAN = hereditary sensory and autonomic neuropathy; mNCV = motor nerve conduction velocity.

onset in the first or second decade, and (2) *CMT2*, with features suggesting a primary axonal process and later onset of symptoms. An X-linked form also exists, *CMTX*, in which affected males exhibit a more severe phenotype and slower motor nerve conduction than female carriers.

DSD can be viewed as a more severe form of demyelinating neuropathy, with onset in infancy. The term "DSDlike neuropathy" is used to describe such patients with severe and early onset symptoms but without signs of demyelination on electrophysiologic studies.

Congenital hypomyelinating neuropathy (CHN) implies onset at birth. It is characterized by infantile hypotonia, distal weakness, and areflexia, with very slow motor nerve conduction. The muscle weakness and atrophy is due to axonal degeneration, even in the demyelinating neuropathies. The main histologic findings in the peripheral

nerves of demyelinating forms of CMT are (1) segmental demyelination, (2) thin myelin sheaths, (3) cycles of demyelination and remyelination that cause "onion bulb" formation, and (4) Schwann cell and connective tissue proliferation, resulting in hypertrophied nerves.

Hereditary neuropathy with liability to pressure palsies (HNPP) is quite distinct from the CMT syndromes. It is also inherited in an autosomal dominant fashion, with symptom onset in the third to fourth decade. The symptoms are usually caused by painless focal peripheral nerve lesions after minor compression, which typically occurs where the nerve is exposed to pressure (head of the fibula, carpal tunnel). Biopsied peripheral nerves show focal thickenings, sausage-shaped enlargements called tomacula.

Clinical Approach

As with any other neurologic problem, a careful history and physical examination are essential in evaluating patients with suspected peripheral neuropathy. In children, this should be considered in the differential diagnosis when the complaint is weakness or muscle wasting, delay in achieving motor milestones, clumsiness or ataxia, gait disorder, foot or wrist drop, tingling or numbness, foot deformity, toe walking, or hypotonia and feeding or breathing difficulties in the neonate. It is absolutely essential to obtain a detailed family history, including questions about the presence of foot deformity, use of a cane or other aid for walking, orthopedic surgical procedures, and use of splints or supports as a child. When possible, family members should also be examined and studied. History and physical examination alone frequently allow exclusion of brain or spinal cord lesions from the differential diagnosis. However, clearly distinguishing between muscle disease, disorders of the neuromuscular junction, and demyelinating versus axonal neuropathy might not be possible on the basis of clinical examination alone. One example where such difficulty arises is in a child with distal muscle weakness and atrophy. Electrodiagnostic testing (nerve conduction studies and electromyography [EMG]) plays a crucial role in the evaluation of these patients.

In most cases, the history alone is sufficient to decide if one is dealing with an acquired disease rather than an inherited neuropathy. The classic exceptions are the rare indolent course of chronic inflammatory demyelinating neuropathy (CIDP) and acute focal neuropathy due to HNPP. Electrodiagnostic testing is also useful in distinguishing acquired from inherited neuropathies. Nerve biopsy is reserved for sporadic cases when electrophysiologic studies are not helpful. The nerve biopsy may exclude acquired disorders (inflammatory disorders or focal tumors) and provide clues to the primary pathology involved, when electrophysiologic studies are not diagnostic.

Electrodiagnostic Testing

To minimize discomfort to the patient, electrophysiologic studies are planned as an extension to and in the context of the clinical examination. Electrophysiologic studies should not only confirm a peripheral disorder, but also localize it to the peripheral nerve, to the spinal motor neuron or motor nerves, to the neuromuscular junction, or to the skeletal muscle. In addition, electrophysiologic studies should categorize the primary pathological process as a demyelinating or an axonal process and help to exclude the rare acquired treatable neuropathies, such as CIDP. The primary pathology identified then may direct the search for genetic cause.

Motor conduction studies and EMG are best done after sensory nerve conduction studies. One could study sensory nerve action potentials (SNAP) by stimulating a mixed nerve and recording distally over a cutaneous branch or vice versa. A pure sensory nerve also could be studied this way. The SNAP recorded represents the summated action potentials of individual fibers. A reduction in SNAP amplitude or slowing of conduction, confirmed in more than one nerve, would localize the process to the peripheral sensory nerve or sensory ganglion. This alone is sufficient to confirm a polyneuropathy, in the appropriate clinical context.

The compound motor action potential (CMAP) is the summated electrical activity recorded from synchronously activated muscle fibers by stimulating the motor axons innervating that muscle (motor nerve conduction studies). By performing distal and proximal supramaximal stimulation on a motor nerve while recording from an innervated muscle, one may determine the distal latency and conduction velocity proximally. More proximal motor conduction velocity in the proximal nerves and roots can be measured by the recording F-wave. The CMAP amplitude provides a physiologic assessment of the motor axon, neuromuscular junction, and muscle fiber activated by the stimuli, and thus is affected by disease at any one of these sites. Significant slowing of conduction (prolonged distal latency, slowing of proximal conduction velocity, or delayed F-wave latencies) and the phenomenon of dispersion and conduction block suggests a demyelinating process and localizes the pathology to the motor components of the peripheral nerves. Studies in two motor nerves are often sufficient to determine these features. Because motor conduction velocity may be normal in axonal neuropathies, the lack of features of demyelination does not exclude a peripheral nerve process. Thus, abnormal motor nerve conduction also helps to determine the underlying pathological process in a patient with peripheral neuropathy.

EMG becomes necessary only when abnormalities of the SNAP or motor nerve conduction have not been seen, essentially to distinguish myopathies from pathological processes that affect the motor neuron or axon. For this purpose, we

sample a proximal and distal muscle in an upper and lower extremity. The electrical activity of motor units recorded with a needle electrode in a muscle is derived from action potentials of the muscle fibers that are firing singly or in groups near the electrode. Fibrillation and positive sharp waves are spontaneous pathological discharges from individual muscle fibers. Although their presence can easily confirm a peripheral nervous system disorder, they are not useful in distinguishing a primary myopathy from a neurogenic process affecting the muscle. This is achieved by an assessment of the voluntary motor units and their activity, to identify *myopathic* or *neuropathic* potentials. In general, short, low-amplitude motor unit potentials that are rapidly recruited to produce a given force resulting in a full interference pattern on the screen suggest a myopathic process. In contrast, reduced recruitment where fewer motor units have to fire more rapidly to generate a given force is suggestive of a neurogenic process, especially when the motor units show features of reinnervation, such as long duration and high amplitude.

Demyelinating or Axonal Neuropathy

The primary function of myelin is to increase axonal conduction velocity without a significant increase in axonal diameter. This function is achieved by the process of saltatory conduction, in which nerve impulses jump between electrically excitable regions of the axon, called nodes of Ranvier, located between the electrically insulated areas ensheathed by myelinating Schwann cells. A demyelinating process results in local or ephaptic nerve conduction that is slow. It is often accompanied by remyelination, resulting in reduced internodal length, also slowing saltatory conduction. Sensory responses are often too small or absent in polyneuropathies to reliably suggest a demyelinating process. The electrophysiologic abnormalities of a primary demyelinating process—slowing of nerve conduction, dispersion, and conduction block—are best seen in motor nerves. If slowing of greater than 25% is seen in the various measures of motor nerve conduction in two nerves, a primary demyelinating process can be diagnosed. In the absence of such slowed conduction, when a peripheral nerve process has been confirmed by sensory nerve studies, an axonal polyneuropathy is diagnosed.

Most demyelinating neuropathies eventually show secondary axonal loss, resulting in a very small or absent CMAP, where conduction velocities cannot be measured. Conversely, severe axonal neuropathies, with very low CMAPs, may show conduction slowing greater than 25%, making the determination of the primary process and classification difficult. In chronic inherited neuropathies, the last distal muscle to atrophy is the abductor digiti minimi. Thus, ulnar nerve conduction studies may be the only ones with velocities that permit appropriate classification of the disease. The ulnar nerve is also the initial motor nerve studied in the context of an inherited polyneuropathy. EMG is usually not necessary in the diagnostic evaluation of a patient with an inherited neuropathy. However, fibrillation and positive sharp waves are usually seen in either the axonal neuropathies or in the late stages of demyelinating neuropathies. This may also be of some help in classi fying the disorder.

Clues to an Acquired Neuropathy

In an isolated, sporadic patient, it is important to exclude a treatable process. Scattered demyelination, rather than uniform demyelination, favors an acquired disease process, such as CIDP. Scattered demyelination results in variable slowing in different nerves, different segments of the nerves (preserved distal latency, with slowing of the proximal conduction velocity and F-wave latency), and only in some of the nerve fibers in a given segment of the nerve resulting in dispersion or conduction block. In inherited demyelinating neuropathies, the degree of slowing would be nearly identical in distal latency, conduction velocity, and F-wave latency in all the nerves with a lack of dispersion or conduction block, reflecting a uniform pathology (see Table 70-1 for exceptions). It is nearly impossible to distinguish an inherited from an acquired process in patients with an axonal neuropathy on the basis of electrophysiologic criteria. However, multifocal abnormalities recorded in nerve conductions studies usually points toward an acquired process, with the exception of HNPP.

Genetic Lesions

The genetic basis of many forms of inherited neuropathy has been determined (see Table 70-1) and has identified over 30 different genes. The corresponding genes and proteins have been implicated in Schwann cell function (myelination and axon trophic function) or in axonal function (structure of axonal components and axon transport). This has led to an improved understanding of the pathogenesis of the various polyneuropathies. In some cases, the discovery of the causative gene has not led to clarification of the mechanism of pereipheral nerve dysfunction (Scherer 2006). A comprehensive and constantly updated database of mutations in inherited peripheral neuropathies, the Inherited Peripheral Neuropathy Mutation Database (IPNMDB), is maintained by Nelis and colleagues <http://molgenwww. uia.ac.be/CMTmutations>.

PMP22

In 1991, genetic linkage studies in autosomal dominant demyelinating neuropathy (CMT1) located a causative gene at chromosome 17p11.2-p12. The defect was an

intrachromosomal duplication of a 1.5 Mb segment of 17p11.2. Analysis of two murine mutant models of CMT, Trembler (Tr) and Trembler-J (Tr-J), led to the identification of the peripheral myelin protein 22 (*PMP22*) gene. This gene was then shown to be contained within the chromosomal segment duplicated in CMT1. Different types of mutations of *PMP22* result in different clinical syndromes, including CMT1, HNPP, and DSD.

The most common mutation in autosomal dominant CMT1, occurring in about 70% of these cases, is the heterozygous 1.5 Mb tandem duplication that includes *PMP22*. This results in increased *PMP* dosage (three copies of the gene) and is associated with the CMT1 phenotype. Homozygosity for the duplication (four copies of the gene) causes a very severe, early-onset phenotype (DSD-phenotype).

The 1.5 Mb segment is flanked by highly homologous proximal and distal tandem repeat sequences. As a result of unequal crossing over during gametogenesis, one haploid gamete contains a duplication, while the other contains a deletion. This reciprocal deletion of the same 1.5 Mb segment causes a different phenotype, HNPP. This deletion is detected in about 85% of patients with HNPP. These patients are haploinsufficient and have reduced *PMP22* dosage (single copy). Smaller deletions, but still including the coding region of *PMP22*, have also been associated with the HNPP phenotype. This suggests that the level of expression of the PMP22 protein is a critical factor in the maintenance of the myelin sheath.

A total of 56 other PMP22 mutations have been cataloged in the IPNMDB, and most of these are missense point mutations. Of these, 25 result in the CMT1 phenotype (with or without hearing impairment), 16 in the DSD phenotype, 13 in the HNPP phenotype, and 2 in the CHN phenotype. The remaining eight mutations that cause the HNPP phenotype are either small deletions that result in a frame shift, nonsense mutations, or splice site mutations. This is consistent with the idea that mutations that result in a single functional allele cause HNPP. The other point mutations must result in a gain-of-function that mimics the increased gene dosage of the gene duplication.

Naturally occurring murine mutants recapitulate the pathology seen in human patients. The Trembler (G150D) acts via a gain-of-function or dominant negative mechanism and causes a severe hypomyelination with onion bulb formation, similar to DSD patients with the same G150D mutation. The Trembler-J (L16P) has been identified in CMT1 patients, and the pathology in the Trembler-J mice is similar to that seen in human CMT1 patients.

Myelin Protein Zero

Myelin protein zero (MPZ) is the most abundant protein of peripheral myelin and is a transmembrane protein with a single extracellular immunoglobulin domain. It functions as a homophilic adhesion molecule in the formation of compact myelin. The extracellular domain is important in formation of the minor dense line of myelin, and the cytoplasmic domain is important in formation of the major dense line. The human *MPZ* gene is located at chromosome 1q22-q23.

One form of CMT1 (designated CMT1B) was linked to the Duffy blood group antigens on chromosome 1q22-q23 in 1982, but it took another 11 years to demonstrate mutations in *MPZ* in both CMT1 and Dejerine-Sottas families. Just as was the case with *PMP22* mutations, several phenotypes have been associated with *MPZ* mutations, including autosomal dominant demyelinating neuropathy (CMT1B, DSD, or CHN), and autosomal dominant axonal neuropathy (CMT2). About 100 different point mutations (missense, nonsense, and frameshift) in *MPZ* have been described, with the majority resulting in either the CMT1 phenotype (55 mutations) or the more severe DSD phenotype (20 mutations). Two are associated with CHN, and 9 with the CMT2 (axonal neuropathy) or an intermediate phenotype. The question of why certain point mutations cause demyelination and others primarily axonal dysfunction is not understood.

EGR2

Early growth response gene (*EGR2*, chromosome 10q21-q22) is a zinc finger transcription factor. Transgenic mice in which the murine orthologue Krox20 is knocked out show abnormalities of hindbrain development and peripheral myelination. In these knockout mice, Schwann cells are arrested at an early stage of differentiation and do not express many of the late myelin protein genes, including *PMP22*, *MPZ*, connexin 32, and periaxin. This results in a severe hypomyelination. Mutations in *EGR2* were found in patients with a severe demyelinating neuropathy phenotype (CMT1, DSD, or CHN), and 12 distinct mutations are catalogued in the IPNMDB. Familial cases with dominant inheritance, *de novo* mutations in sporadic cases, and recessive (homozygous) mutations have been described. Mutations in the zinc-finger deoxyribonucleic acid (DNA) binding domains cause a loss of transcription factor activity but act in a dominant fashion (ie, heterozygous state), suggesting a dominant negative effect. A recessive mutation presenting as CHN has also been described. This mutation (Ile268Asn) causes an increase in transcriptional activity of *EGR2*, perhaps affecting levels of myelin protein messenger ribonucleic acids (mRNAs) by a gene dosage effect.

GJB1 and Connexin 32

Gap junction protein, beta one (*GJB1*) gene, encoding the connexin 32 protein, is currently the only identified

Xchromosome gene implicated in peripheral neuropathies. Connexin 32 is expressed in myelinating Schwann cells, and is localized to the paranodal loops and Schmidt-Lanterman incisures. Connexins oligomerize to form connexons, which then form channels allowing transport of small molecules between the Schwann cell body and the periaxonal region of the myelin sheath. Connexins may thus play a role in maintenance of the myelin sheath, or may permit transport of molecules that are important in axon–Schwann cell interaction.

Mutations in *GJB1* cause CMTX, which can be either X-linked dominant or recessive, and have a demyelinating or axonal phenotype. In some families, the distinction between autosomal and X-linked inheritance may be difficult—female carriers may have a subclinical neuropathy, leading to the conclusion of X-linked recessive instead of dominant inheritance. Male-to-male transmission within a family would exclude X-linked inheritance. CMTX is the second most common form of CMT, after the dominant form caused by *PMP22* gene duplication. In most cases, males are more severely affected than females, with motor nerve conduction velocities (mNCVs) in the 25 to 40 m/s range, whereas female carriers have mNCVs between 25 and 50 m/s. About 265 different mutations in *GJB1* have been reported to date and include missense, frameshift, and nonsense mutations, small and large deletions, and noncoding region mutations. Some mutations result in a loss-of-function (severe phenotype), whereas others result in functionally altered channels (milder phenotype).

LITAF

A rare form of autosomal dominant demyelinating neuropathy, CMT1C, was localized to chromosome 16p13.1-p12.3. The responsible gene has been identified as *LITAF* (lipopolysaccharide-induced tumor necrosis factor-, also known as *SIMPLE*), a protein component of lysosomes and endosomes. The mechanism by which this mutation causes demyelination is not clear but it has been suggested that this protein might function in the ubiquitin-mediated proteasome processing pathway.

Autosomal Recessive Forms of CMT: Mutations in *GDAP1*, *MTMR2*, *NDRG1*, and Periaxin

Autosomal recessive forms of demyelinating peripheral neuropathy, classified as subtypes of CMT4, are rare. Genetic studies in a few families (often in isolated populations) have led to identification of mutations in several genes. These include *GDAP1* (ganglioside-induced differentiation-associated protein 1) located at 8q13-q21; *MTMR2* (myotubularin-related protein 2) located at 11q23; *NDRG1* (N-myc downstream-regulated gene 1); and *PRX* (periaxin) located at 19q13. Mutations in GDAP1 can also cause an axonal neuropathy phenotype (CMT2), and mutations in the periaxin gene can cause the Dejerine-Sottas phenotype. The onset of symptoms in these recessive forms is typically in early childhood, with progression to wheelchair-dependence. Nerve biopsies typically show demyelination and onion-bulb formation, except in *MTMR2* defects, which show focal infolding and redundant loops of the myelin sheath. The precise function of these genes in myelination is unknown.

Inherited Axonal (CMT2) Neuropathies: *KIF1B*, *NEFL*, *RAB7*, and *LMNA*

The axonal neuropathies can be inherited in an autosomal dominant or a recessive fashion and are characterized by normal or near normal mNCVs. They are about one-half as prevalent as the demyelinating form of CMT. As mentioned above, mutations in MPZ/P0, GDAP1, GJB1/Cx32 can result in an axonal neuropathy phenotype. In addition, mutations have been described in *KIF1B* (kinesin family member 1B), *NEFL* (neurofilament light chain), *RAB7* (an RAS-related GTPase), and *LMNA* (lamin A/C), MFN2 (mitofusin 2) and GARS (glycyl-tRNA synthetase). Initial reports of *NEFL* mutations were associated with an axonal neuropathy, but subsequent reports suggest a demyelinating form as well. KIF1B, like other kinesins, plays an important role in axonal transport, and neurofilament is a major component of the neuronal cytoskeleton. Mutations in these genes might, thus, disrupt normal axonal function. The exact mechanism by which mutation of RAB7, LMNA, and GARS leads to axonal neuropathy is unknown. A recent study reports that mutations of mitofusin 2 (MFN2) are the most common cause of the hereditary CMT2 phenotype, with over 40 distinct mutations. Mutations of MFN2 also cause the form of CMT2 that is associated with optic atrophy. Mitofusin is a dynamin-like GTPase that acts in the fusion of the mitochondrial membranes, stressing the importance of mitochondria in both axonal and retinal function.

Sensory and Autonomic Neuropathies: *SPTLC1*, *IKBKAP*, and *NTRK1*

The most prevalent form of hereditary sensory neuropathy is caused by mutations in *SPTLC1* (serine palmitoyltransferase, long chain base subunit 1) located on 9q22. It is characterized by distal lancinating pain, ulcerations, and a severe distal sensory deficit in pain and temperature sense. *SPTLC1* codes for an enzyme involved in sphingolipid synthesis.

Familial dysautonomia or Riley-Day syndrome, an autosomal recessive disorder mapped to 9q31, is caused by mutation in the *IKBKAP* gene (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex–associated protein). This disorder is characterized by neonatal feeding difficulty and autonomic problems (temperature, sweating, blood pressure).

Congenital insensitivity to pain and anhidrosis (CIPA) is also an autosomal recessive disorder, characterized by unexplained fever, anhidrosis, and absence of reaction to pain. This disorder is caused by mutations in *NTRK1* (neurotrophin tyrosine kinase, receptor, type 1), a receptor nerve growth factor. Around 30 different point mutations (missense, nonsense, and splice site) of the *NTRK1* gene have been described in CIPA. Mice with the *NTRK1* gene knocked out have a similar phenotype.

An Approach to Genetic Testing

There are several reasons for pursuing an accurate genetic diagnosis. Genotype–phenotype correlations: (1) allow for anticipation of the clinical course of the disease, (2) permit (noninvasive) testing and counseling of at-risk individuals in families, and (3) allow for preimplantation or *in utero* diagnosis and appropriate genetic counseling. Currently, mutation analysis of seven hereditary neuropathy genes is available commercially but at a cost that is significantly higher than the cost of a discerning electrophysiologic study. There are few clinical clues in nonsyndromic neuropathies that allow one to restrict the number of genes to be tested. Soon, the number of genes related to HMSN will be so numerous that an economical, efficient, DNA chip–based method for mutation identification will become available. One possible approach to molecular diagnosis of hereditary neuropathy is presented in Figure 70-1.We incorporate clinical, electrophysiologic, histopathologic, and genetic tests in our approach:

- If the neuropathy is part of a systemic disorder or is associated with central nervous system involvement, other investigations are necessary.
- Does electrodiagnostic testing confirm a neuropathy and suggest a pathogenic mechanism (demyelination or axonal)?
- Are there clinical or electrophysiologic features to suggest an acquired, treatable disorder?
- What is the likely mode of inheritance?
- Specific gene testing (commercial or clinical lab):
  - Commercial genetic testing has the highest yield when electrophysiologic studies identify a demyelinating neuropathy.
  - Electrical features of an axonal neuropathy may be seen as a result of mutations in the genes more commonly associated with demyelinating neuropathy (*GJB1*, *P0*, and *GDAP*).
  - If the inheritance pattern were known with certainty, genetic testing after electrophysiologic studies could be more selective. Sequential evaluation of these genes based on the frequency of that particular gene abnormality for the type of pathology in the ethnic group being studied would be the ideal approach, rather than the "shotgun" approach offered commercially.
  - If the electrophysiologic studies are unable to characterize the pathology in a sporadic case, genetic tests are unlikely to yield a diagnosis.
- Evaluating the other genes in research laboratories as part of a research study may yield results, if there are additional clinical or histopathologic clues that implicate a specific gene (see Figure 70-1). A good example of this would be *CMT2D*.

Management

During the past 15 years, the genetic basis of many hereditary neuropathies has been identified or mapped. The process of mutation detection should become even faster with the improvements in genomic technology. The information relating gene mutations to clinical phenotype has already provided insights into the molecular mechanisms of disease pathogenesis, but much work remains to be done.

Treatment of patients with such hereditary neuropathies is limited to physical therapy and prevention or delay of complications. Physical therapy and exercise are aimed at minimizing the weakness and atrophy of affected muscles and at preserving range of motion and preventing joint contractures. Orthotic devices are useful in correcting the foot drop and in optimizing hand use. Selected patients benefit from arthrodesis in the feet, by tendon transfer surgery, and release of contractures to reduce deformity and to improve mobility and dexterity.

Summary

Inherited peripheral neuropathies are quite prevalent (about 1:2,500) and are clinically and genetically heterogeneous. Clinical history and physical examination lead to the suspicion of a peripheral neuropathy. Family history is crucial not only in suggesting a genetic cause, but also in distinguishing autosomal dominant from recessive and Xlinked patterns of inheritance. Electrodiagnostic testing plays a vital role in differentiating a hereditary neuropathy from rare acquired (treatable) neuropathies and also allows differentiation between a demyelinating process and an axonal process. The most common genetic lesions are duplication or reciprocal deletion of a 1.5 Mb segment of chromosome 17p11.2 containing the *PMP22* gene, causing the CMT1 phenotype or the HNPP phenotype, respectively. Mutations of *GJB1* causing an X-linked dominant or reces-

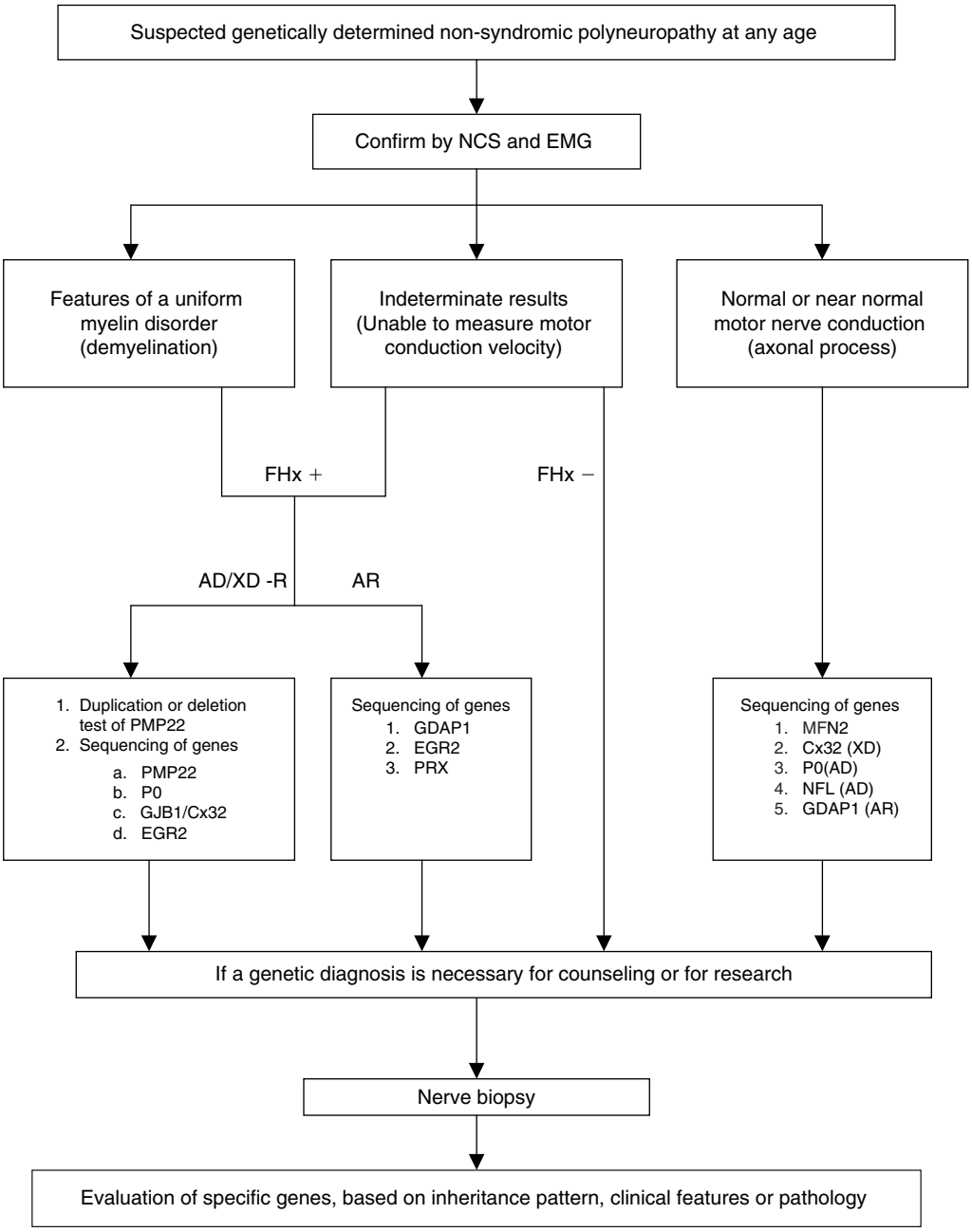

FIGURE 70-1. Flow chart for clinical evaluation and molecular diagnosis of inherited neuropathies.

sive neuropathy and mutations of *MPZ* and *EGR2*, are all associated with a demyelinating neuropathy. Genes responsible for several of the recessive demyelinating neuropathies, dominant and recessive axonal neuropathies, and the sensory or autonomic neuropathies have been identified (see Table 70-1). Testing for mutation detection in many of these genes is available from several laboratories (see <http://www.genetests.org> for laboratories that test on a clinical or research basis). However, when the more common mutations are not discovered (eg, *PMP22*, *MPZ*, *EGR2*, and *GJB1*), one has to contact individual research labs that are studying particular forms of neuropathies. Many more genes responsible for inherited neuropathy have been mapped. Such progress in the molecular pathology of hereditary neuropathy will lead to a better understanding of pathogenesis, a better ability to predict the course of disease based on genetic testing, and, eventually, to specific cellular or genetic therapies.

Suggested Readings

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Practitioner and Patient Resources

International Peripheral Neuropathy Mutation Database (IPNMDB)
http://molgen-www.uia.ac.be/CMTmutations
The IPNMDB aims to offer the scientific community useful and relevant information on IPN mutations in a comprehensive manner.

Online Mendelian Inheritance in Man
http://www.ncbi.nlm.nih.gov/omim/
This database is a catalog of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere, and developed for the World Wide Web by National Center for Biotechnology Information (NCBI). The database contains textual information and references. It also contains copious links to Medline and sequence records in the Entrez system, as well as links to additional related resources at NCBI and elsewhere.

Neuromuscular Disease Center
Washington University, St. Louis, MO
http://www.neuro.wustl.edu/neuromuscular/
This informational Web site is geared toward physicians.

CHAPTER 71

NEUROMUSCULAR JUNCTION DISORDERS

JIRI VAJSAR, MD, MSC, FRCPC

Neuromuscular junction disorders must be considered in all cases of fluctuating weakness in children. They can be fatal because of bulbar or respiratory compromise. Diagnosis and treatment are challenging but lead to remission and cure of the disease in many children.

Disorders of the neuromuscular junctions are rare in childhood. In these disorders, failure of muscle activation and clinical weakness results from a process that interferes with the synthesis, storage, or release of acetylcholine; disrupts the structure of the synapse; or interferes with either the acetylcholine receptor (AChR) or the acetylcholinesterase (AChE) molecule. The clinical presentation of neuromuscular transmission disorders is variable. Patients develop fluctuating weakness of extraocular, facial, oropharyngeal, and limb muscles, and if untreated, this will progress to permanent weakness. At times, they can develop life-threatening respiratory failure. Patients with weakness in which there are no upper motor signs or sensory loss should be carefully evaluated for neuromuscular junction disorders. Both genetic and acquired neuromuscular diseases can present in children, and the more common ones are listed in Table 71-1.

TABLE 71-1. Pediatric Neuromuscular Junction Disorders

Autoimmune myasthenia gravis
Neonatal myasthenia gravis
Congenital myasthenic syndrome
Presynaptic defects
Synaptic defects
Postsynaptic defects
Lambert-Eaton syndrome
Medications
Magnesium
Organophosphates
Antibiotics
Toxins
Botulism
Tic paralysis
Spider and snake venom

Diagnosis and Management

Autoimmune Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disease in which there is production of autoantibodies against the nicotinic AChR. The prevalence of MG is about one in 10 to 20,000 people and about 10% of those are children. Although rare in infancy, MG can develop at any age, and girls are affected more often than boys. Associated autoimmune disease occurs in up to 10% of patients with MG and is most commonly thyroid disease. MG can occur as part of graft versus host disease or with D-penicillamine or interferon α therapy.

The hallmark of MG is fluctuating and fatigable weakness. The patient is usually better when waking in the morning. The symptoms build up toward the end of the day and improve with rest. Ptosis and extraocular muscle involvement are present in over 50% of patients at the onset and eventually in about 80 to 90% of cases. A careful history will usually reveal fatigable muscles, such as intermittent diplopia with prolonged reading, progressive difficulty with chewing and swallowing during the course of a meal with a tendency to an open "hanging" jaw, and slurring or weakening of speech after prolonged talking. About two-third of children with MG will develop generalized disease with

bulbar, truncal, and limb weakness. The progression of ocular to generalized MG may be rapid, within a few months, but it may be slow in other patients. After 2 to 3 years of a stable course, it is likely that the ocular MG will not spread to other muscle groups, although delayed generalization of muscle weakness is possible.

Diagnosis of MG

The diagnosis is based on a history of fluctuating weakness and clinical findings of fatigable weakness. There are several ways to confirm the diagnosis.

Edrophonium (Tensilon) test is run in a clinical setting where possible side effects such as hypotension, bradycardia, and respiratory compromise can be managed. If the latter is already present, the airways have to be secured. Video recording of the weak muscles during the test is useful, in particular in children with mild signs and symptoms or in those who do not cooperate fully. Intravenous administration is preferable, and atropine (0.01 mg/kg up to 0.4 mg) should be available in the event of extreme cholinergic side effects (Table 71-2). Edrophonium (0.1–0.2 mg/kg up to 10 mg) is drawn in a syringe, and one-fifth is given as a test dose to check for hypersensitivity while monitoring the heart rate. Some patients may resolve the symptoms with the test dose, at which point the test can be stopped. If after 1 minute there is no improvement, the remaining dose is injected. If the patients develop muscarinic symptoms or signs (sweating, salivation, gastrointestinal symptoms), one can assume that enough edrophonium has been provided in order to see improvement and the test can be stopped. The improvement lasts for several minutes only. Occasionally, the test needs to be performed in a double-blind, placebo-control fashion with saline as a placebo. Sensitivity of the edrophonium test is about 90%. The specificity is unknown since patients with other neuromuscular diseases and muscle weakness may respond as well. Neostigmine by the intramuscular injection can also be used as a diagnostic test and may be preferable in very young or uncooperative children. The dose is 0.02 to 0.04 mg/kg to 2.5 mg/dose, and improvement is maximal in 1 to 2 hours and lasts up to 3 to 4 hours.

Serologic Tests

The main serologic test for MG is the circulating AChR binding antibody assay. The IgG antibodies are present in 50 to 90% of childhood patients with MG. The lower percentage is seen in ocular MG and some prepubertal generalized cases of MG, while almost all cases with rapid progression to generalized form will show positive results. The sensitivity of this test can be improved by testing for modulating and blocking antibodies. The AChR may show false positivity in patients with autoimmune liver disease. No correlation exists between the severity of clinical course and the level of AChR antibodies. Recently, muscle-specific kinase (MuSK) antibodies have been reported in up to 40% patients who are negative for AChR antibodies. MG patients with MuSK IgG antibodies often have mild generalized disease but prominent ocular, bulbar, and respiratory muscle weakness.

Electrophysiologic Tests

Repetitive nerve stimulation and single-fiber electromyography (SFEMG) are the two main electrophysiologic tests for MG. Concentric needle electromyography may show variation of motor unit potentials and occasionally fibrillation potentials and small polyphasic units, but these are rare in children with MG. The size of compound muscle action potential (CMAP) in response to a single stimulus is normal in a mildly or moderately weak muscle and decreased in a severely weak muscle. Repetitive stimulation with supramaximal current at a slow rate of 2 to 5 Hz brings a decrement of the muscle response in weak muscles. The greatest change in the size of the CMAP occurs between the first and the second potential, reaching maximal decrement by the fourth or fifth potential. Brief exercise, fast repetitive nerve stimulation, or administration of AChE inhibitors will repair the decrement. In mildly weak muscles, the decrement is often absent with slow rates of stimulation but may develop 1 to 2 minutes following isometric exercise. In severely weak muscle with low CMAP, following brief exercise and with fast repetitive rates of 30 to 50 Hz, there may be an increment of up to 300% thus mimicking the response in patients with Lambert-Eaton syndrome or other presynaptic disorders of neuromuscular junction. The sensitivity of the repetitive nerve stimulation test depends on the disease severity and location of the tested nerve and muscle. In children, we test the ulnar nerve and follow with the facial or spinal accessory nerve if necessary. The decrement is abnormal if greater than 8% amplitude drop, and the values depend on the muscle tested. Abnormal decrement in moderate to severe disease is present in up to 60% in distal muscles and 80 to 90% in proximal muscles.

SFEMG, with a sensitivity of about 90%, requires patient's cooperation and is time consuming. In children, stimulation SFEMG may be used instead and the patient can be asleep. It may need to be performed if the diagnosis of MG is still in doubt and the results of other tests are inconclusive. The most common muscles studied are the extensor digitorum communis and muscles in the face.

Management of MG

Although the onset and progression of symptoms is usually insidious, some patients may present acutely in myasthenic crisis with life-threatening respiratory failure and will need intubation and ventilation along with the medications.

The criteria for intubation include a drop in forced vital capacity (FVC) below 15 mL/kg, below 30% of predictive value for age, severe aspiration from bulbar weakness, or labored breathing regardless of FVC values. The goal of drug therapy is to produce normal function with rapid onset of the effect with no or only minimal side effects. The severity and distribution of the weakness and the rate of its progression influence the therapeutic decisions.

AChE inhibitors are the first line of therapy, and they improve symptoms in most children with MG. Pyridostigmine bromide (Mestinon) is the most widely used medication for long-term oral treatment. Onset of effect is within 15 to 30 minutes, peaking within 1 to 2 hours, and wearing off by 3 to 4 hours. The starting dose is 0.5 to 1 mg/kg up to 60 mg given every 4 to 6 hours during the daytime. The dosage and interval may need to be individualized based on clinical observation to obtain maximal response. Response to a specific dose is not only variable between patients but also in any patient from time to time. Muscarinic cholinergic side effects are common with larger doses. The most common side effects are gastrointestinal hyperactivity and increased upper respiratory airway secretions. If necessary, an anticholinergic drug such as atropine sulfate or glycopyrrolate (Robinul) is added on a PRN basis. If the patient has been managed with cholinesterase inhibitors for a longer time and, in particular, in increasing doses, more weakness may occur. This may lead to "cholinergic crises," which may be, at times, difficult to distinguish from myasthenic crises. The features of these two are summarized in Table 71-2.

TABLE 71-2. The Acutely Deteriorating Myasthenic Patient

Myasthenic crisis*
Respiratory distress/arrest
Cyanosis
Increased pulse and blood pressure
Diaphoresis
Poor cough
Inability to handle oral secretions
Dysphagia
Weakness
Cholinergic crisis†
Abdominal cramps
Diarrhea
Nausea and vomiting
Excessive secretions
Decreased pulse and blood pressure
Miosis
Fasciculations
Diaphoresis
Weakness

*Improves with edrophonium.

†Worse with edrophonium.

Thymectomy

Although thymoma is extremely rare in children, thymectomy has shown favorable results in children treated for generalized MG. This, however, has not been validated by any prospective controlled trials. The youngest children who underwent thymectomy were about 2 years old. In milder cases and in ocular MG, most patients will not need thymectomy and can be managed medically. Eye surgery is optional for permanent ptosis.

Thymectomy with median sternotomy with cervical exploration has been the traditional approach. Some centers perform combined transsternal and transcervical thymectomy in order to insure complete removal. Other less invasive techniques, such as transcervical or more recently thoracoscopic thymectomy, have been reported. They appear to be equally effective and cosmetically more acceptable than sternotomy but require long-term evaluation.

Immunosuppressive Therapy

All immunosuppressive drugs carry the risk of increased infection, and each of them has potential additional side effects. Choice of one or more drugs should be made cautiously with consideration for short- and long-term outcomes for the patient. Children with moderate to severe limb weakness or rapidly progressive weakness that involves bulbar muscles will generally require immunosuppressives, and these can be used in ocular MG.

Corticosteroids

Prednisone, 1 mg/kg, is most commonly used in North America. Within the first few days of therapy, there may be exacerbation of weakness and the patient may need to be admitted to the hospital. Administration of low dose of prednisone generally avoids this early deterioration. The patients begin to improve within the first week or two, and the improvement continues for the next several weeks to months. With stabilization, the dose can be gradually reduced with most children maintaining the improvement. Many patients can be weaned off corticosteroids. Some require prolonged treatment with minimal dose of 5 to 20 mg on alternate days in order to maintain remission. Steroid side effects are numerous including weight gain, Cushing syndrome, steroid skin changes, psychologic changes, cataracts, gastrointestinal ulcers, diabetes mellitus, hypertension, osteoporosis, and increased susceptibility to infections.

Azathioprine (Imuran)

Azathioprine, 2 to 3 mg/kg, has a slow onset of action with improvement in strength occurring after about 3 months. Side effects include bone marrow suppression and hepatotoxicity, and there is a concern that long-term use may

increase the risk of malignancy. Nausea, vomiting, joint pain, diarrhea, rash, and flu-like symptoms can be improved and reversed with reduction of the dose. Imuran has to be discontinued only rarely.

Cyclosporine and cyclophosphamide have been used in the treatment of childhood MG, though side effects may be an issue. Also Cellcept, Tacrolimus, and Rituximab have been shown beneficial in the treatment of MG. The reported side effects were minimal.

Plasmapheresis and Intravenous Immunoglobulin

Both are effective short-term therapies for patients with severe weakness or in preparation for thymectomy if needed. The goal for plasma exchange is to remove about 50 mL/kg of plasma every other day or 3 times per week for total of up to 5 or 6 exchanges. Complications include hypotension, bradycardia, electrolyte imbalance, hemolysis, infection, and access problems.

Administration of plasmapheresis and intravenous immunoglobulin (IVIG) in the dose of 2 g/kg administered over 2 to 5 days results in improvement of muscle strength within several days in most children with MG. The effect usually lasts only several weeks. Complications of IVIG include headaches, fever, and chills, which respond to decreasing the rate of the infusion and giving diphenhydramine. Patients with IgA deficiency can develop anaphylactic shock, and there have been a few reports of aseptic meningitis, renal failure, nephrotic syndrome, and stroke, mostly in older patients.

Neonatal Myasthenia

About 10 to 15% of newborns born to mothers with autoimmune MG will experience weakness, hypotonia, and weak cry or suck and may require mechanical ventilation. The condition is believed to be caused by maternal antibodies that cross the placenta, but the pathobiology appears to be more complex. The symptoms gradually disappear, usually within a few weeks, with subsequent normal outcome. Electrodiagnostic findings show normal amplitude of the CMAP, and an abnormal decrement is observed at low-rate repetitive nerve stimulation in a weak muscle. Neonates with severe weakness improve with oral or parenteral AChE inhibitors. Rarely, some of the newborns may be born with arthrogryposis multiplex congenita.

Congenital Myasthenic Syndromes

Congenital myasthenic syndromes (CMS) are rare. The CMS are genetic diseases with autosomal inheritance. Their presence in children may be first indicated by reduced fetal movements, which may result in arthrogryposis multiplex congenita. Children with CMS may experience a turbulent postnatal period, with frequent attacks of apnea, recurrent aspiration, failure to thrive, and inability to feed and suck. Delayed motor development is variable. Mildly affected children may be initially seen in the first or second year of life with ocular signs only. Associated systemic signs may be mild in some cases and severe in others. The CMS are characterized mainly by immuno histochemical and microelectrode studies. The syndromes include those with abnormalities of the presynaptic region, ie, familial infantile myasthenia; syndromes with abnormalities of the postsynaptic region, ie, slow channel myasthenic syndrome; and syndromes where there is a combination of a presynaptic and postsynaptic abnormality. A few other syndromes are less well characterized, ie, AChR deficiency with a paucity of secondary synaptic clefts. The diagnosis of CMS is confirmed by several tests. Tensilon test can be positive and similarly, a patient may respond positively to a trial of pyridostigmine. Electrophysiologic studies may detect decremental response on repetitive nerve stimulation. SFEMG will show unstable neuromuscular transmission with abnormal jitter and blocking. Detailed microphysiological, ultrastructural, and histochemical studies in specialized labs are required for accurate diagnosis and classification. Treatment in these patients is generally supportive. Individual cases may respond to AChE inhibitors, fluoxetine, quinidine, and 3,4-diaminopyridine.

Botulism

Infant botulism is a serious illness often leading to respiratory insufficiency in only a few days. Infants present with weakness, hypotonia, eye findings, and dysphagia. They have mydriasis, fatigable ptosis, and external ophthalmoplegia. Severe cases will require ventilation and parenteral nutrition. There is frequently a history of constipation and a history of honey ingestion although contamination from soil is the most common cause. Fast, repetitive nerve stimulation shows facilitation in a weak muscle, and Clostridium botulinum (or toxin if early) can be identified in stool. The disease is protracted, but motor function usually returns over the weeks and months. Human botulinum immunoglobulin (http://www.infantbotulism.org) when given in the first few days of the disease at 50 mg/kg shortens the duration of ventilatory support.

In older children, botulism is acquired through poorly cooked, contaminated food or through wounds infected by Clostridium botulinum present in soil. The condition is characterized by an acute course including constipation, ptosis, and diplopia with fast progression to bulbar, respiratory, and limb weakness. There is usually internal ophthalmoplegia

with mydriasis. Botulinum toxin can be detected in both the stool and the serum of the patient.

Lambert-Eaton Myasthenic Syndrome

This rare condition, with antibodies directed against the voltage-gated calcium channels of the nerve terminal, has been reported in only a few children. In children, it presents as an idiopathic autoimmune disease rather than the more common paraneoplastic disease of adults. Hip-girdle weakness followed by shoulder-girdle weakness with diminished to absent tendon reflexes are the typical findings. Fast-rate repetitive nerve stimulation produces a greater than 200% increment in clinically affected muscles. Antibodies to voltage-gated calcium channels are found in the serum of most patients with Lambert-Eaton myasthenic syndrome. Patients respond to guanidine, 3,4-diaminopyridine, and immunosuppressive therapy. Plasma exchange and intravenous gammaglobulin are other beneficial treatments.

Medication-induced Neuromuscular Transmission Diseases

Organophosphate poisoning due to accidental exposure to insecticides and hypermagnesemia can produce clinically significant weakness. Organophosphates permanently inhibit AChE thus producing an acute cholinergic crisis characterized by weakness, cramps, fasciculations, gastrointestinal hypermotility and diarrhea, sweating, salivation, confusion, and generalized seizures. In the case of suspected poisoning, blood should be drawn for both erythrocyte ChE and butyrylcholinesterase to confirm the diagnosis. Treatment is atropine and pralidoxime.

Magnesium intoxication in infants born to mothers treated with high doses of magnesium sulfate for eclampsia presents with generalized weakness and hypotonia. Magnesium competitively blocks the calcium entry at the motor nerve terminal thus inhibiting ACh release. There may also be a postsynaptic effect. Patients with renal failure are predisposed to developing hypermagnesemia and should avoid magnesium-containing antacids and laxatives. Elevated serum magnesium levels due to oral use of magnesium-containing compounds are very uncommon so long as the patient has normal renal function. Treatment of the hypermagnesemic patient depends on the severity of clinical symptoms. Discontinuation of the magnesium is the first step. If the patient is significantly weak, then slow administration of intravenous calcium gluconate can produce rapid although temporary improvement.

Some antibiotics and other medications such as aminoglycosides can produce weakness that is dose dependent and associated with high serum levels. Gentamicin, neomycin, streptomycin, tobramycin, and kanamycin have been reported to produce clinically significant muscle weakness on occasion even in non-MG patients. Cholinesterase inhibitors, infusion of calcium, and aminopyridines can partially reverse the weakness induced by aminoglycosides.

There are several other medications that have been implicated as potentially harmful in patients with MG. The clinician should be alert to the possibility of an adverse effect in β-blockers, calcium channel blockers such as verapamil, and other cardiovascular drugs such as quinidine, quinine, procainamide and bretylium; also with anticonvulsant medications such as phenytoin, barbiturates, ethosuximide, and carbamazepine; with ophthalmologic medications such as timolol and betaxolol hydrochloride; and in psychiatric drugs such as phenothiazines, lithium, amitriptyline, imipramine, amphetamines, and haloperidol. D-penicillamine must not be given to patients with MG. Prolonged paralysis in patients receiving anticholinesterase medication can be expected after receiving depolarizing and some of the nondepolarizing neuromuscular blocking agents.

Tics, Spiders, and Snakes

Ascending paralysis is caused by a potent neurotoxin produced by an attached tic. This usually develops over several days, and severe cases may develop pharyngeal weakness and respiratory insufficiency. Removal of the tic leads to prompt recovery within several days. The neurotoxin inhibits nerve terminal conduction and acetylcholine release at the presynaptic neuromuscular region and causes blockade of transmission at the myoneural junction. Motor conduction studies show reduction in muscle compound action potentials with normal or slightly reduced conduction velocities.

Snake venoms from rattlesnakes (pit vipers family) have an effect on the presynaptic and postsynaptic regions of the neuromuscular junction in addition to other neurotoxic, hematotoxic, and cytotoxic reactions. Toxins from cobra and krait venoms block the AChR binding site on AChRs. Toxin from the venom of the Mojave rattlesnake inhibits neuromuscular transmission by blocking ACh release from the nerve terminals. The most severe cases are treated with polyvalent crotaline antivenom that is effective against all American pit vipers envenomations.

In North America, the black widow spider and the North American brown recluse spider cause most toxic reactions. The venom of the black widow spider contains α-latrotoxin, which binds to presynaptic neuronal membranes causing release of ACh and norepinephrine at the synapses. This results in excessive muscle depolarization and autonomic hyperactivity. Children present with muscle cramping, nausea, vomiting, diaphoresis, agitation, and hypertension with

tachypnea and tachycardia. Benzodiazepines help to relax the muscle, and opiates are given for pain. If symptomatic therapy does not resolve the symptoms, antivenom is used.

Venoms of different scorpion species contain neurotoxins that can bind to the presynaptic membrane causing release of ACh. Symptoms are, however, mostly due to sympathetic and parasympathetic nervous system hyperactivity. Symptomatic treatment is usually sufficient, but in more severe cases with cardiovascular instability, administration of antivenom resolves symptoms within 1 to 2 hours.

Suggested Readings

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Practitioner and Patient Resources

Infant Botulism Treatment and Prevention Program
Phone: 1800-843-7477
http://www.infantbotulism.org
A Web site providing information from the Division of Communicable Disease Control, California Department of Health Services.

Muscular Dystrophy Association
http://www.mdausa.org
The Muscular Dystrophy Association is a voluntary health agency—a dedicated partnership between scientists and concerned citizens aimed at conquering neuromuscular diseases that affect more than a million Americans.

Muscular Dystrophy Canada
http://www.mdac.ca/
Muscular Dystrophy Canada (MDC) endeavors to provide relevant and current information about many types of neuromuscular disorders in an easy-to-understand format. Its publications cover important topics such as causes, symptoms, and treatments for these disorders. All of MDC's information documents are written with its clients in mind and can be downloaded from this site.

Myasthenia Gravis Foundation of America
http://www.myasthenia.org
Myasthenia Gravis Foundation of America (MGFA) is the only national volunteer health agency dedicated solely to the fight against myasthenia gravis. MGFA's Web site contains programs of patient services, public information, medical research, professional education, advocacy, and patient care.

Myasthenia Gravis and Neuromuscular Junction Disorders
http://www.neuro.wustl.edu/neuromuscular/synmg.html
This site contains information on acquired neuromuscular junction (NMJ) disorders as well as congenital and familial NMJ disorders.

CHAPTER 72

MUSCULAR DYSTROPHY AND MYOPATHY

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This chapter reviews the inherited and acquired diseases of muscle presenting in infancy, childhood, and adolescence, with an emphasis on clinical evaluation, laboratory investigations, and long-term management.

Dramatic advances, particularly over the past two decades in molecular neurogenetics, have led to new diagnostic tests that can confirm diagnoses accurately and noninvasively. Traditional diagnostic tests, such as nerve conduction studies, electromyography (EMG), and open muscle biopsy, continue to be useful when molecular genetic analysis fails to confirm the initial clinical impression.

Neuromuscular disorders are classified according to the anatomic structure of the motor unit. Diseases of the anterior horn cell are referred to as *neuronopathies*, of the peripheral nerve as *neuropathies*, of the neuromuscular junction as *neuromuscular transmission disorders*, and of the myofiber as *myopathies*. The first goal in approaching a patient with a suspected muscle disease is to determine the correct site of the lesion. Once localized to the muscle, the next step is to identify whether the myopathy is due to a defect in the muscle channel, muscle structure, or a dysfunction in muscle metabolism. The second goal is to determine the etiology of the myopathy. Myopathies can be broadly classified into hereditary (Table 72-1) and acquired (Table 72-2) disorders. Further categorization is made on the basis of the characteristic pattern of the particular disorder. Thus, for example, the term *muscular dystrophy* is used for genetically determined, progressive, degenerative myopathies. Genetically based muscular disorders usually present in an indolent fashion, with fixed weakness and delay in acquisition of motor skills (see Table 72-1). Acquired muscle disorders may present with either rapid or subacute progression of weakness and loss of motor function, often with substantial muscle pain (see Table 72-2).

Evaluation

The role of the clinician has changed little since the nineteenth century, when neuromuscular disorders were first recognized. A detailed medical history and comprehensive physical exam form the basis for sound clinical judgment. The clinical presentation and pattern of disease progression over time enable categorization of possible clinical conditions. In general, genetically determined muscular dystrophies are relentlessly progressive from the time of onset. However, in young children, disease progression is often mitigated by normal childhood development. In addition, parents may report a seasonal improvement related to increased outdoor activities, such as swimming. In contrast, older children typically exhibit a saltatory pattern in their clinical symptoms, suggesting an underlying metabolic or ion channel disorder. When the serum creatine kinase (CK) is markedly elevated, saltatory progression of the illness favors an inflammatory disease of muscle rather than a muscular dystrophy. When evaluating the patient ask yourself six questions based on the presenting symptoms and signs.

History

Symptoms associated with muscle disease can be broadly divided into "negative" symptoms, such as weakness, fatigue, and exercise intolerance, and "positive" complaints, such as muscle pain, cramping, contractures, stiffness, and dark or red urine (Table 72-3). Most children

TABLE 72-1. Classification of Myopathies

Hereditary
Muscular dystrophies
Myotonias
Channelopathies
Congenital myopathies
Metabolic myopathies
Mitochondrial myopathies
Acquired
Inflammatory myopathies
Endocrine myopathies
Toxic myopathies
Drug induced myopathies
Myopathies associated with other systemic illness

with neuromuscular disorders present with hypotonia, weakness, fatigue, pain, or an elevated serum CK value. Parents may report certain activities that the child has difficulty with, such as climbing stairs or getting upfrom a sitting position. With upper extremity involvement the patient will have difficulty brushing teeth or combing hair. Distal muscle weakness will manifest with tripping due to a foot drop. Patients complaining of global weakness or fatigue usually do not have a muscle disorder. Exercise induced fatigue can result from certain metabolic and mitochondrial myopathies.

Myalgia, like fatigue, is a nonspecific symptom and may be episodic (metabolic myopathies) or nearly constant (inflammatory muscle disorders) (Table 72-3). Cramps are characterized by a localized involuntary muscle contraction and are seldom the presenting feature of a primary myopathy. The EMG during a cramp demonstrates rapidly firing motor unit discharges. Muscle contractures can superficially resemble a cramp but last longer and are electrically silent with needle EMG. Contractures are typically provoked by exercise in patients with glycolytic enzyme defects (Table 72-4). Myotonia is the phenomenon of impaired muscle relaxation following forceful voluntary contraction and most commonly involves the hands and eyelids. Myotonia is due to repetitive depolarization of the muscle membrane. Myotonia classically improves with repeated exercise. In contrast, patients with paramyotonia congenita demonstrate "paradoxical myotonia" in that symptoms are worsened by exercise. Exposure to cold results in worsening of both myotonia and paramyotonia. (Table 72-5).

Myoglobinuria is a relatively uncommon manifestation of muscle disease and follows the excessive release of myoglobin from muscle during periods of rapid muscle destruction (rhabdomyolysis). Patients with exercise-induced weakness and myalgia should be questioned as to the occurrence of red or darkly colored urine during or after theses episodes. Recurrent myoglobinuria is usually associated with a metabolic muscle disorder. (Table 72-6)

TABLE 72-2. Symptoms and Signs Associated With Myopathies

Negative symptoms
Weakness
Fatigue and exercise intolerance
Muscle atrophy
Positive symptoms
Pain/myalgias
Cramps
Contractures
Dark/red urine (myoglobinuria)
Stiffness/inability to relax muscle-myotonia

TABLE 72-3. Muscle Disorders Causing Myalgia

Generalized Myalgia
Infectious myalgia (especially viral)
Inflammatory muscle disease
Dermatomyositis
Polymyositis (rare in children)
Toxic myopathies
Hypothyroidism
Mitochondrial myopathies
Myoadenylate deaminase deficiency
Localized Myalgia
Post exercise myalgia
Focal pressure necrosis
Trauma
Focal infiltrative process (eg, sarcoidosis, focal myositis)
Localized infection
Vascular occlusion

What is the temporal evolution?

The age of onset of symptoms is of major importance in establishing a diagnosis. Did the weakness first manifest at birth (Table 72-7), or in the first or second decade (Table 72-8). It is also important to determine the evolution and duration of the disease. Myopathies can present with either constant weakness (muscular dystrophies, inflammatory myopathies) or episodic periods of weakness on a baseline of normal strength (periodic paralysis, glycolytic myopathies). The tempo of progression is helpful to assess. Acute or subacute progression is observed in dermatomyositis. Chronic slow progression over years is a feature of most dystrophy. Formal muscle testing is easier to perform in the older child. Focus on

TABLE 72-4. Causes of Muscle Cramps/Contractures

Occurring at rest.
Usually not a muscle disorder.
Occurring with exertion. Relieved by rest.
Muscular dystrophy
Metabolic disorders: glycogenoses and disorders of lipid metabolism
Other myoglobinuric syndromes (Table 72-)

TABLE 72-5. Myopathies Associated with Muscle Stiffness.

Myotonic dystrophy
Paramyotonia congenita
Myotonia congenita
Hyperkalemic periodic paralysis
Hypothyroid myopathy

the neck flexors, pelvic and shoulder girdles, biceps and triceps, iliopsoas, quadriceps, hamstrings, and distal muscles of the hands and feet. Formal assessment should be based on the Medical Research Council grading system (Table 72-13).

With few exceptions, most disorders of the neuromuscular system are relatively symmetrical and involve limb and axial musculature. Distal weakness, more typical of neuropathic disorders, may be the presenting feature of several myopathic disorders, including these:

- Myotonic dystrophy
- Fascioscapulohumeral dystrophy
- Emery-Dreifuss dystrophy
- Distal myopathies
  - Early adult onset distal myopathy type 1 (Nonaka)
  - Early adult onset distal myopathy type 2 (Miyoshi)
  - Early adult onset distal myopathy type 3 (Laing)
- Metabolic myopathies (debrancher deficiency, acid-maltase deficiency)
- Congenital myopathies (nemaline, central core, and centronuclear myopathy)

A distinctive pattern of weakness involving the proximal upper extremity periscapular muscles (often with winging) and the anterior compartment of the distal lower extremity is typical of fascioscapulohumeral dystrophy. Predominant involvement of ocular and pharyngeal muscles occurs in a relatively restricted group of disorders:

TABLE 72-6. Causes of Myoglobinuria

Prolonged and intensive exercise
Viral and bacterial infections
Drugs and toxins
Neuroleptic malignant syndrome
Trauma (crush injuries)
Heat stroke
Severe metabolic disturbances including prolonged fever
Inflammatory myopathies
Limb-girdle muscular dystrophy 2C-2F (scarcoglycanopathies)
Metabolic myopathies
Myophosphorylase deficiency
Carnitine palmitoyltransferase deficiency
Malignant hyperthermia
Central core myopathy
Duchenne muscular dystrophy

TABLE 72-7. Myopathies Presenting at Birth

Congenital muscular dystrophy (CMD)
Classical CMD (Structural CNS changes are absent)
Merosin (laminin α2) deficient CMD
Primary (MDC1A)
Secondary (MDC1B) (Represents an α-dystroglycanopathy)
Merosin-positive CMD
Classical CMD without distinguishing features
Rigid spine syndrome
CMD with distal hyperextensibility (Ulrich type) (Collagen VI disorder)
CMD with mental retardation or sensory abnormalities
CMD with CNS abnormalities
Fukuyama CMD
Muscle-eye-brain disease
Walker-Warburg syndrome
Congenital myotonic dystrophy
Congenital mopathies
Centronuclear (myotubular) myopathy
Central core disease
Nemaline (rod) myopathy
Congenital fiber-type disproportion
Lipid storage diseases (carnitine deficiency)
Glycogen storage diseases (Acid maltase and phosphorylase deficiency)

- Ptosis with opthalmoplegia
  - Mitochondrial cytopathies
  - Oculopharyngeal muscular dystrophy
- Ptosis usually without opthalmoplegia
  - Myotonic dystrophy
  - Centronuclear myopathy
  - Nemaline myopathy
  - Central core myopathy

Clinical Examination

Observing the child's behavior and motor activities while talking a history from the parents often provides significant

TABLE 72-8. Myopathies Presenting in Childhood

Muscular dystrophies
Myotonic (MD)
Duchenne (DMD)
Becker (BMD)
Facioscapulohumeral (FSHD)
Limb-girdle (LGMD)
Congenital (CMD)
Inflammatory myopathies
Dermatomyositis, polymyositis
Congenital myopathies
Mitochondrial myopathies
Endocrine-metabolic disorders
Thyroid, parathyroid, adrenal.
Hypokalemia, hyocalcemia, hypercalcemia
Lipid storage diseases (carnitine deficiency)
Glycogen storage diseases (Acid maltase and phosphorylase deficiency)
Toxic myopathies
Cortcosteroids

TABLE 72-9. Diagnosis of Myopathy Based on Pattern of Inheritance

X-Linked
DMD
BMD
Emery Dreifuss muscular dystrophy
Autosomal Dominant
FSHD
LGMD (1A-1E)
Occulopharyngeal muscular dystrophy
Myotonic dystrophy
Periodic paralysis
Paramytonia congenita
Thomsen disease
Central core myopathy
Distal
Autosomal Recessive
LGMD (2A-2J)
Metabolic myopathies
Becker myotonia
Maternal Transmission
Mitochondrial myopathies

clinical information. An appreciation of motor milestones during late infancy and early childhood is of vital importance (Table 72-6). Observe the stance and gait and determine if the child is rising up on his or her toes unnecessarily or walking flat on the feet. Engage the child in play and observe how the child rises from the floor, reaches over the head, and pulls an object from the examiner's hand. A wide-based waddling gait with hyperlordosis is an early sign of pelvic weakness. Observe eye movements (often impaired in mitochondrial and myasthenic disorders), the position of the upper eyelids, and facial expression, and examine for the presence of dysmorphic features. Weakness of the facial musculature is demonstrated by an inability to close eyes completely or whistle during expiration and nasality of voice. Inspect for patterns of atrophy and hypertrophy. Facioscapulohumeral dystrophy is suggested by the presence of periscapular atrophy with scapular winging. Diffuse hypertrophy is observed in myotonia congenital and calf pseudohypertrophy in Becker's and Duchenne's dystrophy.

TABLE 72-10. Mopathies Associated with Cardiac Disease

Arrhythmias
Kearns-Sayre syndrome
Myotonic muscular dystrophy
LGMD 1B, 2C-2F, 2G
Emery-Dreifuss
Congestive Cardiac Failure
Myotonic muscular dystrophy
LGMD 1B, 2C-2F, 2G
Emery-Dreifuss
BMD
DMD
Nemaline myopathy
Acid maltase deficiency
Carnitine deficiency

TABLE 72-11. Myopathies Associated with Respiratory Failure

Muscular dystrophies
DMD
BMD
LGMD
CMD
Myotonic
Mitochondrial myopathies
Congenital myopathies
Nemaline
Centronuclear
Metabolic myopathies
Acid maltase deficiency
Carnitine deficiency

Other features suggestive of a neuromuscular disorder include a deep crease running from the axilla obliquely toward the neck, a step-like appearance where the base of the neck and clavicles meet, winged scapula, atrophy of the intrinsic muscles of the hand, exaggerated lumbar lordosis, protuberance of the abdomen, wasting of the quadriceps, and tightness of the heel cords. Reflexes are often diminished and may be absent in the congenitally acquired myopathies. Contractures are a feature of many chronic myopathies but are characteristic of Emery-Dreifuss muscular dystrophy. In patients complaining of muscle stiffness, the physician should attempt to elicit myotonia. Ask the patient to squeeze the examiner's finger and then observe for inability to relax the handgrip. The thenar eminence can be directly percussed to look for a slow persistent contraction and delayed relaxation ("percussion myotonia"). Formal muscle testing is easier to perform in the older child. Focus on the neck flexors, pelvic and shoulder girdles, biceps and triceps, iliopsoas, quadriceps, hamstrings, and distal muscles of the hands and feet. Formal assessment should be based on the Medical Research Council grading system (Table 72-7). With few exceptions, most disorders of the neuromuscular system are relatively symmetrical and involve limb and axial musculature. Distal weakness, more typical of neuropathic disorders, may be

Table 72-12. Important Motor Milestones

6 months:	Sits leaning forward on hands, lifts head spontaneously in supine, takes weight on legs well
1 year:	Walks with help, cruises
18 months:	Walks independently, some are starting to run, climbs stairs without assistance
2 years:	Runs well, kicks a ball, goes up and down stairs without difficulty
3 years:	Able to stand on one leg, most can jump off a step
4 years:	Hopping on one foot is attempted by 4 years
5 years:	Able to hop on either leg well

Table 72-13. Medical Research Council Grading Scale for Muscle Testing

0	No movement of the muscle
1	A flicker or trace of movement
2	Active movement with gravity eliminated
3	Active movement against gravity
4–	Active movement against slight resistance
4	Active movement against moderate resistance
4+	Active movement against strong resistance
5	Normal power

the presenting feature of several myopathic disorders, including these:

- Myotonic dystrophy
- Facioscapulohumeral dystrophy
- Emery-Dreifuss dystrophy
- Metabolic myopathies (debrancher enzyme deficiency, acid maltase deficiency)
- Congenital myopathies (nemaline, central core, and centronuclear myopathy)

A distinctive pattern of weakness involving the proximal upper extremity periscapular muscles (often with winging) and the anterior compartment of the distal lower extremity is typical of facioscapulohumeral dystrophy. Predominant involvement of ocular and pharyngeal muscles occurs in a relatively restricted group of disorders:

- Ptosis with opthalmoplegia
- Mitochondrial cytopathies
- Oculopharyngeal muscular dystrophy
- Ptosis usually without opthalmoplegia
- Myotonic dystrophy
- Centronuclear myopathy
- Nemaline myopathy
- Central core myopathy

Prominent neck extensor weakness may be a feature of myasthenia gravis, congenital and metabolic myopathies, myotonic dystrophy, and dermatomyositis. Involvement of organs and tissues other than muscle can provide additional clues to the diagnosis of a specific myopathy.

Cardiac disease can be associated with myotonic dystrophy and Duchenne's, Becker's, and Emery-Dreifuss muscular dystrophies. Hepatomegaly is observed with deficiencies of acid maltase, carnitine, and debranching enzyme. Pulmonary involvement can occur in some inflammatory myopathies. Evidence of a diffuse systemic disease can indicate a mitochondrial cytopathy.

Laboratory Assessment

The initial approach is to confirm the presence of a disease of muscle. Then, a focused diagnostic plan should be pursued that establishes the specific diagnosis in the least invasive, quickest, and most cost-effective manner.

Serum Muscle Enzymes

Serum CK is the most commonly obtained blood test to screen for a disease of muscle. CK level is elevated modestly in some myopathies and often 10-to 100-fold in some dystrophies. However, it must be emphasized that the absence of an elevated CK does not rule out a primary myopathic disorder. Modest elevations, usually less than 1,000 international units (IU)/L, may also represent a neurogenic disorder and can be seen in otherwise healthy individuals (usually teenage males with substantial muscle bulk). Elevations acutely following exercise or contact sports should return to normal after 2 to 3 days. Other enzymes released from injured skeletal muscle include aldolase, aspartate aminotransferase (AST), alanine aminotransferase (ALT,), and lactate dehydrogenase. I have observed patients with Duchenne's muscular dystrophy who have unnecessarily undergone extensive workups for suspected hepatic disease due to elevated ALT and AST. The liver-specific enzyme γ-glutamic transferase is invariably elevated in patients with primary hepatic disease but is within the normal range in primary muscular disorders. Obtain blood lactate and pyruvate and carnitine profiles when a mitochondrial disease of muscle is suspected. Consider thyroid function studies. When infectious etiologies are a possibility, complete blood count (CBC) with differential, sedimentation rate, cultures, and in some case specific antigen studies should be obtained.

Specific Molecular Genetic Studies

This includes testing for a mutation (deletion, duplication, point mutation, or expansion of a triplet repeat) within a gene from a peripheral blood sample or muscle tissue and testing for the gene product in muscle. It is important to be aware of the limitations of these studies. For example, a deletion in the dystrophin gene is identified in only 60% of patients with DMD. In deletion-negative cases, a muscle biopsy is then needed to examine for the presence of dystrophin protein in immunostaining and to measure protein quantity and size by Western blot analysis.

EMG and Nerve Conduction Studies

These studies have diminished in their utility with the advent of molecular deoxyribonucleic acid (DNA) testing; however, they remain valuable in differentiating disorders of the anterior horn cell, peripheral nerve, and neuromuscular junction. In addition, they may be useful in demonstrating characteristic features of certain myopathies.

TABLE 72-14. Typical Paradigm for Duchenne's Muscular Dystrophy

Topic and *Intervention*	Time Frame in Years: Birth	2	4	6	8	10	12	16–20	20–30
1. Overview	[preclinical]			[diagnosis]		[progression of disease .....]			[death]
Genetic counseling: after the diagnosis has been established and when the parents are emotionally capable of addressing this topic.									
2. Gross motor skills:									
Normal	.....								
Slowly gaining		.....							
Plateau phase			.....						
Regression in gait						.....			
Loss of ambulation							.....		
Regression in upper limb function								.....	
Maintain mobility:									
Bracing					.....				
Power chair						.....			
Adaptive equipment:									
Hydraulic lift for transfers, toileting						.....			
Laptop computer							.....		
School adaptation:									
School bus lift and classroom aide							.....		
3. Musculoskeletal:									
Scoliosis							.....		
Joint Contractures									
heel cords					.....				
tensor facia lata							.....		
hamstrings							.....		
Physiotherapy:			.....						
Bracing and/or tendon releases (variable)					.....				
Spinal fusion (variable)							.....		
4. Pulmonary:									
Restrictive lung disease						.....			
Obstructive sleep apnea							.....		
Pulmonary function tests (and sleep study?)							.....		
Annual influenza vaccination						.....			
Pneumococcal immunization: at time of diagnosis									
Non-invasive ventilatory support (variable)								.....	
5. Cardiomyopathy:							.....		
Annual ECG							.....		
6. Obesity: (variable)						.....			
Nutritional consultation						.....			
7. Learning disability: (variable)			.....						
Psychoeducational evaluation, Individualized Educational Plan (IEP)									
8. Depression: (variable)								.....	
Individualized and family counseling							.....		
Antidepressant medication (selective serotonin reuptake inhibitor)								.....	
9. Medication:									
Prednisone, deflazacort	*(?* ..... *)*								

ECG = electrocardiogram.

Muscle Biopsy

Muscle biopsy remains important for evaluating many of the metabolic myopathies and congenital muscular dystrophies. Western blot analysis can be of considerable assistance in distinguishing the various subtypes of limbgirdle muscular dystrophy. Biopsies are usually performed on the deltoid, biceps, quadriceps, or gastrocnemius muscles.

Other Tests

Urine analysis can detect the presence of myoglobinuria. The ischemic forearm exercise test is useful to assess for disorders of glycogen metabolism. In unaffected patients, lactate normally rises 3-to 5-fold above baseline, with a peak at 1 to 2 minutes post exercise, whereas ammonia increases more than 5-fold. Affected patients show less than a 1.5-fold increase in lactate, with an exaggerated increase in ammonia.

Treatment

Management

The development of a realistic and cost-effective management program necessitates an understanding of the natural course of the disease. Once a specific diagnosis has been established, a long-term treatment algorithm can be formulated for that patient, based upon the knowledge of the natural history of that condition and when in the time course particular issues are likely to arise (Table 72-8). Optimal management is best achieved through a multidisciplinary team approach. The primary-care physician is crucial to maintaining continuity of care and to coordinating the evaluation and treatment regimens.

The following topics should be addressed in every child with a neuromuscular disorder.

General Nutritional Status

Adequate nutrition is essential to avoid muscle catabolism during times of illness and to promote optimal growth. Failure to thrive is a frequent concern in infants with dysphagia. A gastrostomy feeding tube, often with fundoplication, is considered early for the infant with limited or hazardous oral intake. For the child on steroid treatment (eg, some DMD patients and with dermatomyositis) it is important to address excessive weight gain and to ensure adequate calcium and vitamin D intake. Creatine may enhance energy stores in developing muscle; unfortunately, there is insufficient evidence to provide definitive guidance for its use. (Some studies have used a dose of 5 g/d.)

Cardiomyopathy and Arrhythmias

Cardiomyopathy and arrhythmias frequently coexist in neuromuscular disease. In DMD, clinically apparent cardiomyopathy is first evident after 10 years of age and is present in all patients older than 18 years of age. Arrhythmia is a frequent cause of sudden death in myotonic dystrophy. Patients should be screened with electrocardiography. If abnormal, an echocardiogram, Holter monitoring, or cardiac consultation should be obtained.

Restrictive Lung Disease

Restrictive lung disease from weakness of the diaphragm and intercostal muscles may be a presenting concern in an infant with a neuromuscular disorder or can arise insidiously in the older child several years after diagnosis. Respiratory complications may arise from a weak cough, preventing effective clearance of secretions and risking aspiration and atelectasis. Sleep apnea should be addressed in the history, searching for symptoms of noisy breathing or significant pauses in the breathing pattern when asleep, headaches upon awakening, irritability, or excessive daytime somnolence. A sleep study and pulmonary consultation is then indicated. Reliable pulmonary function tests can be obtained by a trained technologist in a child over age 5 to 7 years, in the absence of cognitive limitation. Measures of maximal inspiratory-expiratory pressures, spirometry, and lung volumes can be done serially to monitor a patient's trend and identify when a heightened level of concern evolves. Noninvasive assisted ventilation is often used when significant hypoventilation is present. Options include nasal continuous positive airway pressure, BiPAP ventilators, the CoughAssist In-Exsufflator respiratory device, and, occasionally, the negative pressure ventilator ("iron lung") or vest. An ethical dilemma may arise when intubation is considered and the prospects for future extubation are limited. An annual influenza vaccination and the pneumococcal vaccination are recommended for all patients with a chronic neuromuscular disorder and significant respiratory compromise. For infants, respiratory syncytial virus prophylaxis in the winter months is often pursued.

Scoliosis and Joint Contractures

The presence and evolution of *scoliosis* and *joint contractures* is important to address to determine functional limitation and a patient's level of discomfort. The rate of progression of scoliosis often increases dramatically with full-time use of a wheelchair. Bracing with a thoracolumosacral orthosis, side-supports in the wheelchair, and spinal fusion surgery often help stabilize a progressive scoliosis and maintain optimal lung function and comfort in the face of chronic progressive weakness of the truncal musculature. For patients with DMD, there are considerable advantages to the performance of an early spinal arthrodesis with curvatures as small as 10 to

20 degrees. Modified ankle-foot orthoses help maintain a neutral ankle posture and stabilize the stance and gait of a patient with significant foot-ankle weakness. When used as night splints they may also limit progression of heel-cord contractures. Knee-ankle-foot orthoses may prolong ambulation for an additional 24 months in patients with DMD. Tendon release procedures can prolong safe ambulation and facilitate proper positioning when used selectively.

Physical Therapy

Physical therapy with passive range of motion is particularly important when there is acute weakness and evolution of contractures, as in severe dermatomyositis. With more slowly progressive weakness, the therapist also instructs caregivers in stretching techniques and guides the family in appropriate activities (swimming, horseback riding, and adapted skiing, for example). The fitting of orthotics or braces and addressing mobility options (eg, scooter or power chair) are also a specialized role of the physiatrist and physical therapist.

Exercise and Weight Training

The challenge of *exercise and weight training* in patients with neuromuscular disorders is to augment strength in remaining healthy muscle tissue while minimizing any accentuation of damage to vulnerable diseased fibers. The goals are to increase strength and endurance, enhance aerobic capacity, maximize independent daily function, and promote inclusion in sports and peer activities. Variables to consider in an exercise regimen are:

1. The load that is appropriate for the degree of weakness of the muscle being exercised
2. The intensity of the workout (ie, the number of repetitions and the total work done)
3. The rest periods between exercise sessions
4. Avoiding overuse to joints
5. Stretching of contractures before exercising

Isotonic exercise with more concentric than eccentric activity is usually recommended. Isometric exercise (muscle contraction without joint movement) is helpful when there is related joint involvement, as in dermatomyositis, but curtailed during an active flare in disease activity. In general, the more acute the evolution of the weakness, the more frequent and less intense the workout and the more emphasis placed on stretching. Aerobic exercise can also be pursued, but caution must be maintained if there is a cardiac or pulmonary component of disease. Low-resistance activity such as "spinning" on a stationary bicycle is often tolerated, even when there is significant weakness. A supervised program with a trained therapist or experienced neuromuscular physiatrist is highly recommended to individualize the exercise regimen and to modify it as the course of disease evolves.

Occupational Therapist

The *occupational therapist* addresses limitations in fine motor skills and related activities of daily living (dressing, bathing, toileting, food preparation, and eating). Evaluation of the home and school settings are often needed to ensure proper adaptive equipment and safety devices are obtained.

Speech Therapist

The *speech therapist* evaluates oral-motor function relating to feeding and speech limitation. Augmentative communication devices can facilitate communication when speech is not possible.

Constipation

Constipation is a frequent complication when there is abdominal wall weakness and limited fluid intake. This needs to be treated vigorously with adequate fluid intake and the use of fruit juices, senna-based herbal tea or granules (Senokot®: < 5 yr, 1–2 tsp syrup; > 5 yr, 2–3 tsp syrup), mineral oil preparations (1–2 mL/kg/dose bid po), or an occasional suppository. Milk of magnesia (1 mL/kg/dose bid PO) and docusate (5 to 10 mg/kg/24 hours) may be helpful.

Malignant Hyperthermia

The risk of *malignant hyperthermia* in patients with certain muscle diseases undergoing anesthesia needs to be placed prominently in the patient's chart and the family counseled.

Psychosocial Support

Psychosocial support at home, school, and in the community. The clinic nurse and social worker are indispensable in inquiring about these issues and in identifying local services. The Muscular Dystrophy Association (MDA) is an excellent resource for patients and their families. The annual MDA camp provides a sense of community and affirmation, building relationships and establishing lifelong friendships.

Medication

Corticosteroids have been demonstrated to slow the rate of progression of weakness in DMD and also transiently improve strength in some cases. At present, the optimal treatment with prednisone is 0.75 mg/kg/d, with the maximal dose not to exceed 40 mg/d. Trials were performed on patients between the ages of 5 and 15 years. (Carefully performed randomized studies have not taken place in boys younger than 5 years of age.) Deflazacort, not available in the United States, is equally effective at 0.9 mg/kg/d and has fewer side effects. The decision to use chronic high-dose steroids should not be undertaken lightly, and the parents should be counseled as to the

acute and chronic side effects. Administration of calcium (1,000 mg daily) and vitamin D supplements to maintain bone mass and preventive treatment with bisphosphonates (such as Fosamax®) or Miacalcin® nasal spray are potentially useful. Annual screening for cataracts and bone density measurements should be obtained and the patient monitored closely for excessive weight gain, growth retardation, hypertension, glucose intolerance, gastrointestinal bleeding, insomnia, and behavioral changes. Urine analysis is recommended at 3-month intervals and CBC, electrolytes, liver, and kidney function tests at 6-month intervals. The benefit in patients with severe Becker's muscular dystrophy is probably similar, but in milder forms the chronic side effects probably outweigh the benefits.

The use of steroids in other dystrophies is more empiric and occasionally of benefit. Prednisone is typically the first-line treatment for dermatomyositis and polymyositis. A low dose of 10 mg/d may be sufficient to achieve remission in a mild case, whereas with severe weakness and dysphagia dosages of up to 2 mg/kg/d divided twice daily are needed. Pulse intravenous methylprednisolone, 15 to 30 mg/kg every 2 to 4 weeks, may be needed in refractory cases, along with intravenous immunoglobulin, azathioprene, methotrexate, cyclosporine, or cyclophosphamide.

Albuterol has demonstrated limited benefit in facioscapuloperoneal dystrophy. (The study used a slow release preparation of albuterol, at a dose of 8 mg twice daily.) L-Carnitine supplementation (100 mg/kg/d in four divided doses) may be useful in selected mitochondrial myopathies, but indiscriminate use in other muscle diseases has not been demonstrated to be of benefit.

Creatine, glutamate, selenium, penicillamine with vitamin E, and allopurinol have been used in variably controlled studies in DMD, without convincing benefit. The use of such supplements in other neuromuscular disorders is empiric.

Table 72-8 illustrates the principal clinical aspects of DMD and related therapeutic interventions for each phase of the disease. This approach can be adapted to other inherited and acquired muscular disorders, adjusting for the age of onset, rate of progression, and extent of related musculoskeletal, respiratory, and cardiac issues. Enzyme replacement therapy was recently approved for the treatment of infants with Pompe's disease (acid maltase deficiency) using a recombinant human α-glucosidase. This treatment dramatically prolongs survival and stabilizes cardiac and pulmonary function.

Conclusion

The symptoms and signs of neuromuscular disease are extraordinarily common in infancy, childhood, and adolescence. Early diagnosis enables the physician to initiate prompt treatment, minimize complications, promote quality of life measures, and, when indicated, provide genetic counseling regarding carrier status of relatives and risk of disease recurrence with future pregnancies.

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Practitioner and Patient Resources

Neuromuscular Disorders
Dubowitz V, editor. The official journal of the World Muscle Society. Published six times a year by Elsevier Science (Amsterdam). Each issue updates an extensive listing of gene locations.

CenterWatch Clinical Trials Listing Service
http://www.centerwatch.com
CenterWatch is a publishing and information services company dedicated to providing patients and their advocates with a variety of information services about clinical research.
The Web site provides extensive list clinical trials being conducted internationally.
http://www.cc.nih.gov/nihstudies

Office of Dietary Supplements (ODS)
http://dietary-supplements.info.nih.gov/
The ODS, established at the National Institutes of Health, promotes scientific research in the area of dietary supplements.

Muscular Dystrophy Association (USA)
Phone: 800-572-1717
http://www.mdausa.org

Muscular Dystrophy (Canada)
Phone: 800-567-2873
http://www.mdac.ca
The Muscular Dystrophy Association of the United States and Muscular Dystrophy Canada provide information to patients and families on 43 neuromuscular disorders, fund clinics in the United States and Canada for the evaluation and management of patients with suspected neuromuscular disorders, sponsor regional summer camps, and fund extensive research. The Web sites are extensive and useful to patients, family members, and professionals.

The Parent Project Muscular Dystropy
Phone: 800-714-5437
http://www.parentdmd.org
The Parent Project provides clinical information and research funding on Duchenne and Becker muscular dystrophy and sponsors an annual symposium for patients and families.

The Myositis Association of America
http://www.myositis.org
The Myositis Association of America provides clinical information and research funding on dermatomyositis, polymyositis, and inclusion-body myositis.

CHAPTER 73

PEDIATRIC NEUROTRANSMITTER DISORDERS

PHILLIP L. PEARL, MD

The pediatric neurotransmitter disorders are characterized by primary abnormalities of neurotransmitter synthesis, breakdown, or transport. Lumbar puncture for analysis of neurotransmitter precursors and metabolites is required for diagnosis in some of the conditions. Increasing therapeutic relevance, from dopa-responsive dystonia to pyridoxine-dependent and pyridoxal-5-phosphate-dependent seizures, highlight the importance of these disorders to pediatric neurologic practice.

The currently recognized pediatric neurotransmitter disorders refer to an inherited group of neurometabolic syndromes attributable to a disturbance of neurotransmitter metabolism (Table 73-1). Broadly, they are organized as clinical disorders of monoamine (catecholamine and serotonin), glycine, and γ-aminobutyric acid (GABA) metabolism. Many of these disorders involve deficiencies in enzymes directly involved in the synthetic or degradative pathways of the neurotransmitters themselves. Other disorders involve enzymes that are involved in the synthesis of essential cofactors. For example, tetrahydrobiopterin (BH_4) and pyridoxine (vitamin B6) are necessary cofactors for enzymes that are involved in monoamine synthesis.

Disorders of Monoamine Metabolism

The monoamine neurotransmitters include the catecholamines (dopamine, norepinephrine, and epinephrine) and serotonin. Figure 73-1 illustrates the key pathways involved in their synthesis and degradation. Deficiencies in tyrosine hydroxylase (TH), aromatic amino acid decarboxylase, monoamine oxidase (MAO), and dopamine β-hydroxylase (DBH) have been identified in human patients.

BH_4 is a necessary cofactor for both tryptophan hydroxylase and TH, which lead to the synthesis of serotonin and dopamine, respectively. BH_4 is synthesized in three steps from guanosine triphosphate (GTP)

TABLE 73-1. Pediatric Neurotransmitter Disorders

Disorders of Monoamine Metabolism
Disorders of monoamine synthesis
Tyrosine hydroxylase (TH) deficiency
Aromatic L-amino acid decarboxylase (AADC) deficiency
Disorders of BH_4 synthesis
Autosomal dominant GTP cyclohydrolase (GTPCH) deficiency (Segawa disease)
Autosomal recessive GTPCH deficiency
Pyruvoyl-tetrahydropterin synthase (PTPS) deficiency
Sepiapterin reductase (SR) deficiency
Dihydropteridine reductase (DHPR) deficiency
Pterin-4a-carbinolamine dehydratase (PCD) deficiency
Disorders of vitamin B6 dependency
Pyridoxine-dependent seizures (amino-adipic dehydrogenase deficiency)
Pyridoxal-5-phosphate-dependent seizures (pyridox(am)ine phosphate oxidase deficiency)
Disorders of monoamine degradation
Monoamine oxidase deficiency
Dopamine β-hydroxylase deficiency
Disorders of Glycine Metabolism
Glycine encephalopathy
Disorders of GABA Metabolism
Disorders of GABA synthesis
GAD Deficiency
Pyridoxine and pyridoxal-5-phosphate dependency*
Disorders of GABA Degradation
GABA-transaminase deficiency
SSADH deficiency
Homocarnosinosis

GABA = γ-aminobutyric acid; GAD = glutamic acid decarboxylase; SSADH = succinic semialdehyde dehydrogenase.

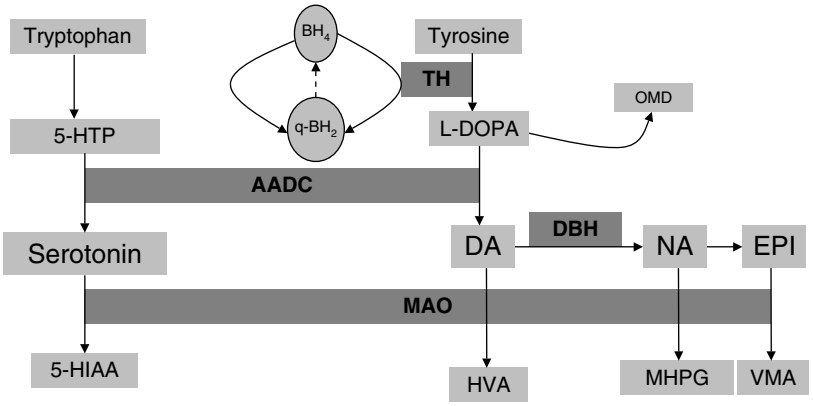

FIGURE 73-1. Monoamine metabolism. BH_4 = tetrahydrobiopterin; q-BH_2 = q-dihydrobiopterin; TH = tyrosine hydroxylase; 5-HTP = 5-hydroxytryptophan; OMD = 3-O-methyldopa; AADC = aromatic L-amino acid decarboxylase; DA = dopamine; NA = norepinephrine; EPI = epinephrine; DBH = dopamine β-hydroxylase; MAO = monoamine oxidase; 5-HIAA = 5-hydroxyindole acetic acid; HVA = homovanillic acid; MHPG = 3-methoxy-4-hydroxyphenylgycol; VMA = vanillylmandelic acid.

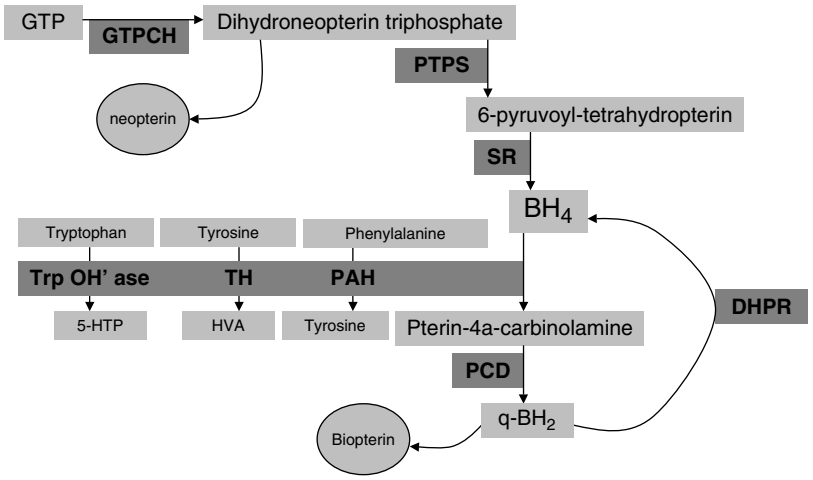

FIGURE 73-2. Tetrahydrobiopterin (BH_4) metabolism. GTP = guanine triphosphate; GTPCH = GTP cyclohydrolase I; PTPS = 6-pyruvoyl-tetrahydropterin synthase; SR = sepipterin reductase; BH_4 = tetrahydrobiopterin; DHPR = dihydropterin reductase; Trp OH'ase = tryptophan hydroxylase; TH = tyrosine hydroxylase; PAH = phenylalanine hydroxylase; 5-HTP = 5-hydroxytryptophan; HVA = homovanillic acid; PCD = pterin-carbinolamine reductase; q-BH_2 = q-dihydrobiopterin.

(Figure 73-2). Deficiencies have been identified in each of the enzymes in this pathway: GTP cyclohydrolase I, 6-pyruvoyl-tetrahydropterin synthase (PTPS), and sepiapterin reductase (SR). When BH_4 acts as a cofactor for various hydroxylases (including tryptophan hydroxylase, TH, and phenylalanine hydroxylase [PAH]), it is converted to pterin-4a-carbinolamine. This is then recycled back into BH_4 in a two-step process involving the enzymes pterin-4a-carbinolamine dehydratase and dihydropteridine reductase (DHPR). Deficiencies in these enzymes are associated with elevated blood phenylalanine with the exceptions of autosomal dominantly inherited GTP cyclohydrolase deficiency (Segawa disease) and autosomal recessively inherited TH and SR deficiencies. Therefore, these disorders require cerebrospinal fluid (CSF) analysis for laboratory diagnosis.

Disorders of Monoamine Synthesis

TH Deficiency

TH catalyzes the conversion of tyrosine to L-dopa. Enzyme deficiency leads to impaired synthesis of dopamine, as well as epinephrine and norepinephrine. This is an autosomal recessive condition, with gene locus 11p15.5. It is represented by a progressive encephalopathy and poor prognosis. This condition is also known as the recessive form of dopa-responsive dystonia (in contrast to Segawa disease, to be covered below). Clinical features

include dystonia that is at best partially responsive to L-dopa, ptosis, miosis, and postural hypotension.[1,2]

Aromatic Amino Acid Decarboxylase Deficiency

Aromatic amino acid decarboxylase deficiency is an autosomal recessive disorder that combines serotonin and catecholamine deficiencies. The gene locus is 7p11. This enzyme catalyzes the decarboxylation of L-dopa and 5-hydroxytryptophan (5-HTP) to dopamine and serotonin, respectively. Enzyme deficiency is characterized by a CSF profile of low homovanillic acid (HVA) and 5-hydroxyindoleacetic acid, high L-dopa, 5-HTP, and O-methyldopa (an L-dopa metabolite), and normal pterin levels. The associated clinical features are hypotonia and extrapyramidal movement disorders, such as torticollis, dystonia, blepharospasm, athetosis, and myoclonus. Other manifestations are profound developmental delay, irritability, sleep disturbances, and autonomic manifestations, such as temperature instability, impaired diaphoresis, hypersalivation, recurrent syncope, or cardiorespiratory arrest. The syndrome may present in the neonate with hypothermia, lethargy, poor sucking, ptosis, and hypotension. Treatments reported in this condition with variable efficacy are L-dopa, pyridoxine (cofactor for the enzyme), dopamine receptor agonists, trihexyphenidyl, MAO inhibitors, antiepileptic agents, and serotonergic agents.[3–5]

PTPS Deficiency and Other BH_4 Defects with Peripheral Hyper-Phenylalaninemia

In addition to acting as a cofactor for tryptophan hydroxylase and TH, BH_4 is also a cofactor for PAH, the enzyme responsible for converting phenylalanine to tyrosine. Thus, several of the secondary disorders of monoamine metabolism are associated with high levels of serum phenylalanine detected on newborn screening or assessment of plasma amino acids. These include autosomal recessive GTP cyclohydrolase deficiency, pterin-carbinolamine dehydratase deficiency, DHPR deficiency, and PTPS deficiency. Measurement of urinary biopterin helps distinguish the disorders with peripheral hyperphenylalaninemia, with decreased biopterin in PTPS deficiency and elevated biopterin in DHPR deficiency (versus normal in phenylketonuria).

PTPS deficiency is the most prevalent and heterogeneous form of hyperphenylalaninemia not attributed to phenylketonuria. Common symptoms are truncal hypotonia, appendicular hypertonia, bradykinesia, cogwheel rigidity, generalized dystonia, and marked diurnal fluctuation. Other clinical features include difficulty in swallowing, oculogyric crises, somnolence, irritability, hyperthermia, and seizures. Chorea, athetosis, hypersalivation, rash with eczema, and sudden death have also been reported. Patients with mild phenotype may deteriorate if given folate antagonists, such as methotrexate, which can interfere with a salvage pathway through which dihydrobiopterin is converted into BH_4 via dihydrofolate reductase. Treatment options include substitution with neurotransmitter precursors (L-dopa, 5-hydroxytrptophan), MAO/COMT inhibitors, and BH_4. In DHPR deficiency, there are basal ganglia calcifications that are reversible with folinic acid supplementation.[6]

BH_4 Defects Without Peripheral Hyperphenylalaninemia

Segawa Disease (GTP Cyclohydrolase 1 Deficiency)

Dr. M. Segawa described hereditary dopa-responsive dystonia with diurnal fluctuation.[7] Typically, patients have dystonia that worsens in the late afternoon or evening. The syndrome was ultimately recognized as an autosomally dominant inherited partial deficiency of guanosine triphosphate cyclohydrolase-1 (GTPCH 1) activity. This enzyme represents the rate-limiting step in BH_4 synthesis. The responsible gene has been mapped to chromosome region 14q22.1-q22.2 spanning a 30 kb region and containing six exons. There are multiple mutations of the gene with highly variable penetrance.

The cardinal clinical features of GTP cyclohydrolase deficiency, or "Segawa dopa-responsive dystonia," are fluctuating dystonia and tremor in the presence of normal cognition.[8] Both the dystonia and tremor may have a prominent postural component. Isolated toe gait, a female predominance, and presentation with only prominent postural tremor in adulthood have all been described. The response to L-dopa in this syndrome is gratifying and sustained throughout life. A trial of L-dopa can be diagnostic although other forms of dystonia may appear dopa responsive. Hence, CSF neurotransmitter metabolite is recommended for identification of low HVA, 3-O-methyldopa, and neopterin levels (Table 73-2). The dopamine synthesis line appears more involved than the serotonergic line; hence, serotonin reuptake inhibitors are not standard therapy.

TABLE 73-2. Cerebrospinal Fluid Neurotransmitter Metabolite Profiles for Pediatric Neurotransmitter Diseases

Defect	Metabolite Concentrations				
	BH_4	Neopterin	HVA	5-HIAA	3-OMD
GTP-CH (dominant)	↓	↓	↓	±↓	N
Tyrosine hydroxylase	N	N	↓	N	N
AADC	N	N	↓	↓	↑

AADC = aromatic L-amino acid decarboxylase; BH_4 = tetrahydrobiopterin; GTP-CH = GTP cyclohydrolase; 5-HIAA = 5-hydroxyindoleacetic acid; HVA = homovanillic acid; 3-OMD = 3-O-methyldopa.

Segawa disease is not associated with high serum levels of phenylalanine; there is adequate intrahepatic conversion of phenylalanine to tyrosine. Clinicians should be aware of atypical presentations, such as spastic diplegia, asymmetric limb dystonia, or even writer's cramp. There may be highly variable phenotypes within the same family.

SR Deficiency

SR catalyzes the final step in BH_4 synthesis. The clinical phenotype includes progressive psychomotor retardation, dystonia with diurnal variation, oculogyric crises, choreoathetosis, seizures, temperature instability, hypersalivation, microcephaly, and irritability. A murine model confirms that in the absence of enzyme, there are greatly reduced levels of the catecholamines and serotonin, the neurotransmitters that depend on BH_4 for their synthesis.

Pyridoxine and Pyridoxal-5-Phosphate Dependency

The biologically active form of pyridoxine, pyridoxal 5-phosphate, is a cofactor for many enzymatic reactions. While pyridoxine-dependent epilepsy was formerly considered a disorder of GABA synthesis due to the role of pyridoxal-5-phosphate as a cofactor for glutamic acid decarboxylase (GAD), recent findings indicate that other biochemical pathways are involved. Pyridoxine is a cofactor for aromatic amino acid decarboxylase and is therefore required for monoamine synthesis. CSF analysis in pyridoxine dependency will have a similar profile to aromatic amino acid decarboxylase deficiency.

Pyridoxine-dependent seizures are typically suspected in a neonate with refractory seizures, often of prenatal onset perceived by the mother as a fetal hammering sensation, and an electroencephalogram (EEG) showing continuous epileptiform activity or a burst-suppression pattern that then responds dramatically to a trial intravenous dose of 50 to 100 mg of pyridoxine. Additional clinical features include jitteriness, hypothermia, neonatal dystonia, and a prodrome of restlessness, irritability, and emesis preceding seizures. Atypical phenotypes have been described with later onset and clinical response only after repeated trials. The syndrome indicates a lifelong dependence on pyridoxine therapy.

Pipecolic acid was identified as a marker in plasma and CSF in pyridoxine-dependent epilepsy, and subsequent gene linkage studies identified mutations in the *ALDH7A1* gene, which encodes α-aminoadipic semialdehyde dehydrogenase (also called antiquitin). When antiquitin activity is reduced, pipecolic acid and Δ-piperideine-5-carboxylate accumulate (Figure 73-3). The accumulating carboxylate forms a condensation product with pyridioxal-5-phosphate, which presumably sequesters the latter from brain.[10]

Dietary intake of pyridoxine comes from vegetables (as pyridoxine) and meat (originally as pyridoxamine). These are both oxidized to pyridoxine-5-phosphate via an enzyme known as pyridox(am)ine oxidase. A newly recognized disorder, pyridox(am)ine oxidase deficiency, has been associated with fetal distress and intractable seizures.[11] As with pyridoxine dependency, the CSF neurotransmitter profile will resemble aromatic amino acid decarboxylase deficiency. This metabolic error is correctable by administration of pyridoxal-5-phosphate, but not pyridoxine. While aminoadipic semialdehyde dehydrogenase and pyridox(am)ine oxidase deficiencies lead to a presumed brain deficit of pyridoxal-5-phosphate, the mechanism for the seizures remains unexplained.

Disorders of Monoamine Degradation

MAO Deficiency

MAO-A and B catalyze the deamination of the biogenic amines including serotonin, epinephrine, norepinephrine, and tyramine. Both have been mapped to locus

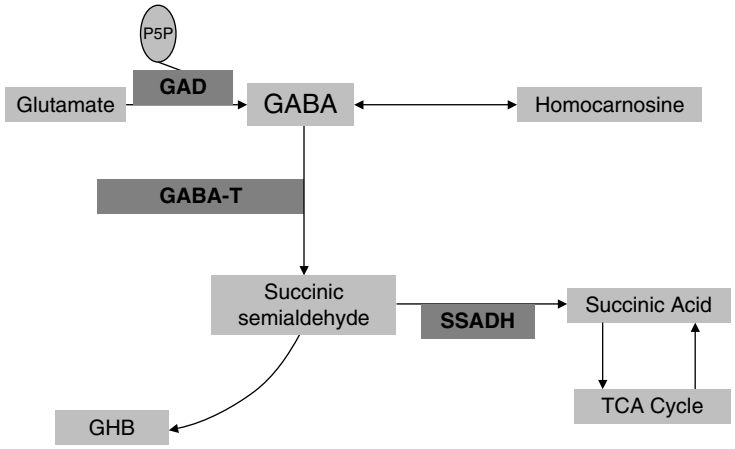

FIGURE 73-3. GABA metabolism. GABA = γ-aminobutyric acid; GAD = glutamic acid decarboxylase; P5P = pyridoxine-5-phosphate (cofactor for GAD); GABA-T = GABA transaminase; GHB = γ-hydroxybutyric acid; SSADH = succinic semialdehyde dehydrogenase.

Xp11.23-11.4. MAO-A deficiency has been documented in a single family of affected males with mild mental retardation and violent aggressive behavior.[12] MAO-B deficiency has been associated with Norrie disease, a syndrome of congenital blindness, deafness, and mental retardation mapped to Xp11.4.

DBH deficiency

DBH catalyzes the synthesis of norepinephrine from dopamine. Patients with this disorder have low levels of norepinephrine, epinephrine, and their metabolites in plasma, CSF, and urine. In addition, norepinephrine normally acts as an inhibitor of TH. Thus, in this disorder, TH is overactive, resulting in an even higher concentration of dopamine.

DBH deficiency is typically diagnosed in adults presenting with orthostatic hypotension and noradrenergic failure. There is no other evidence of neurologic problems. Retrospective case histories, however, have indicated ptosis, hypotension, hypothermia, and hypoglycemia in the perinatal period. It is suspected that adults living with this disorder have the mildest end of the phenotypic spectrum. Mothers of affected patients have a notable history of a high rate of spontaneous abortions.[13]

Disorders of Glycine Metabolism

Glycine, a simple amino acid structurally but ubiquitous and vital, functions as a neurotransmitter with dual excitatory (cortical) and inhibitory (spinal cord and brain stem) effects. Glycine has multiple properties, as it is gluconeogeneic via pyruvate, constitutes over 15% of amino acids of essential structural proteins, such as collagen, elastin, and gelatin, is incorporated into purines, glutathione, and the heme protein, and is involved in important detoxifying conjugation reactions. Nonketotic hyperglycinemia, commonly termed NKH, was originally named to distinguish it from ketotic hyperglycinemia (now recognized as propionic acidemia), and the preferred term is glycine encephalopathy.

Glycine encephalopathy is a group of autosomal recessive conditions related to varying defects of the complex tetrameric protein that constitutes the glycine cleavage system. This tetramer consists of a P protein containing a pyridoxal-5-phosphate-dependent glycine decarboxylase, an H protein with a lipoic acid containing hydrogen carrier, a T protein which is tetrahydrofolate dependent, and an L protein which is a lipoamide dehydrogenase moiety. Defects of the glycine cleavage system are detected by a ratio of CSF to plasma glycine > 0.08.

The classic phenotype is a neonatal encephalopathy with seizures (often of prenatal onset), lethargy, hypotonia, myoclonus, and apnea. EEG tracings reveal a burst-suppression pattern. Neuroimaging studies have demonstrated agenesis of the corpus callosum, and neuropathologic findings are those of spongiform white matter degeneration. Magnetic resonance (MR) spectroscopy may reveal a peak corresponding to glycine.[14] Variations on this theme include an infantile pattern with presentation after 6 months of partial seizures or hypsarrythmia; a childhood later variant with mild mental retardation, delirium, chorea, and vertical gaze palsies, and a late-onset pattern in adults with progressive spastic diplegia and optic atrophy. The P protein defect is associated with the neonatal-onset forms. While H and T protein defects are associated with later-onset forms, there are also milder phenotypes of the neonatal-onset form showing mutations in the glycine decarboxylase gene. Measurements of glycine cleavage activity in liver or cultured lymphoblasts, or genetic identification, are available. Secondary causes of hyperglycinemia include valproic acid and D-glyceric acidemia.

Sodium benzoate has been used to reduce glycine concentrations in plasma and CSF, and dextromethorphan has been used as an N-methyl-D-aspartic acid receptor blocker. The outcome is generally poor, although benefit was described in three affected siblings with a mild phenotype and considerable residual enzymatic activity.[15]

Disorders of GABA Metabolism

GABA, the major inhibitory neurotransmitter of the brain, is synthesized primarily from glutamate via GAD (Figure 73-3). The first enzymatic degradative step of GABA involves the enzyme GABA-transaminase, which utilizes α-ketoglutarate from the Krebs cycle to regenerate a molecule of glutamate for every molecule of GABA that is catabolized. Hence, the vital neurotransmitter pools of GABA and glutamate are constantly replenished and tightly regulated. The product of the GABA-transaminase reaction is succinic semialdehyde, which is normally converted to succinic acid via the enzyme succinic semialdehyde dehydrogenase (SSADH). Succinic acid, thereby, enters the Krebs cycle, where α-ketoglutarate is formed. The ongoing conversion of glutamate to GABA and then back to glutamate is known as the GABA shunt.

Disorders of GABA Synthesis

GAD Deficiency

GAD is a pyridoxal-5-phosphate requiring enzyme, which converts glutamate to GABA. It exists in two isoforms, GAD65 and GAD67. GABA has an important role in embryonic development, as substantiated by the association of cleft palate in transgenic mice deficient in the GAD67. Mice null for GAD67 are born at the expected

frequency but die of severe cleft palate shortly after birth. A population study reported linkage in patients with nonsyndromic cleft lip with and without cleft palate and specific GAD67 haplotypes.[16] This supports a role for the GABA-synthesizing GAD67 gene in normal human facial development and represents a newly recognized disorder of GABA synthesis.

Disorders of GABA Degradation

GABA-Transaminase Deficiency

GABA-transaminase deficiency is an autosomal recessive disorder characterized by abnormal development, seizures, and high levels of GABA in serum and CSF.[17] The disorder appears to be extremely rare and has been confirmed in a single family.

SSADH Deficiency

Jakobs and colleagues described the index case of SSADH deficiency (γ-hydroxybutyric aciduria) in 1981.[18] Since then, more than 350 cases have been identified and more than 60 of them reported.[19] SSADH activity is deficient, impairing the predominant oxidative conversion of succinic semialdehyde to succinic acid. Instead, succinic semialdehyde is reduced to 4-hydroxybutyric acid (γ-hydroxybutyric acid [GHB]).

The phenotype of SSADH deficiency encompasses a wide spectrum of neurologic manifestations and universally leads to a significant neurodevelopmental disorder including severe expressive language deficits with a high incidence of psychiatric dysfunction. The most common clinical findings are developmental delay, mental retardation, hypotonia, sleep disturbances, inattention, hyperactivity, and anxiety.[20] Approximately, half of patients have epilepsy, usually with generalized tonic-clonic seizures and also atypical absence and myoclonic. Other common neurologic features are hyporeflexia and nonprogressive cerebellar ataxia. The disorder typically has a static course and not the progressive or intermittent pattern classically associated with a metabolic encephalopathy. There is a minority of patients, involving 10%, with a degenerative course featuring regression and prominent extrapyramidal manifestations. The long-term outlook for affected patients is characterized by variable degrees of mental retardation with persistence of severe expressive language deficit, neuropsychiatric morbidity with prominent anxiety and hallucinations, and continuing dependence for activities of daily living.

Neuroimaging has typically revealed the presence of increased T2-weighted MR imaging signal most commonly involving the globus pallidus, cerebellar dentate nucleus, subcortical white matter, and brain stem. Specialized editing on MR spectroscopy will reveal elevated parenchymal levels of GABA and γ-hydroxybutyrate. The diagnosis is suggested by the accumulation of 4-hydroxybutyric acid on urine organic acid analysis without an accompanying metabolic acidosis. Enzymatic assay on lymphocytes is available for confirmation. The human gene, *ALDH5A1*, maps to chromosome 6p22 consists of 10 exons encompassing 38 kb of DNA. This is an autosomal recessively inherited disorder. Over 35 mutations have been identified, and there is no clear phenotype/genotype correlation.

Currently, there is no standard treatment. Vigabatrin, an irreversible inhibitor of GABA transaminase, has been associated with decreases in CSF γ-hydroxybutyrate. While there has been an interest in following CSF γ-hydroxybutyrate levels during therapy with vigabatrin in patients with SSADH deficiency, neither laboratory or clinical effects have been consistent with vigabatrin therapy. Benzodiazepines, risperidal, fluoxetine, and methylphenidate have been helpful for anxiety and behavioral problems. Symptomatic treatments for seizures using carbamazepine and lamotrigine have also shown some success. Valproate is avoided, as it inhibits activity of residual SSADH, and its use is associated with increased concentration of GHB and other SSADH deficiency metabolites. Liver-mediated gene therapy in the murine model demonstrated a reduction in GHB levels in liver, kidney, serum, and brain extracts, setting the stage for future clinical trials.

Homocarnosinosis

Homocarnosine is a brain-specific dipeptide of GABA and histidine. Homocarnosine concentrations are highest in the dentate and inferior olivary nuclei, intermediate in substantia nigra and globus pallidus, and lowest in frontal cortex, caudate nucleus, and nucleus accumbens. Homocarnosinosis appears to be rare, although identification requires CSF assays for homocarnosine. The phenotype has been described with progressive spastic paraplegia, mental deterioration, and retinal pigmentation.

Conclusion

Inherited disorders of neurotransmitters include a group of metabolic syndromes having important neurologic manifestations and particular therapeutic implications. Currently, disorders of the metabolism of monoamines (dopamine, serotonin, norepinephrine, epinephrine), glycine, and GABA have been defined. The impressive responsiveness of Segawa fluctuating dystonia to L-dopa is a hallmark feature of previously unrecognized neurologic morbidity becoming treatable at any age. The neonatal entities of glycine encephalopathy and pyridoxine-dependent seizures have widening clinical phenotypes and

new variants including a form of the latter requiring specific pyridoxal-5-phosphate therapy. SSADH deficiency is relatively common in comparison to the remainder of this group of disorders but presents with a typically nonprogressive course that belies the presence of an underlying metabolic encephalopathy. Other disorders of GABA metabolism, as well as heretofore unrecognized neurotransmitter disorders, will require increasing use of CSF analysis and emerging modalities, for example, MR spectroscopy, for diagnosis and treatment.

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CHAPTER 74

ATAXIA, CLUMSINESS, AND TREMOR

EUGEN J. BOLTSHAUSER, MD

Ataxia—literally "lack of order"—can, in general terms, describe problems with movements resulting from incoordination. This may affect gross motor, fine motor, tongue, and ocular movements. Ataxia is not identical to a cerebellar problem.

Motor coordination is a complex function requiring (1) sensory input from muscles and joints, (2) motor output from the cortex and basal ganglia via the efferent motor tracts, including the lower motor neuron, and (3) a modulating control from the cerebellum. In addition, the vestibular system does influence the equilibrium.

Typical signs of cerebellar dysfunction include gait ataxia, limb ataxia, limb dysmetria, tremor, dysarthria, and nystagmus. Depending on the degree of dysfunction, the child with ataxia presents with obvious imbalance and a widebased gait, but standing or walking may not be possible or are declined. Refusal of standing or walking or limb coordination tasks are not specific for a cerebellar disease and may be prompted by, in arbitrary order, (1) pain, (2) weakness, (3) dystonia or spasticity, (4) myoclonus, and (5) vertigo.

Clinical Approach

The relevant questions to be deduced by history and clinical examination are as follows:

- Is ataxia the problem (in contrast to other causes for incoordination)?
- Is cerebellar dysfunction related to the medial structures or a hemispheral lesion?
- Are we dealing with "pure" ataxia, or is there evidence for other system involvement?
- What is the time course of symptoms?

The answers to these questions will determine the diagnostic approach. Before considering differential diagnostic categories, the following should be noted:

- Dysfunction of midline cerebellar structures causes truncal ataxia.
- Truncal ataxia is tested—with increasing difficulties—to assess the patient's ability to maintain posture while standing, walking, tandem walking, or standing on one leg.
- Dysfunction of lateral (hemispheral) cerebellar structures results in ipsilateral limb ataxia.
- To determine limb incoordination, conduct ageappropriate tests of functional coordination while the patient is building a tower, working with peg boards, writing and drawing, and so on.
- Motor incoordination resulting from a disturbance of afferent sensory input is exacerbated by eye closure. Cerebellar ataxia does not worsen, or worsens only slightly, if visual guidance is eliminated.
- Patients with incoordination tend to move fast. Incoordination is more obvious if movements are performed at slow speed.
- Before the diagnostic label of congenital ataxia can be applied, prolonged observation is often required. Ataxia is usually preceded by hypotonia and delay of motor development, sometimes even mimicking a neuromuscular disorder.

Differential Diagnosis

Mode of presentation and time course can be used to discuss the clinical approach. We consider the following categories:

- Acute cerebellar ataxia
- Subacute ataxia
- Intermittent ataxia
- Congenital nonprogressive ataxia
- Chronic progressive ataxia

Obviously, overlaps between categories do exist. Relevant information is given in tabular form. Additional comments are given for each category.

Acute Ataxia

The most likely options are given in Table 74-1. The onset of ataxia is within hours,"overnight," or within a few days. Acute (postinfectious) cerebellar ataxia is the most common form. It commonly affects children aged 1 to 4 years, mostly 1 to 3 weeks after a viral or other infection (in particular varicella, mumps, parvovirus, Epstein-Barr virus). It is a self-limiting condition, with marked improvement seen within 1 to 4 weeks. Steroid medication is not recommended. We tend to be very selective with regard to additional investigations, as the cerebrospinal fluid (CSF), neuroimaging, and electroencephalogram (EEG) are usually normal.

Opsoclonus-myoclonus syndrome (also called Kinsbourne syndrome, myoclonic encephalopathy, or "dancing-eyes, dancing-feet syndrome") may be associated with an occult neuroblastoma. This is considered a paraneoplastic manifestation. Therefore, this tumor has to be searched for with an appropriate work-up (usually involving abdominal and thoracic imaging and scintigraphy, as urinary catecholamine excretion can be normal). The course of this condition is often protracted and fluctuating. Steroid therapy is usually efficient but other or additional immune-modulating treatments may be required for prolonged periods.

The diagnosis of acute disseminated encephalomyelitis is made on the basis of neuroimaging and CSF examination. Depending on the overall situation (marked neurologic disturbance or impaired consciousness), steroid medication may be considered.

Bacterial meningitis or a cerebellar tumor does not present as acute ataxia, and re-examination exposes other findings. Posterior circulation stroke and multiple sclerosis are rare causes of acute ataxia in childhood.

Subacute Ataxia

The onset of ataxia is less dramatic, compared with that of acute ataxia. With subacute presentation, space-occupying lesions must be considered. Neuroimaging is, thus, a key element in the diagnostic work-up. Brainstem tumors initially often lack signs of increased intracranial pressure. Papilledema is not a prerequisite to consider a neoplasm.

Subacute (symmetrical) ataxia may be prompted by sensory neuropathies. Neurologic examination (areflexia) and, if appropriate, neurophysiologic studies will guide further diagnostic steps.

TABLE 74-1. Differential Diagnosis of Acute Ataxia

Intoxication (drugs, alcohol)
Acute (postinfectious) cerebellar ataxia
Acute disseminating encephalomyelitis
Opsoclonus-myoclonus syndrome (Kinsbourne's myoclonic encephalopathy)
Basilar migraine
Miller Fisher syndrome (ataxia-areflexia-ophthalmoplegia)
First episode of intermittent ataxia

Intermittent Ataxia

Children with intermittent ataxia related to a metabolic disturbance may be neurologically intact in the interval, and metabolic screening tests after recovery can be (false) normal (Table 74-2). It is, therefore, important to plan appropriate metabolic investigations (ie, obtain body fluids for later analysis) in advance. The so-called episodic ataxias are the rare, dominantly inherited channelopathies that are responsive to oral acetazolamide medication. The diagnosis depends on family history, personal history, episodic findings, and, if possible, mutation analysis.

Congenital Nonprogressive Ataxia

A list of conditions and syndromes with this presentation is given in Table 74-3. Neuroimaging is important in this category. The final diagnosis often rests on additional disease-specific (clinical, ophthalmologic, and imaging) findings. It is remarkable that many patients with congenital nonprogressive ataxia have cognitive impairment, in keeping with Schmahmann's concept of the "cerebellar cognitive affective syndrome".

TABLE 74-2. Differential Diagnosis of Intermittent Ataxia

Intermittent ataxia in the context of underlying metabolic disorder (eg, organic acidopathies, amino acidopathies, urea cycle disorders, mitochondrial disorder)
Episodic ataxias (EAs) (dominantly inherited channelopathies, acetazolamide responsive)
EA1: resulting from mutations in the sodium channel KCNA1
EA2: resulting from mutations in the calcium channel CACNA1A

TABLE 74-3. Differential Diagnosis of Congenital Nonprogressive Ataxia

Posterior fossa malformations (eg, Dandy-Walker syndrome, rhombencephalosynapsis)
Nonprogressive cerebellar ataxias (with or without cerebellar hypoplasia)
Syndromes (selection)
Joubert (+ other cerebello-ocular-renal)
Ritscher-Schinzel
Gillespie's
Cerebellar hypoplasia-oligophrenia-ataxia-coloboma-hepatic fibrosis (COACH)
Congenital oculomotor apraxia (Cogan)
Rare metabolic disorders (GA type 1, L-2-OH GA, CDG)

CDG = congenital disorders of glycosylation; GA = glutaric aciduria.

Chronic Progressive Ataxia

Table 74-4 includes relevant diseases; however, this list is not meant to be complete. The diagnostic work-up should be tailored to the individual situation. The context of history and findings (in particular "ataxia plus" symptoms) often allow targeted diagnostic investigations. Despite extensive work-up, the final diagnosis actually remains unknown in a considerable proportion of progressive ataxias.

It is particularly important not to miss the rare instances of treatable ataxias: Refsum's disease (serum phytanic acid elevated), primary (isolated) vitamin E deficiency (low serum vitamin E), and abetalipoproteinemia (screening: very low serum cholesterol). It should be noted that ataxia is not the primary leading sign of these treatable forms.

Whether gluten sensitivity is associated with progressive ataxia is controversial.

The recently described group of dominantly inherited spinocerebellar ataxias (most are unstable trinucleotide repeat expansions) are exceptionally rare in the pediatric age group.

Clumsiness

Clumsiness is a difficult topic—not only for trainees but also for experienced pediatricians.

Definition

Clumsiness is a "soft" term. The author is not aware of a generally accepted definition. Clumsy children can be considered slow in motor learning and impaired in motor performance and manual skills with regard to fine and gross motor functions. However, clumsiness is not only a problem of "motor-executive" functions. A successful "performance" requires an intact motor system but also depends on the understanding of the task, visual perceptual abilities, perception of the position of body parts in space, and so on. Clumsiness may represent a problem within the spectrum of normal development (probably the most common presentation). It can be associated with attention-deficit hyperactivity disorder (ADHD) or is the presenting sign of a neurologic disease. We have encountered children labeled as clumsy for a prolonged time before a defined condition, such as muscular dystrophy, peripheral neuropathy, or a metabolic or neurodegenerative disorder (such as Friedreich's ataxia), has been diagnosed.

TABLE 74-4. Differential Diagnosis of Progressive Ataxia in Childhood

Friedreich's ataxia
Ataxia telangiectasia (Louis-Bar's syndrome)
Niemann-Pick disease type C
Neuronal ceroid-lipofuscinoses (late infantile, juvenile form)
Ataxia-ocular apraxia syndromes
Late-onset GM2 gangliosidosis
Leukodystrophies (some forms, eg, vanishing white matter disease, megalencephalic leukoencephalopathy with subcortical cysts)
Mitochondrial encephalopathies (some forms, in particular, Kearns-Sayre syndrome, NARP, MERRF)
Spinocerebellar ataxias
Refsum's disease
Primary isolated vitamin E deficiency
A-beta-lipoproteinemia
Giant axonal neuropathy
Autosomal recessive spastic ataxia (Charlevoix-Saguenay)

NARP = neuropathy/neurogenic weakness, ataxia, retinitis pigmentosa; MERRF = myoclonic epilepsy, ragged red fibers.

Examination and Additional Investigations

Screening tests for clumsiness are not available, at least not for the office visit. A careful history and detailed examination (and experience) are required to potentially separate "developmental" clumsiness from clumsiness in the context of a neurologic disease. Additional investigations depend on the specific situation. Neuroimaging is generally not indicated. It must be remembered that clumsiness is not merely a motor problem. One should consider whether important "afferent" deficits have been ruled out.

Management

What may appear to be a "minimal" motor problem may well be a "maximal" handicap in daily life (especially in a society where motor performance and sports are ranked very high). This often results in teasing by peers, lack of self-esteem, and impairment of social interaction. The child's and parents' complaints have to be taken seriously. Although reassurance may be sufficient in some instances, in other situations a remedial physical program may be warranted. Reassessment of the situation is mandatory at certain intervals.

Tremor

Types of Tremor

There are still many controversial issues with regard to tremor, even among authorities. The Movement Disorder Society has suggested definitions as well as clinical and syndromic classifications of tremors. Because of the numerous etiologies for tremor, a practical etiologic classification or a valid physiologic classification is not available. Tremor is a rhythmic, involuntary, oscillatory movement of a body part. The amplitude and frequency of tremor is not crucial to this definition.

For practical purposes, the following categories are presented.

Resting Tremor

Resting tremor occurs in a body part that is supported in such a way that skeletal muscle activation is neither necessary nor intended. Resting tremor is mostly found in Parkinson's disease and other basal ganglia disorders. This is a rarity in childhood and will not be considered further here.

Action Tremor

Tremors not occurring at rest are categorized as action tremor. This occurs during any voluntary contraction of skeletal muscle. The most relevant forms of action tremor are postural tremor, kinetic tremor, and intention tremor.

Postural Tremor

Postural tremor occurs during an attempt to hold a body part motionless against the force of gravity.

Kinetic Tremor

These are tremors occurring during any voluntary movement.

Tremor during Target-Directed Movements (Intention Tremor)

Classic intention tremor is present when amplitude increases during visually guided movements toward a target at the determination of the movement. It can be inferred that a disturbance of the cerebellum and its afferent or efferent pathway is present. The type and distribution of the tremors in hyperthyroidism and due to sympathomimetic drugs correspond to those of physiologic tremor; most drug-induced tremors are a mixture of postural and kinetic tremors.

Essential Tremor

Essential tremor (ET) is the most frequent movement disorder. Patients exhibit a mixed postural and kinetic tremor without other neurologic abnormalities. The upper limbs are predominantly involved. Other body parts are less commonly involved. Many patients with ET inherit the disease through an autosomal-dominant gene; however, the ratio of hereditary versus sporadic ET is unknown. This diagnosis can be made on clinical grounds if this tremor type is of long duration. The "red flags" are rapid onset, unilateral tremor, rest tremor, and gait disturbance.

Practical Management of a Child with Tremor

History and Examination

The following information should be obtained in the history taking and examination:

- Drugs (such as valproate, sympathomimetics, or centrally acting substances)
- Family history of tremor
- Past history of neurologic disorders
- Type oftremor
- Onset
- Asymmetry
- Evidence of systemic disease (eg, hyperthyroidism)
- Evidence of additional neurologic symptoms (such as dystonia, gait disturbance)

Additional Investigations

This depends on the individual situation. If the constellation is typical for ET, no additional investigations (neuroimaging) are mandatory. Treatable conditions, in particular hyperthyroidism and Wilson's disease, should be considered. Wilson's disease may present in the first decade as hemolytic anemia or as a hepatic problem; a neurologic presentation is not encountered before the second decade and not as an isolated tremor. Serum ceruloplasmin is decreased in 95% of patients with Wilson's disease, and corneal Kayser-Fleischer ring is a consistent finding at presentation.

Treatment

There is no general treatment for tremor per se. ET may be improved with propranolol (0.5 to 1.5 mg/kg bodyweight) and primidone. However, most children and adults with ET are not functionally impaired and manage without drug treatment. Medication can be limited to particular (stressful) events. Long-term use of primidone, which is metabolized, in part, to phenobarbital, is probably not desirable.

Suggested Readings

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Practitioner and Patient Resources

National Ataxia Foundation (NAF)
2600 Fernbrook Lane, Suite 119
Minneapolis, MN 55447
Phone: (763) 553-0020
Fax: (763) 553-0167
E-mail: naf@ataxia.org
http://www.ataxia.org
NAF is dedicated to improving the lives of persons affected by ataxia through support, education, and research. The NAF Web site includes ataxia publications, research, events, support groups, and links to other ataxia resources.

European Federation of Hereditary Ataxias
Haagwindelaan 19
B-3090 Overijse, Belgium
Phone: +32 2 657 1510
Fax: +32 2 657 6176
http://www.euro-ataxia.org/

ADCA-Association of The Netherlands
http://www.ataxie.nl
ADCA-Association of The Netherlands objectives are to increase public awareness on ADCA, provide information on ADCA, to organize meetings of patients and relatives, and support scientific research. Their Web site has English and Dutch versions.

International Essential Tremor Foundation (IETF)
7046 West 105th Street
Overland Park, KS 66212-1803
Phone: (913) 341-3880
Fax: (913) 341-1297
http://www.essentialtremor.org
IETF provides information, services, and support to individuals and families affected by essential tremors. IETF encourages and promotes research in an effort to determine the causes, treatment, and ultimately the cure for ET.

Worldwide Education and Awareness for Movement Disorders (WE MOVE)
204 West 84th Street
New York, NY 10024
Phone: (212) 241-8567 or (800) 437-MOV2
Fax: (212) 875-8389
http://www.wemove.org
The WE MOVE Web site serves as the hub of movement disorder activities on the Web. This site provides detailed information on more than 20 specific movement disorders.

National Pediatric Myoclonus Center
SIU School of Medicine
St. John's Pavillon, Room 3A133
P.O. Box 19658
Springfield, IL 62794-9658
Phone: (217) 545 7635
Fax: (217) 545 1903
http://www.omsusa.org
This opsoclonus-myoclonus syndrome (OMS) site is extremely beneficial for families. It includes information not only on OMS but also insurance information and financial assistance.

Chapter 75

Treatment of Tic Disorders

Harvey S. Singer, MD

Tourette syndrome represents only one entity in a spectrum of disorders that have tics as their cardinal feature. In addition to tics, individuals with these disorders often have a variety of concomitant psychopathologies that may be more significant than the tics themselves. Treatment should be individualized on the basis of the functional impairment of tics and/or associated problems, sources of support, capacity for coping, and challenges associated with various stages of development. Education of the patient and family are essential and medications should be targeted and reserved only for those problems that are functionally disabling and not remediable by nondrug interventions.

Tics, the hallmark of tic disorders, are readily observed but broadly defined (involuntary, sudden, rapid, repetitive, nonrhythmic, stereotyped) movements or vocalizations (phonic productions). This chapter reviews diagnostic approaches and principles of clinical management of tic disorders. Tics are manifested in an extensive variety of forms, have different degrees of severity and duration, and no two patients have exactly the same course. Simple motor tics are brief rapid movements that often involve only one muscle group, eg, eye blink, head jerk, shoulder shrug. Complex motor tics are abrupt movements that involve either a cluster of simple movements or a more coordinated sequence of movements. Complex motor tics may be nonpurposeful (facial or body contortions) or appear to be more purposeful but actually serve no purpose (touching, hitting, smelling, jumping, obscene gestures) or have a dystonic character. Simple vocal tics include sounds and noises such as grunting, barking, yelping, sniffing, and throat clearing. Complex vocalizations include syllables, phrases, echolalia (repeating other people's words), palilalia (repeating one's own words), or coprolalia (obscene words). Coprolalia, one of the most distressing and recognizable symptoms, occurs in only about 10% of patients. Please see Table 75-1 for examples of simple and complex tics.

Tic Disorders

Tourette syndrome (TS) represents only one entity in a spectrum of disorders that have tics as their cardinal feature, ranging from a mild transient form to TS. Tic disorders can be divided into two major categories based on their duration: "transient" (present for less than 12 months) and "chronic" (present for more than 12 months).

Transient Tic Disorder

Mildest and most common tic disorder.

TABLE 75-1. Examples of Simple and Complex Tics

Simple Motor Tics	Complex Motor Tics
Blinking	Scratching
Nose twitching	Touching
Head jerking	Throwing
Oculogyric movements	Hitting
Bruxism	Kicking
Neck twisting (spasmodic torticollis)	Licking
Wide mouth opening	Squatting
Abdominal tensing	Jumping
Imitating gestures (echopraxia)	
Obscene gestures (copropraxia)	
Simple Vocal Tics	**Complex Vocal Tics**
Sniffing	Words
Throat clearing	Phrases
Grunting	Abrupt, unnecessary increased volume of parts squeaking of speech
Moaning	Talking to oneself
Coughing	Repetition of words of others (echolalia)
Blowing	Repetition of one's own words, phrases (palilalia)
Sucking	Obscenities or profanity (coprolalia)

Chronic (Motor or Phonic) Tic Disorder

Diagnosis requires that tics be present for more than one year and individuals have either entirely motor or, less commonly, solely vocal tics.

TS

The formal criteria provided by the TS Classification Study Group includes as follows: the presence of multiple motor and at least one vocal tic (not necessarily concurrently); a waxing and waning course with tics evolving in a progressive manner; the presence of tic symptoms for at least 1 year; the onset of symptoms before age 21; the absence of a precipitating illnesses (eg, encephalitis, stroke, or degenerative disease) or medication; and the observation of tics by a knowledgeable individual. Adult onset tic disorders have been reported and are often associated with potential environmental triggers, severe symptoms, greater social morbidity, and a poorer response to medications. TS occurs worldwide with increasing evidence of common features in all cultures and races. The prevalence (number of cases in population at a given time) of TS varies widely in published reports but is estimated at 1 to 10 of 1,000 children and adolescents.

Tourettism, Tourette-like or Secondary Disorder

Terms used for tic syndromes that do not meet the criteria for TS, such as those associated with another medical condition, such as infection, drugs, toxins, stroke, and head trauma, or found in a variety of sporadic, genetic, and neurodegenerative disorders.

Natural History of Tics

Tics have a waxing and waning course. They typically begin at about 6 years of age and may have a period of worsening. Investigators have suggested that maximum tic severity occurs between the ages of 8 to 12 years and is then followed by a steady decline in symptoms. Although variable, most studies suggest that tics improve in late adolescence or early adulthood. Proposed predictors of severity and longevity are controversial.

Comorbidity

The list of associated problems in TS continues to increase, and individuals solely with chronic tics are less impaired than those with coexisting neuropsychiatric issues.

Obsessive-compulsive behaviors are reported to occur in about 20 to 60% of patients with TS, but some studies report an incidence up to 60 to 89%. Obsessive compulsive disorder (OCD), characterized by recurrent thoughts and/or repetitive behavior that causes marked distress and interferes with normal functioning, is less common.

Attention deficit hyperactivity disorder (ADHD) is characterized by impulsivity, hyperactivity, and a decreased ability to maintain attention. It typically begins about age 4 to 5 years and usually precedes the onset of tics by 2 to 3 years. In TS probands, ADHD is reported to affect about 50% (range 21–90%) of referred cases.

Anxiety and depression: several studies have found an increased incidence of depression and anxiety in patients with TS.

Episodic outbursts (rage) and self-injurious behavior have been described in patients with TS. Whether these behaviors are due to the presence of other disruptive psychopathology, such as obsessions, compulsions, ADHD-related impulsivity, risk-taking, rage, or affective disorders is unclear.

Academic difficulties: severe tics, psychosocial problems, ADHD, OCD, learning disabilities, and medications can result in poor school performance in children with tics. Individuals with TS typically have normal intellectual functioning although there may be decreased executive dysfunction, discrepancies between performance and verbal intelligence quotient, impairments of visual perceptual achievement, or a decrease in visual-motor skills.

General Principles of Treatment

1. Evaluate all potential problems including tics, comorbid conditions, problem severity, and impairment. All patients with tics should have confirmation of the diagnosis and identification of any secondary etiologies. Information should be accrued from various sources in order to identify associated psychopathology and/or academic problems.
2. Determine the priority of symptoms in conjunction with the patient, family, and school personnel. The physician should determine, based on functional impairment, whether it is the patient's tics or associated problems that require initial attention. Treatment must be individualized based on the impairment, the capacity for coping, as well as sources of support.
3. Educate the patient and family by providing basic information on diagnostic criteria for tic disorders and other tic characteristics. The latter includes the following: a waxing and waning course and occurrence in recurrent bouts in a nonrandom pattern; the appearance of tics during inquiries about specific movements or following observation of a movement or sound; exacerbation of tics during periods of anticipation, emotional upset (eg, anxiety, excitement, anger), or fatigue; reduction of tics when absorbed in activities, eg, concentrating, emotionally pleased, or during sleep; and ability to actively suppress tics.

4. Explain that tics are involuntary, caused by biologic factors, and although exacerbated by stress, emphasize that the latter is not the underlying pathophysiologic etiology.
5. Recognize that environmental factors, such as a preceding β-hemolytic streptococcal infection and/or a diagnosis of pediatric autoimmune neuropsychologic disorder associated with streptococcal infections (PANDAS), as an etiology for TS is controversial. The treating physician should possess a working knowledge of proposed PANDAS criteria and recognize areas of debate.
6. Discuss the symptoms and potential treatment of comorbid diagnoses (eg, ADHD, OCD, behavioral and learning problems) as separate entities. This approach enables the family as well as other health care workers to focus on individual needs.
7. Treatment goals are to reduce tics to a level where they no longer cause a significant psychosocial disturbance, not complete suppression of all motor and phonic tic activity.
8. Lastly, treatment of a child with TS requires a chronic commitment and at times a comprehensive multidisciplinary approach.

Treatment of Tics

Just because tics exist is not an adequate reason to initiate pharmacotherapy. Medications should be targeted and reserved for only those problems that are functionally disabling and not remediable by nondrug interventions. Education of the patient and family should be considered the initial and primary treatment for tics. Often, a thorough discussion of the disorder alleviates parental and patient anxieties and corrects misinformation gathered on the internet. Specific points to cover in family discussions include the following: most cases fulfilling the diagnostic criteria for TS have few difficulties secondary to their tics; the majority of cases are mild, and less than 40% require tic-suppressing medication; parents are often more concerned about tics than their affected offspring; most patients improve during the teenage-early adulthood years; treatment is symptomatic and not curative; and all medications come with side effect risks.

Specific Indications for Therapy

1. Psychosocial impairment: psychosocial difficulties include the loss of self-esteem, comments from peers, excessive worries about tics, failure to participate in family, social, or after school activities.
2. Functional impairment: rarely tics may interfere with physical skills such as penmanship, reading, concentration, etc.
3. Classroom disruption: usually due to vocal tics.
4. Musculoskeletal discomfort: repetitive movements can lead to muscle strain/soreness or bone dislocation.
5. Persistence of impairing tic symptoms: tics have a waxing and waning course and a proposed fractal pattern. Hence, decisions to treat should be based on the presence and persistence of significantly impairing tics.

Nonpharmacologic Therapy

Classroom strategies of potential benefit include education of teachers and fellow students, providing optional study breaks, and eliminating unnecessary stressful situations. Behavioral approaches are considered in motivated individuals strongly wishing to avoid medications or as an adjunctive therapy in those with stressful life situations or in whom increasing the medication dose may result in excessive side effects. A variety of behavioral treatments (relaxation training, biofeedback, hypnosis, conditioning techniques, massed negative practice, awareness training, and habit reversal) have been proposed as alternative therapeutic approaches for tics, but few have been adequately evaluated.

Recognizing that tics are generally exacerbated by stress and anxiety, relaxation therapy has been considered an alternative treatment. Relaxation is broadly defined to include a variety of procedures including progressive muscle relaxation, deep breathing, visual imagery, autogenic training (ie, repetition of statements suggesting a relaxed state), and producing postures and activities characteristic of a relaxed state. In a randomized, double-blind, placebo-controlled study assessing relaxation techniques, tic severity was reduced in the formally trained group, but improvement was short-lived and not significant. In contrast to relaxation training, a growing body of research is accumulating, supporting the efficacy of habit reversal therapy (HRT). HRT is a multicomponent approach including awareness training, self monitoring, relaxation training, competing response training, and motivational techniques. It is based on the belief that tic reduction is possible if an individual can become aware of tics and if the affected individual performs a physically competing response to prevent or interrupt tic occurrence. Several small trials have documented the efficacy of HRT in suppressing tics and larger studies are currently underway. The mechanism by which HRT is effective is speculative.

There is little or no supporting scientific evidence for the use of alternative dietary therapies (ie, vitamins, herbs, protein supplementation, elimination diets, and others) or acupuncture.

Pharmacotherapy for Tics

The goal of treatment is not to suppress movements entirely but to eliminate the specific reason for starting

therapy (eg, psychosocial or physical discomfort). A predrug EKG should be obtained prior to starting neuroleptics as well as some atypical neuroleptics. Therapeutic agents should be prescribed at the lowest effective dosage and the patient monitored for efficacy and side effects. Medications should be started at low doses with gradual increases in dosage. Monotherapy should be used whenever possible. Generally, after several months of successful treatment, I consider a gradual taper of the medication during a nonstressful (eg, summer vacation) time.

A two-tiered pharmacotherapy approach is recommended, recognizing that tic-suppressing medications can be broadly divided into two groups: Tier 1, "milder" nonneuroleptic medications and Tier 2, neuroleptic and atypical neuroleptic medications. Tier 1 medications should be used first, especially in patients with milder tics. A variety of medications are prescribed for tic suppression, but only two, pimozide and haloperidol, are approved by the FDA. In general, most medications have not had efficacy documented in adequate double-blind trials, and only a limited number have been evaluated in direct comparison protocols. Additionally, in studies showing drug superiority to placebo, the percent improvement of tics ranged from only 30 to 65%. A recent publication (Scahill and colleagues, 2006) has evaluated pharmacologic treatments and classified medications into three categories: *A*, *good* supportive evidence for short-term safety and efficacy derived from at least two randomized placebo-controlled trials with positive results; Category *B* corresponds to treatments with *fair* supportive data as evidenced by at least one positive placebo-controlled study; and Category *C* represents *minimal* supportive evidence, such as open-label studies or accumulated clinical experience. Although these categories are included in this chapter, the reader should be aware that they represent the extent of evaluation and not necessarily the relative degree of improvement.

First Tier Pharmacotherapy

Category A

None.

Category B

Medications in this category include the α-adrenergic antihypertensive medications clonidine and guanfacine and represent my initial pharmacologic therapy. Nevertheless, despite their frequent usage over the past 20 years, controlled trials are limited and effectiveness ranges from being equal to placebo to 50%.

Clonidine: This α_2-adrenergic receptor agonist primarily activates presynaptic autoreceptors and reduces norepinephrine release and turnover. Start with a test dose of 0.05 mg, and if there are no side effects, the dose is increased to 0.05 mg bid. Doses are then gradually increased about every 5 to 7 days up to a daily dose of 0.1 to 0.4 mg. Response to treatment may be delayed for 6 to 8 weeks. Blood pressure and pulse should be measured at baseline and monitored. The most common side effect is drowsiness that often resolves spontaneously. A transdermal patch preparation is not recommended since in active children, it may be difficult to keep the patch in place and there can be local skin hypersensitivity reactions. Clonidine should be gradually tapered to avoid rebound tic exacerbation, anxiety, and hypertension.

Guanfacine: Guanfacine is a longer acting α_2-adrenergic receptor agonist that is more selective for postsynaptic 2a receptors located in the prefrontal cortex. The initial dose is 0.5 mg at bedtime with gradual increases, as needed, to final doses up to 3 mg per day in two divided dosages. Guanfacine is less sedating and generally well tolerated; the most common side effects are sedation, fatigue, and headaches.

Category C

Baclofen: Baclofen, a $GABA_B$ receptor agonist used in the treatment of spasticity, has been variably effective as a treatment for TS. In a double-blind, placebo-controlled crossover study, baclofen in doses of 20 mg tid statistically improved overall well being but did not reduce motor or vocal tic activity.

Clonazepam: Clonazepam, a benzodiazepine, has shown only a modest tic-suppressing effect in limited studies. Side effects include drowsiness, dizziness, fatigue, short-term memory problems, and disinhibition.

Topiramate: Open-label studies have suggested a potential beneficial effect.

Levetiracetam: Despite two open-labeled trials claiming improvement in all patients, a double-blind placebo-controlled protocol has found improvement to be only equal to that of placebo.

Second Tier Pharmacotherapy

If an individual fails initial therapy or presents with severe tics, medications in the Tier 2 (classical neuroleptic or atypical neuroleptics) category should be initiated. Medications in this tier may be more beneficial than 1st tier treatments, but side effects often limit their usefulness. Adverse effects with antipsychotics may occur even with low doses and include sedation, parkinsonism, acute dystonic reactions, bradykinesia, akathisia, tardive and withdrawal dyskinesias, cognitive blunting, depression, aggression, "fog states," weight gain, prolonged cardiac conduction times (QTc), endocrine dysfunction, and poor school performance with or without school phobia. Neurologic side effects occur with use of atypical neuroleptics but possibly less frequently than seen with

some typical neuroleptics. Differences in the effectiveness of atypical antipsychotics may be related to their potency of dopamine receptor antagonism. My personal preferences is to use monotherapy, to start with pimozide, and then, if necessary, to use sequentially fluphenazine, risperidone, aripiprazole, olanzepine, and haloperidol in that order. In individuals with significant behavioral issues, one should consider using typical neuroleptics as the initial Tier 2 therapy.

Category A

Pimozide: Pimozide, a diphenylbutylpiperidine derivative, is a D2 receptor antagonist that also blocks calcium channels. Before starting pimozide, an EKG should be obtained in order to detect a prolonged Q-T interval, a contraindicating factor. Medication is started at 0.5 to 1 mg/d given at bedtime. The dose is gradually increased, if necessary, in 1mg increments on a weekly basis and used in a bid dosing schedule. A general target range is 2 to 8 mg/d. The use of macrolide antibiotics (clarithromycin, erythromycin, troleandomycin, and ditromycin), azole antifungals (ketoconazole, itraconazole), and protease inhibitors should be avoided. Grapefruit juice may also inhibit the metabolism of pimozide, resulting in increased serum concentrations of this medication.

Risperidone: This atypical neuroleptic acts at low doses on 5-HT2 receptors, while at higher doses, it is a potent D2 antagonist. It also has moderate to high affinity for α_1-adrenergic, D3, D4, and H1 histamine receptors. Risperidone, suggested to be equally effective to pimozide, is started at 0.5 mg/d, given at night, and increased as necessary at 5- to 7-day intervals to a maximum of about 4 mg per day in two divided doses.

Haloperidol: Haloperidol, a butyrophenone and D2 blocking agent, was the first traditional antipsychotic shown to be an effective tic suppressor. Studies comparing haloperidol to pimozide have usually identified equal efficacy, but pimozide was better tolerated at equivalent doses. Medication is started at 0.5 mg per day and increased by small amounts every week, to a target range of about 1 to 4 mg per day.

Category B

Fluphenazine: Fluphenazine, a traditional antipsychotic, is an antagonist at both D1 and D2 dopaminergic receptors. It is an effective tic-suppressing agent that may have fewer side effects than other neuroleptics. Treatment is started with a dose of 1 mg at bedtime and increased by 1 mg every 5 to 7 days. A typical daily dose is 2 to 4 mg/d.

Ziprasidone: Ziprasidone, an atypical neuroleptic, has been shown to be more effective than placebo in suppressing tic symptoms in patients with TS. The starting dose is 5 mg in the evening with gradual increases to 40 mg in divided doses if tolerated. Ziprasidone uses more than one metabolic pathway and is not vulnerable to drug-drug interaction. An EKG should be performed before and after starting treatment to detect possible cardiac conduction abnormalities.

Category C

Olanzepine: Olanzepine, an atypical antipsychotic, exhibits moderate to high affinity for D2, D4, 5-HT2A, 5-HT2C, and α_1-adrenergic receptors and also binds to D1 receptors. The initial dose is 2.5 mg at bedtime, and, if necessary, the dose is gradually raised to 5 to 10 mg per day in divided doses.

Aripiprazole: Aripiprazole, a partial dopamine agonist, has been shown in case reports and open-labeled studies to be beneficial in suppressing tics. The starting dose in adults is 2.5 to 5 mg with a usual dose range of 10 to 20 mg

Quetiapine: Quetiapine, based on case reports, may be an effective treatment for tics.

Other Dopaminergic Pharmacotherapy

Category B

Pergolide: Pergolide, a mixed D1/D2/D3 dopamine receptor agonist, has been shown to improve tics at a dose about one-tenth of that used in treating Parkinson's disease, ie, 0.1 to 0.3 mg per day in divided doses. Since this is an ergot medication, reports of ergot-induced cardiac valvuopathy, pericardial and retroperitoneal fibrosis, vasospasm, and cardiac toxicity should limit its usefulness.

Category C

Tetrabenazine: Tetrabenazine, a benzoquinolizine derivative, is a dopamine depleting agent that acts by inhibiting central vesicular monoamine transporter type 2. Several studies have confirmed a tic-suppressing effect at doses of 25 to 100 mg/d. This medication is not available in the United States. The combined use of tetrabenazine and a classical neuroleptic may permit the use of lower doses of each medication with fewer side effects. Drug-related problems include sedation, depression, parkinsonism, insomnia, anxiety, and akathisia.

Other Nondopaminergic Therapies

Category B

Botulinum toxin (Botox): It reduces muscle activity by inhibiting acetylcholine release at neuromuscular junctions. Botox has been successful in treating motor and vocal tics, and injection sites have included face, back, shoulder, cervical and upper thoracic regions, and vocal cords. Benefits appear in 3 to 4 days and last a mean of 14 weeks.

Category C

Deep Brain Stimulation: It is an experimental procedure that in case reports and small studies has been helpful in reducing tics.

Treatment of Comorbid Problems

ADHD

Despite earlier suggestions that stimulants may induce or exacerbate tics in children with ADHD, an expanding number of studies have demonstrated that this is not an invariable or even common manifestation. Hence, psychostimulant medications, generally regarded as the treatment of choice for ADHD, are not contraindicated in children with TS. Alternative medications, with documented superiority to placebo, for the treatment of ADHD symptoms in children with TS include clonidine, guanfacine, atomoxetine, and desipramine. Clonidine and guanfacine are effective for both tics and ADHD, but when used in children for treatment of ADHD, clonidine should be prescribed in a tid to qid dosing schedule. Atomoxetine, a selective norepinephrine reuptake inhibitor, is used in doses of 1.0 to 1.5 mg/kg/d and given in two divided doses. Common adverse effects of atomoxetine include nausea, emesis, diminished appetite, and insomnia.

OCD

Cognitive-behavioral therapy, selective serotonin reuptake inhibitors, and the tricyclic antidepressant clomipramine are effective treatments for OCD. Empirical support for treatment in children is best with clomipramine, fluoxetine, sertraline, and fluvoxamine. All medications should be started in low doses and increased gradually. Side effects of increased concern are behavioral activation and suicidal ideation.

Other Behavioral Disorders

Episodic outbursts (rage), argumentativeness, disruptive behaviors, conduct problems, anxiety, and mood disorders are relatively common in patients with TS. In many, these difficulties are commingled with tics, ADHD, and OCD presenting a major challenge for the family and physician. In complex cases, it is essential that the patient receives a comprehensive evaluation and care from a multidisciplinary team of specialists.

Suggested Readings

Coffey BJ, Shechter RL. Treatment of co-morbid obsessive compulsive disorder, mood, and anxiety disorders. Adv Neurol 2006;99:208–21.

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Piacentini JC, Chang SW. Behavioral treatments for tic suppression: habit reversal training. Adv Neurol 2006;99:2227–33.

Qasaymeh MM, Mink JW. New treatments for tic disorders. Curr Treat Options Neurol 2006;8:465–73.

Scahill L, Erenberg G, Berlin CM, et al. Contemporary assessment and pharmacotherapy of Tourette syndrome. NeuroRx 2006;3:192–306.

Woods DW, Himle MB, Conelea CA. Behavior therapy: other interventions for tic disorders. Adv Neurol 2006;99:234–40.

Patient and Practitioner Resource

Tourette Syndrome Association
42-40 Bell Boulevard
Bayside, NY 11361-2874
Phone: (718) 224-2999
<http://www.tsa-usa.org/>

Chapter 76

Paroxysmal Movement Disorders

Donald L. Gilbert, MD, MS

Paroxysmal movement disorders in children are rare but should not be missed, as they can cause significant impairment. The diagnosis is based on careful history, physical examination, and directly observing or viewing home videos of the episodes.

This chapter gives a succinct review of evaluation and management of paroxysmal movement disorders in children. Although paroxysmal movement disorders are rare, paroxysmal neurologic events in children are extremely common. Thus, the appropriate diagnostic approach is a common one in child neurology. That is, the patient and family present with a description of spells where neurologic function is altered. The neurologic examination is normal. The spells often do not occur during the face-to-face evaluation. A detailed history is critical.

Paroxysmal movement disorders discussed in this chapter involve symptoms categorized as "movement disorders" and not other conditions that intermittently affect movement. The phenomenology of these is hyperkinetic, not rigid or parkinsonian. That is, the pathologic movements generated include dystonia, athetosis, chorea, ballismus, and other dyskinesias: problems where movement, posture, and/or tone are affected in a dynamic fashion. These disorders localize anatomically to the basal ganglia and to cortical-subcortical pathways and may involve neurotransmission or fluctuations in membrane potentials. By convention, the episodic ataxias are often included in some discussions of paroxysmal movement disorders; however, these are addressed in Chapter 74 on "Ataxia."

Several paroxysmal movement problems that are usually not classified with this group of disorders are described elsewhere in this book. Tics and stereotypies are paroxysmal movement disorders. These common disorders often require evaluation of developmental problems and psychiatric comorbidities. Myoclonus may occur alone or as a symptom of a wide variety of neurologic diseases and disorders and is addressed in chapters covering those topics. Psychogenic movement disorders may also be paroxysmal but are addressed in Chapter 80 on "Conversion Reaction."

Overlap with Epilepsies

Seizures are paroxysmal and usually affect movement but are not classified as paroxysmal movement disorders. The anatomic origin of seizures, with few exceptions, is cortical. Although the epilepsies are an enormous and distinct topic in child neurology, it is worth noting that the paroxysmal movement disorders represent an area of overlap between the epilepsies and chronic movement disorders, for three main reasons: First, although the anatomic localization of the dysfunction differs, the cellular pathophysiology may be quite similar. That is, seizures may occur due to episodic, inappropriate hypersynchronous discharges in cortical neural networks because of dysfunction in, for example, membrane ion channels. Some paroxysmal movement disorders may result from similar or identical processes, which localize instead to basal ganglia nuclei. Second, the medical treatments may be the same for some paroxysmal movement disorders; the treatment of choice is anticonvulsant medication. Third, for both seizures and paroxysmal movement disorders the most accurate, cost-effective diagnostic tool available to a clinician is a good history.

Paroxysmal Movement Disorder Syndromes: Clinical Features and Treatment

Benign Paroxysmal Torticollis of Infancy

This disorder generally begins in the first 3 to 12 months of life. The phenomenology is torticollis, laterocollis, or retrocollis, sometimes triggered by changes in posture. An episode may begin with abnormal eye movements. Infants are often irritable, with pallor, vomiting, and ataxia. Duration varies from minutes to days. Attacks may occur with striking periodicity, for example, every 4 weeks. Neurologic examination between attacks is normal. At onset, gastrointestinal reflux, brainstem or cervical spine lesions, or iatrogenic dystonic reactions must be considered in the differential. The diagnosis usually becomes clear after repeated episodes have occurred. Prognosis is good, though some infants subsequently manifest other episodic brainstem disorders, such as benign paroxysmal vertigo or migraines.

Paroxysmal Kinesigenic Dyskinesia

This disorder can begin from infancy to adulthood but typically begins between ages 6 and 15 years. The phenomenology is dystonia, often asymmetric, involving lower or upper limbs. Athetosis, chorea, or other dyskinesias may occur. Consciousness is preserved. The trigger is rapid movement, especially following a period of rest. Specific sensations may precede the episodes, and some patients can abort some attacks at this time. Duration is usually seconds or minutes. Attacks may occur dozens of times per day. Neurologic examination between attacks is normal. Autosomal dominant, recessive, and sporadic cases have been reported. Diagnosis is clinical, though a normal ictal electroencephalogram (EEG) may sometimes be needed to confirm the clinical impression. Other paroxysmal movement disorders and episodic ataxia type I are in the differential. Treatment with carbamazepine is effective. Prognosis is good and frequency of episodes may diminish in adulthood.

Paroxysmal Nonkinesigenic Dyskinesia

This disorder can begin in early infancy. The phenomenology is dystonia or choreoathetosis, often bilateral, affecting laryngeal or facial muscles. Consciousness is preserved. These are not triggered by movement but may be triggered by ingestion of alcohol or caffeine, or by fatigue, hunger, or stress. Duration is usually 10 to 15 minutes but may last for hours. Frequency ranges from less than once monthly to more than once daily. Neurologic examination between attacks is normal. Autosomal dominant cases have been reported. Diagnosis is clinical, though a normal ictal EEG may sometimes be needed to confirm the clinical impression. In cases beginning in infancy, alternating hemiplegia of childhood is in the differential diagnosis. Treatment is not often successful. Small case series report benefit from benzodiazepines, acetazolamide, haloperidol, and some anticonvulsants. Substantial benefit has been reported in two intractable and painful adult cases with deep brain stimulators in the thalamus and globus pallidus interna.

Paroxysmal Exercise-Induced Dyskinesia

This disorder begins from age 2 to age 30. The phenomenology is dystonia or other dyskinesias, preferentially involving legs but sometimes spreading to arm or face. They may be unilateral or bilateral. Consciousness is preserved. The trigger is continuous exercise of over 5 minutes, such as walking or running. Duration is usually 5 to 30 minutes. Attack frequency varies. Neurologic examination between attacks is normal. Most cases are sporadic, but autosomal dominant cases have been reported. Diagnosis is clinical. Treatment is not often successful. Small case series report benefit from levodopa, carbamazepine, and trihexyphenidyl.

Symptomatic Paroxysmal Dyskinesias

These have been linked to many neurologic diseases involving basal ganglia but also cerebral cortex, brainstem, or spinal cord. Etiologies have included trauma, perinatal hypoxic ischemic injury, various metabolic and endocrine disorders, and multiple sclerosis. Treatment of the underlying disease, when possible, is the primary goal. Effectiveness of medication targeting the dyskinesias varies.

Diagnostic Approach to Paroxysmal Movement Disorders in Children

For disorders beginning in infancy, the diagnostic workup needs to be careful and thorough. In infants, one cannot be as confident that (1) consciousness is preserved during spells and (2) that an examination with no abnormalities detected indicates no central nervous system pathology. Thus, in infants, a hypothesis-driven diagnostic evaluation, usually including neuroimaging, and possibly including EEG/video EEG and laboratory testing, is generally required.

In children over the age of 2 years, and particularly in older children who can provide clinical history, if the neurologic examination between episodes is completely normal, and the preservation of consciousness throughout the episode seems certain, then the diagnostic approach involves primarily a careful history,

augmented by direct observation in clinic or through home videos.

Many families tend to describe the events in vague terms. The most helpful history is obtained by asking the individual and family to describe the first event, the most recent event, or some other event they remember well. The clinician should be skilled at obtaining a very detailed description of the "before, during, and after" of the episode. Many families can imitate the movements that occur, to some degree. The diagnostic questions are

1. Is there a consistent trigger such as movement?
2. What is the phenomenology?
3. How long do the episodes last, and how frequent are they?

Subsequently, with patience, kinesigenic, and exercise-induced dyskinesias can often be induced in clinic by having the patient perform the recognized trigger. It is helpful to videotape these in clinic if possible. Otherwise, obtaining a home video for review should be requested.

In this setting, historical information and observation are generally sufficient to make a clinical diagnosis and treatment decisions, in cases that fit the phenotypes described above.

If the neurologic examination is not normal between episodes, a hypothesis-driven diagnostic work-up, usually beginning with neuroimaging, is necessary, as this may represent a symptomatic movement disorder.

Referral to a movement disorder specialist, particularly when the diagnosis remains in doubt, should be considered, for there are even rarer diseases outside the scope of this chapter that may present with paroxysmal movements.

The value of molecular/genetic diagnosis, as for all neurologic disorders, depends on a variety of case-specific factors, and genes available for testing are constantly increasing. At present, for the disorders described in this chapter, there is no routine clinical genetic testing available, but linkage testing in research laboratories may be obtained.

Suggested Readings

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Lotze T, Jankovic J. Paroxysmal kinesigenic dyskinesias. Semin Pediatr Neurol 2003;10:68–79.

Yamada K, Goto S, Soyama N, et al. Complete suppression of paroxysmal nonkinesigenic dyskinesia by globus pallidus internus pallidal stimulation. Mov Disord 2006;21:57–9.

Zorzi G, Conti C, Erba A, et al. Paroxysmal dyskinesias in childhood. Pediatr Neurol 2003;28:168–72.

Physician Resources

A useful strategy for these rare cases is to enter two to three specific features of the case into databases, such as Online Mendelian Inheritance in Man (OMIM), found at <http://www.ncbi.nlm.nih.gov/gquery/gquery.fcgi> and review the text and clinical synopses for the hits. The publicly funded GeneTests Website (<http://www.genetests.org/>) can then be used to find clinical and research laboratories, where testing can be obtained. This site also contains nice reviews.

Practitioner and Patient Resources

In all cases, education of the family should be provided. Useful information for families about paroxysmal dyskinesias is available on the Worldwide Education and Awareness for Movement Disorders (WEMOVE) Web site (<http://www.wemove.org/>).

Chapter 77

Chorea

Bradley L. Schlaggar, MD, PhD

This chapter describes various causes of chorea that can present in pediatric patients. It is not intended to be inclusive. Indeed, the focus is on Sydenham's chorea, the most common acquired chorea of childhood. Diagnostic and treatment approaches are considered as well.

The term "chorea" refers to a hyperkinetic movement disorder characterized by frequent, brief, and purposeless movements that tend to flow from one body part to another body part in an unpredictable manner. The movements of chorea are, by definition, more chaotic and less brief than the shock-like rapidity of myoclonus. They are briefer than the slow, sustained movements of dystonia. When small in amplitude, chorea may cause an individual to appear fidgety or restless. When large in amplitude, chorea can involve dramatic, ballistic limb movements. Chorea and ballismus are perhaps best thought of as a spectrum sharing the same differential diagnosis. Phenotypically, akathisia can appear as chorea, but the former is the result of a sense of a need to move (usually a manifestation of dopamine receptor blockade due to neuroleptic medication), whereas the latter refers to involuntary movements. Choreic movements can be sudden and jerky or can be more continuous and flowing. In the latter case, the term choreoathetosis is used, with athetosis referring to a movement perhaps best characterized as moving from one dystonic position to another.

In current parlance, the term "choreiform" is often used to describe the benign twitching or "piano-playing" movements seen in many normal young children and those with Tourette syndrome and attention-deficit hyperactivity disorder when arms are extended during the neurologic exam. This finding was often noted in patients who, in an earlier era, carried the diagnosis of minimal brain disease. However, historically "choreiform" and chorea have been used interchangeably. Therefore, "minimal chorea" may be a more apt term than "choreiform" for describing the above finding. (It is interesting to note that at the turn of the twentieth century, "chorea" was often used to describe any of the hyperkinetic movement disorders.)

Although these definitions and descriptions of movement types may seem straightforward and categorical, in many cases the semiology of a hyperkinetic movement disorder is difficult to categorize. It is well recognized that movement disorder "experts" will often disagree when confronted with video documentation of a patient's movement problem (a situation certainly not unique to movement disorder specialists). From a neurobiologic standpoint, it is not at all clear that strict borders exist between these categories and that there isn't some fluidity within a particular patient. Serial examinations of a patient may reveal a greater degree of myoclonus than chorea at one moment in time, but more chorea than myoclonus at another moment in time. Apropos of this point, when the famous neurologist Derek Denny-Brown was asked by a resident physician to distinguish between chorea and myoclonus, he said, "That's easy, chorea is a kind of myoclonus" (PK Dodge, personal communication).

Nonetheless, most of the time the principal movement disorder can be readily characterized. When chorea is the primary manifestation, a substantial differential diagnosis follows.

Etiologies

Chorea can be classified by etiology into primary (typically inherited) and secondary (or acquired) disorders.

Primary causes include essential chorea and benign familial (hereditary) chorea. Recently, the genetics of some causes of benign familial chorea have been investigated.

Autosomal dominant, recessive, and X-linked inheritances have been described.

Huntington's disease is perhaps the most famous inherited cause of chorea; the autosomal dominant transmission of an expanded triplet repeat (CAG) at the huntingtin site on chromosome 4. However, Huntington's disease rarely presents in childhood with chorea. Indeed, juvenile-onset Huntington's disease (also known as the Westphal variant) is typically characterized by parkinsonism (ie, bradykinesia and rigidity) and dystonia. Importantly, the number of CAG triplet repeats very clearly predicts the age of onset of Huntington's disease. For example, the normal repeat number is < 35. When the number is > 70, onset of symptoms occurs at less than 18 years of age.

The majority of chorea in childhood is secondary or acquired. Well over 100 causes of secondary chorea have been identified, but for most patients chorea is not the only sign or symptom. The most common cause of chorea in childhood is acute rheumatic fever (ARF). Other important causes include metabolic disorder (hypo-or hypernatremia, hypocalcemia, hyperthyroid, pregnancy, or hypo-or hyperglycemia), perinatal brain injury (cerebral palsy), infectious or peri- or postinfectious disease (in addition to ARF, there is acute disseminated encephalomyelitis, viral encephalitis, and celiac disease), other autoimmune disease (systemic lupus erythematosus [SLE] or antiphospholipid antibody [APLA] syndrome), vascular disorders (post-pump chorea, moyamoya syndrome, or basal ganglia stroke), toxins (methanol, carbon monoxide, manganese), other heredodegenerative disorders (Wilson's disease, ataxiatelangiectasia, Niemann-Pick type C disease, Friedreich's ataxia, Machado-Joseph disease, dentatorubropallidoluysian atrophy, chorea-acanthocytosis gangliosidoses, pantothenate kinase-associated neurodegeneration other lysosomal storage diseases), and other disorders of intermediary metabolism (glutaricaciduria, Lesch-Nyhan syndrome, or pediatric neurotransmitter diseases).

Chorea can present as a paroxysmal dyskinesia, which is covered in the chapter on paroxysmal movement disorders.

Chorea can be the manifestation of conversion. In general, psychogenic movement disorders can be quite difficult to discern. Whereas video-electroencephalography can be of tremendous help when attempting to establish whether a convulsion is epileptic or nonepileptic, physiologic corroboration is harder to come by for so called pseudo movement disorders. We strongly recommend that parents attempt to video-document the movement of concern, particularly if it is paroxysmal, so that it can be scrutinized by a neurologist experienced in movement disorders. It is very important to note that because behavioral changes are often observed as part of rheumatic chorea, one must avoid misconstruing the chorea of Sydenham's chorea as psychogenic.

Common iatrogenic causes of chorea or exacerbations of extant chorea include dopamimetics, antiepileptics (particularly phenytoin), antidepressants (such as selective serotonin reuptake inhibitors), methylphenidate (and other stimulants), antihistamines, anticholinergics, calcium channel blockers, digoxin, and oral estrogens. Dopamine receptor blocking agents can, rarely and paradoxically, produce a tardive dyskinesia that manifests as chorea. These agents can also produce an akathisia that, as stated above, is henotypically indistinguishable from chorea.

Diagnostic Evaluation

A diagnostic strategy that focuses on the more likely causes with an emphasis on treatable causes includes these tests: throat culture with rapid group A β-hemolytic streptococcal (GABHS) testing, serum antistreptolysin O and antideooxyrobonuclease (AntiDNase) B titers, electrocardiogram, echocardiogram, thyroid function tests, complete blood count (with thick smear looking for acanthocytes), antinuclear antibody test, erythrocyte sedimentation rate, magnetic resonance imaging (MRI) of brain with and without contrast, serum ceruloplasmin, APLAs (including lupus anticoagulant, anticardiolipin, and anti-β_2 glycoprotein 1), urine drug screen, and urine pregnancy test. Further investigation may include uric acid, ataxia-telangiectasia (including quantitative immunoglobulin testing and α-fetoprotein), serum amino acid, urine organic acid, and arterial (or better, cerebrospinal fluid) lactate and pyruvate testing, Epstein-Barr virus titers, Lyme disease titers (with Western blot confirmation), testing for human immunodeficiency virus, serum calcium tests, and genetic testing for Friedreich's ataxia, spinocerebellar ataxia type 3 (also known as Machado-Joseph disease) and possibly dentatorubropallidoluysian atrophy (DRPLA) or PANK2 mutation.

Some Chorea Syndromes

Sydenham's (Rheumatic) Chorea

Chorea is one of the major Jones criteria for the diagnosis of ARF. The revised Jones criteria indicate the presence of chorea without any other criteria is sufficient to make the diagnosis of ARF. Although it is widely accepted that chorea can follow a GABHS infection, it is frequently difficult to demonstrate the antecedent infection. The development of ARF after a GABHS infection is thought to occur in only 1 to 2% of those infected. Only a fraction of those patients with ARF will develop Sydenham's chorea. For example, depending on the series, approximately 10 to 40% of

children with ARF have chorea. Sydenham's chorea is most common in children aged 5 to 15 years old, the same age range at greatest risk of other manifestations of ARF. Reasonably good evidence suggests individuals who develop ARF have a genetic susceptibility. There is a roughly 2:1 female predominance after age 10. Typically, the clinical manifestations of Sydenham's chorea begin several weeks to several months after a GABHS infection. The onset of symptoms is usually insidious, with gradually progressive clumsiness and behavior and personality change, usually with emotional lability, aggression, impulsivity, and obsessive–compulsive behaviors. For some patients, the emotional lability and personality change presents the most salient morbidity. This broad neuropsychiatric array of changes in addition to chorea has long been a recognized part of the picture of Sydenham's chorea.

The often-reported typical natural history of Sydenham's chorea is weeks to months of a waxing and waning course, with ultimate resolution of the chorea. Some individuals have behavioral changes that persist for months. Relapse of chorea can occur with or without subsequent GABHS infection. Therefore, it can be very difficult to distinguish between recurrence and relapse. There is a recognized increased risk of relapse associated with pregnancy (chorea gravidarum), oral contraceptives, and probably with intercurrent infection other than GABHS. An estimated 10 to 20% of patients, and perhaps as many as 50%, have a relapsing course. Large-scale longitudinal data are lacking to make firm statements about recurrence and relapse rates.

Recurrence and relapse provoke consideration of whether prophylactic penicillin is effective and whether follow-up investigations of cardiac function are needed. An additional confounding factor is that pharyngeal carriage of GABHS is common and is not necessarily eradicated by antibiotic prophylaxis (see below). Therefore, surveillance testing for GABHS may produce false-positives. In the absence of specific evidence-based recommendations for when to reevaluate cardiac function (by echocardiogram, electrocardiogram, or pediatric cardiology consultation) in patients with the diagnosis of Sydenham's chorea, one must use clinical judgment. Certainly, signs, such as new murmur or abnormal rhythm, and symptoms, such as fatigue, palpitations, and shortness of breath, demand cardiac reassessment.

The diagnosis of Sydenham's chorea is made on the basis of clinical history and can be supported by laboratory data. However, laboratory data should be viewed as ancillary, not confirmatory. Most children with Sydenham's chorea have positive serology (antistreptolysin O and AntiDNase B antibodies) for GABHS, but over 25% are serologically negative. Most children with Sydenham's chorea have negative throat cultures for GABHS. MRI scans occasionally show signal abnormalities in the basal ganglia, but a clear clinical-radiographic linkage has not been seen. Therefore, structural imaging is diagnostically neither sensitive nor specific for Sydenham's chorea. Presence of carditis or valvitis or other manifestations of ARF supports the diagnosis of Sydenham's chorea. Every child thought to have Sydenham's chorea should be evaluated for rheumatic heart disease. Depending on the series, 40 to 75% of children with Sydenham's chorea have carditis. Arthritis is less common. Cerebrospinal fluid parameters in Sydenham's chorea have not been well studied.

ARF remains a quintessential example of postinfectious or peri-infectious autoimmune disease. It is thought to be a consequence of host–bacterial molecular mimicry, such that host-derived antibodies to the infectious agent interact with host organ systems. Although antibrain antibodies have been recognized in a proportion of Sydenham's chorea patients for 30 years, the nature of the pathogenic mechanism has only recently been elucidated. Specifically, sera from patients with active Sydenham's chorea contain antibodies directed at brain lysoganglioside and GABHS glucosamine. This sera, and not sera from convalescent patients or those with nonchorea manifesting ARF, induces a calcium- and calmodulin-dependent protein kinase. Thus, there appears to be a direct effect of antibody on neuronal cell signaling, perhaps leading to inappropriate release of striatal dopamine.

Chorea in SLE and APLA Syndrome

Chorea is an uncommon manifestation of SLE but can be the presenting symptom. When chorea is the sole manifestation of SLE, it can remain so for years. Although fewer than 10% of children with SLE have chorea, about 50% of individuals with chorea due to SLE are younger than 16 years of age. Presence of neurologic manifestations such as chorea in SLE conveys a less favorable prognosis, including relatively increased mortality. Importantly, the chorea of SLE is clinically identical to that seen in ARF.

The diagnosis and treatment of SLE is beyond the scope of this review. However, a few comments are appropriate. When chorea is due to SLE, treatment of the underlying SLE is indicated. Additional symptomatic treatment of the chorea may be indicated if the chorea is bothersome. It is important to consider that the chorea in SLE may be iatrogenic (ie, drug-induced). Haloperidol has been reported to be effective for SLE chorea, but the other treatments described below for Sydenham's chorea may also be effective.

The chorea of APLA syndrome is indistinguishable from that of SLE. Rheumatologic evaluation for autoimmune mechanisms for chorea should include investigations for antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and anti-β_2 glycoprotein 1, even if other elements of APLA syndrome, such as recurrent venous or arterial thrombosis, have not surfaced.

Chorea Associated with Viral Encephalitis

Post- or peri-infectious chorea is not uncommon and is notoriously difficult to treat. MRI signal abnormalities have been described in deep gray matter brain structures, such as basal ganglia and thalamus, as part of an aseptic meningitis or meningoencephalitis as well as in acute disseminated encephalomyelitis.

Wilson's Disease

Though rare, Wilson's disease (hepatolenticular degeneration) needs to be ruled out in children presenting with chorea because it is treatable. Caused by a mutation on chromosome 13 (autosomal recessive inheritance) resulting in deficient ceruloplasmin, Wilson's disease leads to an intracellular accumulation of copper in the brain (particularly the basal ganglia) and liver. Indeed, in some cases, Wilson's presents as fulminant hepatic failure. When Wilson's disease presents with chorea, hepatic function is typically already compromised. Up to 40% of patients, though, will have a neuropsychiatric presenation and the average age of onset in this group is 19 Neuropsychiatric manifestations, in addition to chorea, include dystonia, tremor, dysphagia, dysarthria, dementia, personality changes, and a schizophrenia-like presentation. Slit-lamp examination often reveals copper deposits in the margin of the iris (Kayser-Fleischer ring). The treatment includes chelation therapy or zinc acetate, with recent data suggesting tetrathiomolybdate may also help. Controversy persists regarding optimal treatment.

Chorea of Hyperthyroidism

In both pediatric and adult populations, hyperthyroidism must be ruled out in any patient with chorea or hyperkinesis per se. Treatment of hyperthyroidism is dictated by the etiology. Often, the consequence of radiotherapy is acquired hypothyroid disease requiring supplementation of thyroid hormone. The chorea of hyperthyroidism is indistinguishable from that of other causes. However, other manifestations of hyperthyroid disease, such as weight loss, anxiety, and altered thermoregulation, may be helpful in delineation.

Treatment

As is the case with any pediatric movement disorder, the decision to treat symptoms should be dictated by the extent to which the problem bothers the child or interferes with activities of daily living. When chorea is the consequence of a treatable process, such as hyperthyroidism, SLE, or drug reaction, treatment of the primary problem may sufficiently alleviate the chorea.

A number of pharmacotherapeutic approaches to chorea have been described in the literature. Medications that interfere with dopaminergic transmission tend to be effective for chorea. These medications include dopamine receptor blockers (such as neuroleptics) and presynaptic depleters for neurotransmitters (such as reserpine and tetrabenazine). The principle adverse effect of the presynaptic depleters is hypotension. Regarding the neuroleptics, because antichorea effects are greatest with D2 receptor subtype antagonism, the newer atypical neuroleptics tend to be less effective than the older typical ones. Of course, neuroleptics have a number of significant side effects (including, but not limited to, tardive dyskinesia, weight gain, prolongation of the QT interval) that need to be considered prior to their use in the treatment of chorea. Tetrabenazine appears to be a very effective medication for chorea, but it is not available in the United States.

The antiepileptic drug valproate is considered by many to be an effective treatment for chorea, but reports in the literature vary. Its mechanism of action is not known but may be through nonspecific γ–aminobutyric acid (GABA) potentiation. Other GABA-mimetic medications, such as baclofen and clonazepam, appear to have efficacy as well.

Treatment Issues in Syndeham's Chorea

Treatment of Syndeham's chorea depends on the impairment or disability associated with the chorea. In many cases, the chorea causes only mild disability and symptomatic treatment is not required, because Syndeham's chorea is usually self-limited. When symptomatic treatment is desired, antiepileptic medications, such as valproate, can be effective and are usually associated with fewer side effects than phenothiazines or butyrophenones. Benzodiazepines may also be beneficial. Symptomatic treatment for 2 to 4 months is usually sufficient. Some authors have advocated use of corticosteroids, intravenous immunoglobulin, or plasma exchange for treatment of Syndeham's chorea on the basis of the presumptive autoimmune mechanism. There has been no study of efficacy or long-term outcome of these treatments compared with placebo. Anecdotal reports of efficacy are available in the literature.

Antibiotic prophylaxis to prevent repeated bouts of GABHS is recommended and described in detail by Dajani and colleagues. The specific purpose is to prevent carditis or valvitis, not to prevent chorea. The cardiac manifestations of ARF cause tremendous morbidity (and mortality) and are irreversible. The first-line antibiotic for prevention of heart or valvular disease remains penicillin. To date, no strain of GABHS has developed resistance to penicillin. Therefore, there appears to be no reason to use clavulinic acid containing antibiotics when targeting GABHS. Penicillin can be administered as a monthly intramuscular injection of 1.2 million units of benzathine G.

Alternatively, an oral form (eg, Pen V®) can be given at 250 mg twice daily. The antibiotic sulfadiazine is another option. When children weigh ≤ 27 kg, they can be given 0.5 mg orally each day. For those who weigh > 27 kg, the recommendation is for 1.0 g/d. For patients allergic to both penicillin and sulfadiazine, erythromycin can be administered at 250 mg orally bid.

The duration of secondary ARF prophylaxis also has not been determined through evidence-based studies, but recommendations through the American Heart Association are available as well. When ARF presents with carditis or valvitis, but there is no persistent disease cardiac or valve disease, prophylaxis should continue for 10 years from diagnosis, or "well into adulthood" (whichever is longer). If cardiac disease persists, the duration of ARF prophylaxis should be for at least 10 years subsequent to the prior episode *and* until the patient is older than 40 years of age. When ARF presents without cardiac disease (the most common scenario), prophylaxis should continue for 5 years or until age 21.

Suggested Readings

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Mink JW. The basal ganglia and involuntary movements: impaired inhibition of competing motor patterns. Arch Neurol 2003;60:1365–8.

Sanger TD. Pathophysiology of pediatric movement disorders. J Child Neurol 2003;18:S9–S24.

Schlaggar Blaming JW. Movement disorders in children. Pediatr Rev 2003;24:39–51.

Practitioner and Patient Resources

Worldwide Education and Awareness for Movement Disorders (WE MOVE)
204 West 84th Street
New York, NY 10024
Phone: 800-437-6682 or (212) 875-8312
Fax: (212) 875-8389
E-mail: wemove@wemove.org
http://www.wemove.org
WE MOVE is the Internet's most comprehensive resource for movement disorder information and education and the only organization of its kind. WE MOVE believes that increasing knowledge and understanding promotes timely, accurate diagnosis and up-to-date treatment, resulting in a better quality of life for individuals affected by these often devastating conditions.

Chapter 78

Visual System Problems

Lawrence M. Levine, MD

The pediatric visual system is sensitive to a variety of congenital and acquired diseases. Visual loss in the pediatric population may go unrecognized, because children are highly adaptive to visual loss and do not have the same visual demands as adults. Generally, visual pathway disturbances result in either visual loss or ocular motility abnormalities. To better evaluate and care for these patients, it is important to understand the visual system and its pathways.

The visual system can be divided into sensory and motor pathways. The sensory system is an afferent pathway that carries information from the eye to the occipital cortex. From anterior to posterior, the anatomic components of the sensory system are the retina, optic nerve, optic chiasm, optic tracts, lateral geniculate bodies, optic radiations, and visual cortex. Depending on the location along this pathway, the most common manifestation of insult is either central visual loss or a visual field deficit.

The retina is made of specialized photoreceptors (rods and cones) that coalesce to form the optic nerve. The optic nerve contains approximately 1 million axons and runs 25 mm to the optic chiasm. At the chiasm, decussation of the nasal fibers from both eyes results in a right and left visual field. The right visual field travels to the left side of the brain for processing and the left visual field travels to the right side of the brain.

Insults prior to the optic chiasm will result in a monocular visual loss. Insults at the level of the chiasm or beyond will result in a visual field deficit that affects both eyes (ie, a right or left homonymous hemianopsia). The entire afferent system is a two-neuron system, with the only synapse occurring at the geniculate nucleus. The second neuron projects along the optic radiations to the occipital cortex. True visual perception occurs only at the cortical level. The sensory pathways can be intact, but if the occipital cortex is impaired, the patient can be totally blind, termed cortical blindness. It is equally important to realize that if pathology affects sensory visual input, the child may not learn to process visual information from the eyes. This is termed amblyopia. The most common causes of amblyopia are refractive error and strabismus (ocular misalignment).

Prior to the lateral geniculate body, some of the neurons branch off and travel to the midbrain. From there, they synapse in the Edinger-Westphal nucleus, where the parasympathetic pupillary fibers of the third cranial nerve originate. The Edinger-Westphal nucleus sends efferent information from the midbrain to the pupil along the surface of the third nerve. This loop is independent of cortical visual processing and controls the pupillary light responses. A cortically blind patient can have normal pupillary light reactions. The efferent information from the Edinger-Westphal nucleus is sent to each eye equally. Therefore, information from each eye is transmitted separately to the midbrain along the optic nerves and returned to both eyes equally from the pupillary nuclei of the midbrain. If there is a unilateral optic nerve abnormality, light shined into the eye will create a poor pupil response in both eyes. However, if the same light is shined in the normal eye, there will be a normal pupillary response in both eyes. This relative difference is the basis for understanding afferent pupillary abnormalities, also known as "Marcus Gunn pupils." Afferent pupillary defects indicate optic nerve pathology anterior to the optic chiasm.

The ocular motor system coordinates fixation and tracking. Eye movements are created in a three-level system. The first level is composed of multiple gaze centers within the brain and brainstem. These centers mediate fixation and tracking movements by integrating cortical visual information and affecting the pathways to the brainstem. The nuclei of the third, fourth, and sixth cranial nerves are located in the brainstem, representing the second level of the efferent pathway. The third level comprises the peripheral cranial nerves and eye muscles. Thus, fixation and

tracking problems can be secondary to cortical, brainstem, or peripheral (cranial nerve or eye muscle) problems. Ocular alignment abnormalities are termed strabismus. Such misalignments can be paralytic or nonparalytic. Most nonparalytic forms of ocular motor misalignment are due to congenital strabismus, which represents an idiopathic ocular motor anomaly. These anatomic and physiologic pathways are the foundation on which the evaluation and management of visual system problems in the pediatric population is based.

Evaluation and Diagnosis

Early Visual Development

Abnormalities of the afferent or efferent visual system during childhood will result in one of three general responses: poor fixation and tracking skills, nystagmus, or abnormal ocular motility findings. The first 3 months of life are the most crucial period of visual development. Often, the parent or clinician becomes aware of visual problems during this time period. This is an appropriate time for a referral to an ophthalmologist. The clinician should be aware of age-appropriate visual skills in the pediatric population (Table 78-1).

When assessing premature infants, age should be corrected to gestational age and not birth date. During the first few weeks of life, ocular alignment is often unstable. It is not uncommon for parents to report occasional ocular misalignment. By age 6 weeks, infants should be able to hold the eyes in straight alignment. Vision can be assessed by a "blink to light" reflex during the first weeks of life. By age 6 to 8 weeks, infants often will begin fixating on faces, lights, or patterns. Their eyes should be straight, and the corneal light reflex can be used to clinically assess the alignment. When the child is fixating on a penlight, the light reflex should be centered in the pupil of each eye. By age 3 months, infants should be demonstrating fixation and tracking skills. Initial tracking is saccadic or jerky, becoming smoother by age 6 months.

The most common cause of poor fixation or visual inattentiveness during this time period is delayed visual maturation. This can be a primary problem, and if there are no other neurologic abnormalities, the visual prognosis is generally excellent. In such cases, visual maturation is usually delayed by only a few weeks. If visual maturation is delayed due to an underlying neurologic abnormality, such as hypoxic insult or seizure activity, visual maturation can be greatly delayed, and the final visual acuity becomes less predictable.

TABLE 78-1. Age-Appropriate Visual Skills

Age	Visual Skills
Birth	Blink to light, pupillary light reflex present
6–8 weeks	Fixation, straight ocular alignment
3 months	Fixation and early tracking skills, conjugate eye movements
3–6 months	Reach for objects, smooth tracking skills

Sensory System Problems (Visual Loss)

The visual system is essentially a sensory (afferent) and motor (efferent) loop, with true visual processing occurring within the brain. Abnormalities can be classified into sensory, motor, or cortical (visual processing) problems. Evaluation and diagnosis of sensory system problems will be considered first. Following the pathway from the retina to the occipital cortex allows for a systematic approach to problems. Generally, all sensory pathway abnormalities result in some form of visual loss. Classifying the abnormality by location along the pathway allows for an understanding of the form of visual loss, possible etiologies, appropriate management, and prognosis.

Table 78-2 lists the common signs and symptoms of sensory visual system disease. Beginning at the anterior aspect of the sensory visual system, the most common etiology of visual loss in the pediatric population is refractive error. This is easily corrected with glasses. If light is not properly focused on the retina, a blurred image is perceived in the visual cortex. Uncorrected large refractive errors can result in permanent visual loss (amblyopia). Refractive error is often unrecognized until verbal visual testing is possible. However, in some children, the blurred vision affects the oculomotor (efferent) pathway, and nonparalytic strabismic deviations are noted in the form of esotropia (in-crossing) or exotropia (out-crossing).

Retinal disease also can affect sensory input. The most common forms of retinal disease are retinal dystrophies. These are usually inherited retinal diseases that result in severe bilateral visual loss. Common retinal dystrophies include Leber's congenital amaurosis, achromatopsia, congenital stationary night blindness, and blue-cone monochromatism. Electroretinography is necessary to define these dystrophies. The visual insult is usually so severe that a sensory nystagmus usually develops during the first few months of life. Unfortunately, there are no treatments for retinal dystrophies.

The optic nerve is the conduit of visual information to the optic chiasm. Any disease process that directly or indirectly damages the optic nerve results in ipsilateral visual loss. The most common optic nerve responses to insult are edema and atrophy. Unilateral edema is usually secondary to ischemia, infection, trauma, inflammation, or infiltrative disease. Bilateral edema is usually due to increased intracranial pressure and is termed papilledema. The most common causes are tumor, hydrocephalus, and pseudotumor cerebri.

TABLE 78-2. Sensory Pathway Problems

Location	Common Etiologies	Signs and Symptoms
Retina	Retinal dystrophies or disease	Poor vision, nystagmus
Unilateral optic nerve	Hypoplasia, atrophy, inflammation	Unilateral decreased visual acuity, color, Marcus Gunn pupil
Bilateral optic nerve	Hypoplasia, atrophy, papilledema	Bilateral decreased visual acuity and color, nystagmus
Optic chiasm	Suprasellar tumors	Bitemporal hemianopsia, decreased vision, optic nerve pallor
Optic radiations	CVA, tumor, meningitis	Homonymous hemianopsia, trauma, hydrocephalus; preserved central vision
Occipital cortex	Trauma, meningitis, CVA	Cortical blindness, hypoxia

CVA = cerebrovascular accident.

Pseudopapilledema is a benign condition in which the optic nerve heads appear elevated secondary to deposits known as drusen. Optic nerve atrophy can be secondary to perinatal diseases, such as hypoxia or stroke. Other causes include previous episodes of papilledema, inflammation, or ischemia. Unexplained optic atrophy requires neuroimaging to evaluate for hydrocephalus and tumor, which are frequent causes of atrophy in the pediatric population. Optic nerve hypoplasia is a congenital anomaly that can be unilateral or bilateral. Bilateral cases can be associated with septo-optic dysplasia, and attention should be given to other midline structures in the evaluation, particularly the pituitary gland and septum pellucidum. Optic nerve insult manifests as loss of visual acuity and color sensitivity in the affected eye. Visual loss can vary greatly, and efforts to treat the primary etiology are important, as lost vision is generally not recoverable.

Unilateral or asymmetrical optic nerve damage prior to the optic chiasm will result in an abnormal afferent pupillary light response (Marcus Gunn pupil).

The optic nerves merge to form the optic chiasm. The most common disease processes to affect the chiasm are tumors, such as craniopharyngiomas, pituitary adenomas, and gliomas. Because all visual information merges at the chiasm, visual loss can be catastrophic. An insult at this level will result in a bilateral visual field defect known as "bitemporal hemianopsia." However, in the pediatric population, it is not uncommon for bilateral blindness to be the initial presenting sign of slow-growing suprasellar masses.

Posterior to the chiasm, the visual information travels through the optic tracts, lateral geniculate bodies, and optic radiations to the visual cortex in the occipital lobe. Because there is decussation of the visual fibers at the chiasm, only sections of the peripheral visual fields are lost (ie, hemianopias and quadrantanopias) to injury posterior to the chiasm. Central vision is usually preserved. Visual field testing can be done to localize the site of pathology. A right optic radiation abnormality will result in left visual field defects and left optic radiation defects will result in right visual field defects. Intracranial insults to this pathway include inflammation, infection, stroke, and hydrocephalus.

Visual field deficits can be difficult to detect in the nonverbal child but often are manifested as visual inattention toward the side of visual field loss on confrontational testing. Bilateral insults to the occipital cortex can result in cortical blindness. This is commonly the sequelae of severe trauma, meningitis, hypoxia, or shaken baby syndrome. Poor fixation and tracking abilities associated with cortical blindness are usually obvious. Neuroimaging studies are appropriate in patients with visual loss that cannot be explained as refractive error or intraocular abnormalities. Pathology noted on imaging studies in the anterior visual pathways and optic radiations correlates well with visual loss and is helpful in estimating final visual acuity. Imaging studies in cortical blindness do not correlate well with visual loss or final visual potential. Clinical assessment and visual evoked potential testing can be used in these patients to better quantify the visual loss.

Oculomotor System Problems

The oculomotor visual system is responsible for fixation and tracking skills. Because the motor and sensory systems are interdependent, abnormalities of the sensory pathways should be excluded when evaluating oculomotor abnormalities. Control of eye movements begins in the cortical (supranuclear) gaze centers. These gaze centers are intimately related to the visual cortex and vestibular systems; this relationship allows for coordination of eye movements to sensory input and positional changes. Any cortical insult can damage these gaze centers. Cerebrovascular accidents, meningitis, tumors, and encephalopathies are common etiologies of gaze center abnormalities. Clinical manifestations include gaze palsies, inability to generate eye movements, or inability to track with the eyes in one or multiple directions. Although rare, there is a congenital form of gaze paresis termed "oculomotor apraxia." The cortical gaze centers innervate the nuclei of the cranial nerves in the brainstem. Pathways exist between the nuclei of the third, fourth, and sixth cranial nerves

that allow for balanced innervation of the extraocular muscles. Brainstem disease or insult will result in disconjugate tracking. Such tracking anomalies are termed nuclear or internuclear palsies. Möbius' and Duane's syndromes represent congenital forms of strabismus secondary to nuclear abnormalities.

The peripheral pathway of the efferent visual system comprises the cranial nerves and extraocular muscles. In the pediatric population, the cranial nerves are often subject to paresis secondary to trauma, inflammation, or tumors. It is important to recognize the paralytic strabismus seen with acquired cranial nerve palsies, as it may represent the first sign of intracranial disease. Ocular misalignment with limitation of ocular motility in one or both eyes is the key finding.

The most common etiologies of cranial nerve palsies in the pediatric population are listed in Table 78-3. Cranial nerve VI paresis is the most common acquired cranial nerve palsy in the pediatric population. It presents as an esotropia with limitation of abduction. The most common etiologies are usually serious processes, such as tumor, hydrocephalus, inflammation, or trauma. It also is known to present after an otherwise unremarkable upper respiratory infection and, in such cases, is usually self-limited.

The most common congenital cranial nerve palsy to affect the visual system is fourth cranial nerve palsy. This results in elevation (hypertropia) of the affected eye. It often manifests as a childhood head tilt, and all children with unusual head positioning or tilts should be referred for ophthalmologic evaluation. Congenital third nerve palsies are less frequent, and ptosis is often the obvious presenting feature, in addition to an inability to adduct the eye. Cranial nerve palsies will result in strabismus or ocular misalignment. It is important to differentiate strabismus into paralytic and nonparalytic forms.

Congenital nonparalytic strabismus can occur even in otherwise healthy children and usually presents within the first 6 months of life. Although there is misalignment of the eyes, ocular motility is full in both eyes. It usually does not represent serious neurologic disease, although it is seen more commonly in children with neurologic delays and cerebral palsy. This is probably due to abnormalities in areas of the brain responsible for binocularity and fusion of visual information. The most common forms of congenital nonparalytic strabismus are esotropia (in-crossing) and exotropia (out-crossing). Surgical correction of the eye muscles is often required. Acquired nonparalytic strabismus in older children is usually a benign abnormality but can represent one of the first signs of intracranial disease. Therefore, any acquired strabismus warrants a thorough ophthalmologic and neurologic evaluation.

Esotropia and exotropia are the most common forms of acquired nonparalytic strabismus and are sometimes only intermittently present. Because the pediatric visual system is so plastic during visual maturation, congenital or acquired strabismic deviations may not elicit any visual complaints in the younger child. The visual system simply shuts down in the more deviated eye. Therefore, it is important to recognize these deviations not only as signs of neurologic disease but also to restore useful vision. Older children are more visually mature and often will complain of diplopia with acquired strabismic deviations.

Nystagmus

Nystagmus presents as rhythmic oscillations of the eyes. Most forms of nystagmus are conjugate. Congenital nystagmus often represents very poor vision (an abnormality in the afferent pathway) but does not define the etiology. It usually becomes evident during the first 2 to 3 months of life and is termed "sensory nystagmus." It is the result of poor development of fixation skills. Immediate ophthalmologic evaluation is recommended. If thorough ophthalmologic and neurologic evaluations demonstrate no pathology, the nystagmus is labeled "congenital motor nystagmus," a benign oculomotor abnormality. Children with congenital motor nystagmus often learn to position their eyes to minimize the ocular oscillations. This is termed the "null point" and usually involves unusual head posturing. Children with congenital nystagmus do not have any visual perceptions of environmental movements (oscillopsia) secondary to the nystagmus.

Acquired nystagmus in any child is usually the manifestation of serious neurologic disease and is generally not a sensory visual pathway abnormality. It is often secondary to brainstem, cerebellar, or vestibular pathology. Investigation should be directed toward intracranial pathology or neurodegenerative diseases.

The triad of acquired nystagmus, torticollis, and head nodding can represent spasmus nutans. The nystagmus is often disconjugate. Spasmus nutans is usually a benign and self-resolving entity. However, intracranial tumors must still be ruled out, as on rare occasions they present with similar findings.

TABLE 78-3. Paralytic Strabismus Due to Cranial Nerve: Paresis in Children

Cranial Nerve	Ocular Deviation	Common Etiologies
III	Exotropia (out-crossing), hypotropia (depression), ptosis	Congenital, trauma, neoplasm, aneurysm, inflammation
IV	Hypertropia (elevation), head tilt	Congenital, trauma, encephalitis
VI	Esotropia (in-crossing)	Trauma, neoplasm, postviral

Treatment

Many problems affect the visual system, and it is beyond the scope of this chapter to review the various treatments. However, there are guiding principles that apply to most problems encountered. Because of the susceptibility of the sensory visual pathways, childhood problems can result in permanent visual loss.

Fortunately, this same plasticity during the first 8 years of life provides the opportunity for possible recovery of lost vision. Once visual loss is recognized, it is important to determine the etiology. If treatable, all efforts should be made to correct the underlying insult to the sensory system and restore lost visual potential. The most common source of decreased vision is refractive error. Glasses usually correct this visual loss. The second most common insult to sensory input is congenital nonparalytic strabismus. Eye muscle surgery can correct alignment, allowing for binocular visual input and optimal visual development. If amblyopia persists despite correction of the underlying refractive error or strabismus, patching therapy can restore lost vision. Another form of amblyopia therapy uses cycloplegic eye drops to blur the vision in the nonamblyopic eye, forcing the brain to use the weaker (amblyopic) eye. Amblyopia therapy is much more successful during the first few years of life, but consideration of therapy should be given for children up to age 8 years. After that age, the visual system is considered to be mature, and reversal of amblyopia is generally not possible.

Rapid loss of vision, afferent pupillary defects, nystagmus, visual field deficits, and acquired strabismus (paralytic or nonparalytic) are often manifestations of neurologic disease. Ophthalmic and neurologic investigations into the etiology are aimed at treating the primary disease process and minimizing visual loss. No specific treatments exist for children with extensive visual field deficits or cortical blindness. However, some children with severe cortical visual insults may recover useful vision. These patients require the expertise of local professionals and agencies skilled in the management of visually impaired children. Efforts are centered on providing home and school environments that maximize childhood development, despite the visual impairment.

Discussion

Understanding that the visual system is composed of interdependent sensory and oculomotor pathways is essential in evaluating the child with visual problems. Sensory pathway pathology results in loss of vision. Pathology anterior to the optic chiasm results in monocular visual loss, whereas insults at the level of the optic chiasm or more posteriorly will result in bilateral visual field deficits. Oculomotor abnormalities are most often manifested as strabismus. Acquired strabismus, whether paralytic or nonparalytic, can represent serious neurologic disease.

Suggested Readings

Brodsky MC, Baker RS, Hamed LM. Pediatric neuro-ophthalmology. New York: Springer-Verlag; 1996.

Wright KW. Pediatric ophthalmology for primary care. Baltimore (MD):Williams and Wilkins; 2003.

Practitioner and Patient Resources

American Academy of Ophthalmology
P.O. Box 7424
San Francisco, CA 94120-7424
Phone: (415) 561-8500
http://www.aao.org
The professional society of ophthalmologists in the United States.

American Association for Pediatric Ophthalmology and Strabismus
P.O. Box 193832
San Francisco, CA 94119
Phone: (415) 561-8505
http://med-aapos.bu.edu
The professional society for pediatric ophthalmologists in the United States.

Lighthouse International
111 E. 59th Street
New York, NY 10022
Phone: 800-829-0500
http://www.lighthouse.org
A resource center for blind and visually impaired patients.

CHAPTER 79

CHILDHOOD DEPRESSION

TANYA K. MURPHY, MD

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Depression in children and adolescents may present a diagnostic challenge to the most astute clinician because of its atypical presentation and a high number of associated comorbidities. Depression can seriously disrupt a child's relationships with family and peers. It also can interfere with a child's ability to succeed in school. In the past few years, advances in the treatment of depression have provided clinicians with the ability to treat this disorder more effectively than ever before.

In the past, children were felt to be incapable of experiencing depression because of their incompletely developed cognitive ability. However, recent studies have found the point prevalence rate of depression to be as high as 2% in children and 8% in adolescents. In childhood, the rate is similar in girls and boys, whereas adolescent girls are twice as likely to develop depression as their male counterparts. This gender discrepancy may be due to hormonal changes and sociocultural influences.

A child may experience short-lived forms of mild depression after receiving a low grade or after a breakup with a friend and may say, "I'm stupid" or "Nobody likes me." These overstatements are called cognitive distortions, and children with perfectionist tendencies and high sensitivity to rejection are particularly prone to having them. A child with this psychological makeup may be more vulnerable to severe depression, particularly when stressed. More severe forms of depression may be precipitated by losses such as divorce of parents, death of a relative or perhaps a pet, serious illness, or abuse.

Other causes of increased vulnerability include a family history of depression or bipolar affective disorder (BAD). A positive family history of depression is more likely in childhood-onset depression. These children have an increased risk for later development of BAD. Children with preexisting neuropsychiatric conditions, such as Tourette's syndrome, obsessive–compulsive disorder (OCD), and attention-deficit hyperactivity disorder (ADHD), also are more prone to developing a depressive disorder. Proper diagnosis and treatment of depression are essential, as untreated depression can lead to school failure, substance use, promiscuity, delinquent behaviors, and suicide attempts.

Evaluation

Diagnosis may be more difficult in children with an insidious onset of symptoms, poor language skills (either due to intellect, young age, language disorders, or sociocultural factors), or comorbid conditions. Children may present with separation anxiety, physical complaints (frequent headaches and stomachaches), irritability, aggressive behavior, sleep and appetite changes, more frequent crying, lack of motivation, and thoughts of death.

Adolescents may present with these types of symptoms as well, although they are more likely to have a more 'classic' presentation of depression than are their younger counterparts. Assessment of recent stressors and the duration and stability of symptoms will help determine whether the child is responding to an environmental stressor rather than an endogenous process. Pervasive, long-lasting symptoms are more likely to warrant medical treatment, regardless of a coexisting stressor. School performance is an important diagnostic clue when a child's previous level of performance drops significantly without explanation. A child may start to refuse to attend school or leave once there, withdraw from peers, or join another peer group. Irritability and angry outbursts are often more frequent than complaints of sadness. Children are less likely than adults to present with prominent neurovegetative symptoms, such as changes in appetite, energy, and sleep, but are more likely to present with frequent physical

complaints, such headaches and stomachaches. Recent onset of risktaking behaviors, such as drug or alcohol use, sexual encounters, and self-injurious behaviors (eg, skin carving and burning), may also be seen. These types of symptoms have lead to the term "masked depression" to describe the atypical way a depressed child may present.

Depressed children may think about what it would be like to be dead and may threaten self-harm. Some engage in potentially lethal behaviors, such as reckless driving, overdosing on drugs, alcohol, or medications, handling guns and playing Russian roulette. The most significant risk factor for completed suicide in adolescents is the presence of firearms in the home. Other risk factors include being male and having a peer or family member recently commit suicide. A thorough evaluation of safety issues is imperative in the evaluation of all children and adolescents who are being seen for potential depressive symptoms. In addition, suicidal behaviors can occur independently of clinical depression and should be assessed in any child with decreased functioning or a chaotic family environment and in those engaging in other risk-taking behaviors.

Sleep disturbance, fatigue, impaired concentration, and other somatic complaints may be caused by medical conditions that need to be excluded from the differential diagnosis. Laboratory studies, such as a hematocrit, electrolyte panel, liver function tests, and thyroid stimulating hormone (TSH), are recommended when neurovegetative symptoms are prominent. Beyond ruling out underlying medical conditions, biologic markers and neuroimaging studies have little value in diagnosing depression; therefore, diagnosis is often determined by a careful history and examination.

In the primary care setting, screening for depression is very important. There is evidence that screening is important at both well-child checkups and during non-routine visits, as depression is often present although it is not the presenting complaint. In general, children and adolescents are able to more accurately report 'internalizing symptoms' such as depression and anxiety, while parents and teachers are better able to give reports on 'externalizing symptoms' including ADHD and disruptive behaviors. For this reason, it is important to ask the child about symptoms of depression in order to get an accurate account and more thorough assessment. When the history is taken only from the parents, half of all cases of prepubertal depression will be missed.

In both the primary care setting, and in the psychiatric office, screening tools for depression can help assess for symptoms, although diagnosis should not be based exclusively on the use of these instruments. Several self-report assessments are available, and can be filled out by the patient in less than 15 minutes. They are fairly straightforward for review by the clinician and can give valuable information about how the child is feeling. For some children, it is easier to report symptoms of depression or anxiety in this manner, which then opens the door for further exploration through conversation.

One commonly used assessment tool, which is frequently used in primary care settings, is the Beck Depression Inventory (Publisher: Harcourt Assessment, Inc.) It assesses symptoms in four main areas: cognitive, behavioral, affective and somatic. It consists of 20 or 21 items, depending on the version, and can be completed by children as young as 7 (with some help from an adult). It can typically be completed within 5–10 minutes. An example question is:

(a) I do not feel sad.
(b) I feel sad.
(c) I am sad all the time and I can't snap out of it.
(d) I am so sad or unhappy that I can't stand it.

It can be a valuable tool for assessing symptom improvement over time, and has been shown to accurately discriminate depressed from non-depressed adolescents.

Another commonly used assessment tool is the Child Depression Inventory (Publisher: Pearson Education, Inc.). It consists of 27 items and can be used to assess for depression in children aged 7 to 17 years old. It takes 10–15 minutes to complete, although there is also a short form with 10 items that takes about 5 minutes to complete. An example question is:

(a) "I am sad once in a while."
(b) "I am sad many times."
(c) "I am sad all the time."

It may not be as useful for assessing changes in symptoms over time, but does include questions about some externalizing behaviors, which may indicate depression in this population.

Other assessment tools are available, including the Child Behavior Checklist (Publisher: Achenbach System of Empirically Based Assessment), which has versions for youth self-report, parent report and teacher report. It is also available for a variety of age ranges, beginning as early as 1 1/2 years of age. These forms are more extensive, covering both externalizing behaviors such as aggression, rule-breaking and hyperactivity and internalizing behaviors including anxiety and depression as well as physical complaints and social interactions. It takes a bit longer to complete and the data may be compiled using a computer program to compare the child against norms in multiple areas. It is a useful tool for gathering information from multiple sources and for a variety of symptom clusters.

Diagnosis

According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), a child or adolescent may be diagnosed with one of a number of depressive disorders, depending on symptom severity and duration. Major

depressive disorder (MDD) is characterized by depressed or irritable mood or anhedonia that is present nearly every day for > 2 weeks. In addition, to receive a diagnosis of MDD, a child must meet five of the nine symptom criteria. Dysthymia requires the presence of depressed or irritable mood for > 1 year (adults are required to have symptoms for 2 years), in addition to two other symptom criteria. Adjustment disorders can be diagnosed when an emotional or behavioral response to an identifiable stressor occurs within 3 months of its onset and remits within 6 months of the stressor's termination. The diagnosis of adjustment disorders with depressed mood is considered when a child presents with symptoms of depression beyond the extent expected for the psychosocial stressor to which he was subjected. Depressive disorder not otherwise specified (NOS) is a category for those episodes that do not meet criteria for the above-noted diagnoses. This includes premenstrual dysphoric disorder and minor depressive disorder (symptoms presenting for a least 2 weeks but not meeting criteria for major depression). Bereavement is not considered a mental disorder. When present, depressive symptoms should not persist longer than 2 months or be characterized by a marked sense of worthlessness, severe impairment in functioning, suicidal ideation, psychotic symptoms, or psychomotor retardation.

TABLE 79-1. Symptoms of Major Depressive Disorder

Depressed or irritable mood nearly every day for a 2-week period*
Diminished interest or pleasure*
Loss of appetite, weight loss (without dieting) or failure to make expected weight gains
Insomnia or hypersomnia nearly every day
Psychomotor agitation or retardation
Fatigue or loss of energy
Poor concentration or indecisiveness
Feelings of worthlessness or guilt
Recurrent thoughts of death, suicidal ideations or attempts

Adapted from the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR).

*One of the first two symptoms is necessary for diagnosis to be made.

TABLE 79-2. Dysthymia Symptoms

Poor appetite or overeating
Insomnia or hypersomnia
Low energy or fatigue
Low self-esteem
Poor concentration or difficulty making decisions
Feelings of hopelessness
Symptoms lasting for a 1-year period, more days than not

Adapted from the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR).

TABLE 79-3. Adjustment Disorder Subtypes

With depressed mood
With anxiety
With mixed anxiety and depressed mood
With disturbance of conduct
With mixed disturbance of emotions and conduct
Unspecified

Adapted from the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR).

TABLE 79-4. Differential Diagnosis

Medical Conditions
Neurologic (epilepsy, hydrocephalus, head trauma, etc)
Endocrine (thyroid disorders, diabetes)
Infectious (HIV, mononucleosis)
Miscellaneous (cancer, renal disease, vitamin deficiencies)
Substance-Induced Depression
Antihypertensives (clonidine, beta-blockers)
Antiepileptic drugs
Steroids and hormones
Stimulants
Antipsychotics
Alcohol, illicit drugs (ie, cocaine withdrawal)
Oral contraceptives
Psychological Conditions
Attention-deficit hyperactivity disorder
Eating disorders (anorexia nervosa, bulimia nervosa)
Generalized anxiety disorder
Panic disorder
Separation anxiety disorder
Social phobia
Posttraumatic stress disorder
Obsessive-compulsive disorder
Somatization disorder
Oppositional defiant disorder
Conduct disorder
Schizophrenia
Bereavement

HIV = human immunodeficiency virus.

Treatment

Cues from initial assessment will inform the next treatment steps. Assessing for severity, length of episodes, precipitating factors, support systems and psychiatric emergencies including suicidal ideation, homicidal ideation, self-injurious behavior and psychosis are important factors.

The first step for all patients is to assess for suicidality and psychosis. Asking children if they have any thoughts of dying or harming themselves should be followed by inquiries about plan, means, and intent. Some physicians are reluctant to ask a depressed child about suicidal thoughts, fearing that it may implant such a notion. This is rarely the case. A suicidal or psychotic child should be evaluated by a psychiatrist and possibly hospitalized if the child's safety cannot be guaranteed.

For brief episodes of depression, depression occurring in younger children and more mild episodes of depression, supportive therapy has been shown to be beneficial. For some of these patients, having someone who will listen to their feelings in a supportive and impartial fashion can be of significant help. One goal may be to focus on the positive aspects of their life, and to help the child further develop those areas. Helping to cement social supports in the community or discussing ways to expand the social support system can also be helpful. If the family can enlist the help of a mentor, some children's symptoms will significantly improve by having a relationship with an additional caring adult.

In cases involving older children and adolescents or those with more severe episodes of depression, a referral for therapy is often warranted. There are many types of therapy available, but recent evidence has shown the clear efficacy of interpersonal therapy and cognitive behavioral therapy in the treatment of depressed children and adolescents.

Cognitive behavioral therapy is designed to be time-limited, with a course of weekly therapy sessions lasting 12–16 weeks. The sessions are generally fairly structured and specific homework assignments in the form of thought records are typically given to patients. There is a focus on the interaction between thoughts, feelings and behaviors and how distortions in automatic thoughts can lead to depressive symptoms. A major goal of this type of therapy is to identify the automatic thoughts that are leading to depression and then to challenge faulty reasoning to help form a more realistic view of a situation. For adolescents, common cognitive distortions include feelings like 'everyone hates me' or 'no one will ever like me'. In cognitive therapy, statements like this would be challenged with more realistic thoughts, for example: my friend is mad at me right now, but after previous arguments she has always forgiven me. By challenging these distortions, feelings and behaviors change and depressive symptoms improve.

Interpersonal therapy is another time-limited form of therapy, typically lasting 12–16 weeks, which has been shown to be efficacious in the treatment of depression in the adolescent population. There are clear goals outlined with the patient at the outset and psychoeducation is a key component, with the theory that the more patients understand about depression and why they are depressed, the more effective treatment will be. The main focus is to link the patient's feelings to social interactions and life situations. The patient's way of interacting with others is examined to help understand how they affect the relationship. There is often a focus on building social skills to improve interpersonal interactions, which will ultimately lead to a decrease in depressive symptoms. While there is generally no homework, there is often encouragement to practice the social skills between sessions.

For many children, one of these therapeutic approaches may improve depressive symptoms fairly quickly and effectively without the use of medications. However, a child with severe depression may not benefit from counseling until they are treated with an antidepressant, and many patients will gain the most benefit from a combination of medications and psychotherapy.

Medications

The choice of antidepressant should take into consideration the safety and efficacy of the medication in treating children, the presence of comorbid disorders, other concurrent medication therapy, and compliance. Most research into older antidepressants, such as tricyclic antidepressants (TCAs), has shown they are of little benefit in the treatment of depression in children and adolescents but have more promise for frequent comorbid conditions, such as nocturnal enuresis, anxiety disorders, ADHD, and OCD. Other drawbacks are associated with using TCAs. TCAs pose a serious cardiac toxicity risk with electrocardiogram (ECG) changes, such as prolonged QT, PR, and QRS intervals. ECGs need to be obtained at baseline, at dosage increases, and at quarterly intervals while the child is on maintenance therapy. Nine cases of sudden death have been associated with the use of TCAs in children. In depressed children and adolescents, intentional and accidental overdoses can present a serious and lethal threat. Care will need to be taken in the storage of the medication and the quantity prescribed.

Recent studies support the safety and efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of OCD in children and adolescents, with only fluoxetine obtaining U.S. Food and Drug Administration (FDA) approval for depression in children. SSRIs are much safer than TCAs when there is risk of overdose. The side-effect profile is generally more favorable (initial mild headache and GI upset) with SSRIs, with the most troublesome side effects being the neuropsychiatric side effects. The most common of these are tremor and behavioral activation. Behavioral activation may present at any time during treatment but is most common in the initial 2 weeks of therapy and often is dose-dependent, warranting use of the lowest possible starting dose. Children may be described as more hyperactive, impulsive, talkative, or "mean." This period is likely when children and adolescents are at greatest risk of acting on impulsive urges that may be lead them to harm themselves or others. Close monitoring for these symptoms is important throughout therapy but especially during the first weeks after initiation of medication treatment. Symptoms of activation usually abate after decreasing or discontinuing the medication. Frank mania is possible but much less frequent. This behavioral activation, which can

Table 79-5. Selected Antidepressants and Recommended Doses

	Initial Dose Recommended		Target Dose Recommended		Maximum Dose Recommended	
Medication	Child	Adolescent	Child	Adolescent	Child	Adolescent
Prozac (fluoxetine)[a]	≤ 5 mg qam	≤10 mg qam	10–20 mg	10–30 mg	40 mg	60 mg
Celexa (citalopram)[b]	≤ 5 mg	≤10 mg	10–20 mg	20–30 mg	40 mg	60 mg
Zoloft (sertraline)[b]	≤ 12.5 mg qam	≤ 25 mg qam	25–50 mg	75 mg	100 mg	200 mg
Lexapro (escitalopram)[c]	≤ 2.5 mg qam	≤ 5 mg qam	5–10 mg	10–20 mg	20 mg	30 mg
Luvox (fluvoxamine)[c]	≤ 25 mg qhs	≤ 37.5 mg qhs	100 mg	150 mg	200 mg	300 mg
Wellbutrin (bupropion)[c]	≤ 75 mg IR or ≤100 mg SR or ≤ 150 mg XL	same as child	150–250 mg	150–350 mg	300 mg	450 mg
Remeron (mirtazapine)[c]	≤ 7.5 mg qhs	≤ 7.5 mg qhs	7.5–30 mg	15–30 mg	45 mg	45 mg
Effexor XR (venlafaxine)[c]	≤ 37.5 mg qam	≤ 37.5 mg qam	75mg	150 mg	150 mg	225 mg
Paxil (paroxetine)[c]	≤ 5 mg qhs	≤10 mg qhs	10–20 mg	20–30 mg	40 mg	60 mg
Pamelor (nortriptyline)[d]	≤10 mg qhs	≤ 25 mg qhs	1 mg/kg	75–100 mg	3 mg/kg	150 mg

IR = immediate release; SR = slow release; XR = extended release.

*Not recommended for children until trials on safety are conducted.

[a]Evidence exists for safety and efficacy in the treatment of depression in children and adolescents.FDA approved.

[b]Evidence exists for safety and efficacy in treatment of children and adolescents. Not FDA approved.

[c]Efficacy and safety data questioned or little data available.

[d]More studies are needed.

include behaviors that cause harm to child or others, may be more likely in those with personal or family history of bipolar disorder as well as those children with comorbid anxiety disorders. Because of the possibility of increased suicidal behavior in children and adolescents, the FDA issued a "black box" warning regarding the use of all antidepressants in the pediatric (18 and younger) population for the treatment of depression. This conclusion was based on analysis of findings from placebo-controlled trials submitted to the FDA. None of the approximately 4,000 pediatric subjects in these trials committed suicide although 2 to 3% of these individuals exhibited suicidal behavior. Prescribing guidelines will include a careful risk/benefit analysis, lower starting doses, and more frequent monitoring (at least weekly in initial phase of treatment). More information is available at the FDA Web site <http://www.fda.gov>.

Serotonin syndrome is possible when multiple serotonergic agents are combined (Table 79-5). Symptoms may be mild or severe and may consist of any combination of agitation, nausea, vomiting, diarrhea, chills, muscle twitching, fever, confusion, dizziness, and diaphoresis. Symptoms usually abate with discontinuation of the medications. Severe presentations of delirium, coma, and seizures are possible but rare. Frontal lobe amotivational syndrome is characterized by apathy and forgetfulness and is more likely to be found in cases of SSRI therapy of several months' duration. Many may mistake this presentation as a return of the depression and increase the dose, whereas the best treatment is to lower the dose. Generally, symptoms of depression, such as irritability and sadness, are absent. Other considerations include drug interactions, and the more common are highlighted in Tables 79-6 and 79-7.

Of the SSRIs, fluoxetine and paroxetine have the most complicated interaction profile, affecting other classes of psychotropic medications, anticonvulsants, and benzodiazepines. Fluoxetine also has a very long half-life, such that clearance may take 3 to 6 weeks after discontinuation. This delayed elimination is mainly due to its active metabolite, norfluoxetine. This long half-life can be beneficial when treating patients with poor compliance but detrimental if

TABLE 79-6. Medications at Risk for Inducing Serotonin Syndrome

Selective serotonin reuptake inhibitors (SSRIs)
Serotonin/norepinephrine reuptake inhibitors (SNRIs)
Buspar
Tramadol
Dextromethorphan
Lithium
Risperidone and other atypical antipsychotics
Monoamine oxidase inhibitors (MAOIs)
Saint John's-wort
Tryptophan
Mirtazapine
MDMA
LSD

TABLE 79-7. Common Medication Interactions with Antidepressants

Which Antidepressant	Cytochrome P450 Interactions	Medication Levels Affected By Antidepressant	Medications Affect Levels of Antidepressant
Paroxetine (Paxil)	2D6 (I) 2D6 (S)	TCAs (↑) Atomoxetine (↑) Phenothiazines (↑) Aripiprazole (↑) Risperidone (↑)	Buproprion (↑ level)
Fluoxetine (Prozac)	2C19 (I) 2D6 (I) 2C19 (S) 2D6 (S)	Aripiprazole (↑) Atomoxetine (↑) Diazepam (↑) Phenytions (↑) Stimulants (↑) TCAs (↑)	Buproprion (↑ level) Methylphenidate (↑ level)
Fluvoxamine (Luvox)	3A4 (I) 1A2 (I) 2C19 (I) 2C9 (I-weak) 1A2 (S) 2D6 (S)	Alprazolam (↑) Aripiprazole (↑) Buspar (↑) Clozapine (↑) Diazepam (↑) Phenytions (↑) Thioridazine (↑)	Buproprion (↑ level) Methylphenidate (↑ level)
Sertraline (Zoloft)	3A4 (I-weak) 2D6 (I-weak) 3A4 (S) 2C9 (S) 2D6 (S)	Aripiprazole (↑) Atomoxetine (↑) Clozapine (↑) Diazepam (↑) Phenothiazines (↑)	minimal
Buproprion (Wellbutrin)	2D6 (I)	Aripiprazole (↑) Atomoxetine (↑) Clozapine (↑) Phenothiazines (↑) SSRIs (↑) TCAs (↑)	minimal
Duloxetine (Cymbalta)	2D6 (I) 1A2 (S) 2D6 (S)	Aripiprazole (↑) Haloperidol (↑) Risperidone (↑) SSRIs (↑) TCAs (↑)	SSRIs (↑ level)

Citalopram (Celexa), escitalopram (Lexapro) and venlafaxine (Effexor) have minimal drug-drug interactions

S: Substrate

I: Inhibitor

an adverse side effect or need to switch medication occurs. Paroxetine is often more sedating and may have a higher incidence of weight gain and galactorrhea. Its elimination kinetics are nonlinear, and it is the most anticholinergic of the SSRIs. This is of some concern for elderly patients and others who are susceptible to anticholinergic side effects. Abrupt withdrawal from an SSRI can lead to uncomfortable symptoms, such as feeling like having the flu. Those SSRIs with a short half-life, such as paroxetine, should be *slowly* tapered before discontinuation.

In general, children and adolescents tolerate all SSRIs reasonably well. Children tend to have fewer side effects when doses are started as low as possible and, when feasible, given in divided doses (particularly TCAs, paroxetine, and fluvoxamine). With greater tolerance, larger and less frequent dosing regimens may be possible. Although not FDA approved for pediatric depression, sertraline and citalopram are often favored, because these two SSRIs are relatively devoid of cytochrome P450 enzyme interactions, so they are unlikely to interact with most other medications and are often the drugs of choice when treating a patient with a complex medication regimen.

Bupropion is a non-SSRI antidepressant with dopaminergic and noradrenergic properties and may be beneficial

for those who cannot tolerate an SSRI or those who have comorbid depression and ADHD. Because of the increased risk for seizure, caution should be taken in those patients at risk for a seizure or a history of head trauma. Individual doses should not exceed 150 mg, with a maximum daily dose of 450 mg for the immediate release (IR) form. Wellbutrin XL (extended release) is gaining more favor in the psychiatric community because of its longer half-life, with once-a-day dosing and milder side effect profile.

Venlafaxine is a combined serotonin–norepinephrine reuptake inhibitor and is effective in the treatment of melancholic depression. It may have a high tendency to cause behavioral activation in some children, particularly those with comorbid ADHD. Venlafaxine may also lead to sustained elevations in diastolic blood pressure with sustained use, and some patients have noted difficulty with initial insomnia. Venlafaxine has gained FDA approval for generalized anxiety disorder and major depression in the adult population, but studies do not support efficacy in children and adolescents. A recent warning from the parent company, Wyeth-Ayerst, indicated concern that venlafaxine could also be associated with agitation and potential suicidal ideation. Caution should be given when beginning a child on Effexor. As with the SSRIs, a conservative approach is useful in minimizing any potential agitation from the medication, beginning with doses as low as XR 37.5 mg for several days or a week before titrating upward. For adolescents with severe insomnia, mirtazapine may be useful, as sedation is a very common side effect of this medication. Nefazodone has received a black box warning for potential of liver failure and is not recommended in children. Table 79-7 lists common antiepileptic drugs and medications whose metabolism they affect. Carbamazepine is an inducer of 3A4,5,7 and lowers blood levels of many psychoactive medications in addition to other commonly used medications. The other antiepileptic drug of common concern is valproic acid, which inhibits the metabolism of many drugs. The new generation of anticonvulsant medications (ie, vigabatrin, tiagabine, lamotrigine, and zonisamide) has little documented literature on their drug interactions.

If the patient has not responded to the chosen medication after 6 to 8 weeks on the standard dose and is not experiencing adverse effects, it is reasonable to increase the dose. Switching to another antidepressant, either from the same class or from a different class, is recommended when it appears the patient is not responding to the current therapy. Some psychiatrists advocate adjunctive therapy with triiodothyronine or lithium; however, these types of augmentations are best left to the care of a child psychiatrist.

A final option in refractory depression is electroconvulsive therapy (ECT). ECT is a viable treatment option for adults and has also been used to treat refractory depression in adolescents since the 1950s. Its use has waned in recent years, more because of popular misconceptions than because of lack of supportive research. Less than 2% of all ECT cases currently involve children or adolescents. The American Academy of Child and Adolescent Psychiatry (AACAP) has recent guidelines for screening candidates for ECT.

Maintenance and Discontinuation

If the patient has not responded to the chosen medication after 6 to 8 weeks on the standard dose and is not experiencing adverse effects, it is reasonable to increase the dose. Switching to another antidepressant, either from the same class or from a different class, is recommended when it appears the patient is not responding to the current therapy. Some psychiatrists advocate adjunctive therapy with triiodothyronine or lithium; however, these types of augmentation are best left to the care of a child psychiatrist. After the patient has achieved a reasonable therapeutic response, the medication should be continued for another 6 months and then gradually tapered over the next 3 months. This is a generally accepted rule for patients with first episodes of depression. For children with previous episodes of depression, maintenance therapy should continue for 12 months or longer. The family should be educated about the signs of early relapse so that medications can be reinstituted as quickly as possible, if need be. The greater the number of previous episodes of depression, the greater the likelihood of relapse. Data suggest that individuals with three previous episodes are nearly certain (> 95% chance) to have future episodes of depression if withdrawn from their medications.

Abrupt withdrawal from an SSRI can lead to a discontinuation syndrome which is characterized by flu-like symptoms. This is more common in antidepressants with a short half-life. Paroxetine and venlafaxine are particularly prone to this syndrome. Patients should be advised of the possibility of this reaction, and care should be taken to avoid missing doses of the medication. Discontinuation symptoms can be managed by very slowly tapering these medications, or by switching to a medication with a longer half-life (eg, fluoxetine) and then tapering.

Treatment of Comorbid Disorders

Whenever a child has depression, there is a good chance that other illnesses may exist as well. There may be a preexisting serious medical illness or a minor neurodevelopmental problem, such as nocturnal enuresis. Generally, unless the depression is severe, treatment of the other condition is indicated first. For example, a child with ADHD may have poor self-esteem and feel like a failure. But when treated with a stimulant, the child's academic performance improves, and the feelings of lack of self-worth may dissipate. On the other hand, some symptoms

of depression may appear similar to symptoms of ADHD, but the history indicates a recent onset. These children would benefit more from antidepressant therapy. In many cases, children need treatment for both ADHD and depression. Antidepressants with possible efficacy for treating both depression and ADHD symptoms may be indicated (ie, bupropion or TCAs). However, if initial therapy with a stimulant is only partially successful and depressive symptoms persist, it may be reasonable to combine an SSRI with the stimulant. With any combinations of medications, drug interactions need to be monitored. Most stimulant–SSRI combinations are well tolerated; however, there have been some reports of increased bruising with a normal pro-thrombin and thromboplastin, platelet count, and mildly elevated bleeding time. Decreasing the dose of the SSRI usually helps. When using bupropion and a stimulant together, some children complain of palpitations, and premature atrial contractions have been found on the ECG. Likewise, the combination of a TCA with a stimulant may lead to cardiovascular complaints, such as orthostatic hypotension. Atomoxetine has been shown to be efficacious in treating ADHD and may prove useful for mild depression, but research is lacking on specific mood effects. In treating a child with a comorbid tic disorder, the combination of an antipsychotic and an SSRI is generally well tolerated, although a risk for the development of dystonia and parkinsonism exists. Combining pimozide with a TCA should be monitored especially carefully with serial ECGs, because both cause QT prolongation. A warning about combining sertraline with pimozide was recently issued because of risk of QTc prolongation. Monitoring ECGs on all children with antidepressant–pimozide combination therapy is prudent. Bupropion has few drug interactions but may exacerbate tics in a few patients.

Suggested Readings

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Practitioner and Patient Resources

American Academy of Child and Adolescent Psychiatry (AACAP)
3615 Wisconsin Avenue NW
Washington, DC 20016-3007
Phone: (202) 966-7300
www.aacap.org
This site is designed to serve AACAP members as well as parents and families. Information is provided as a public service to aid in the understanding and treatment of the developmental, behavioral, and mental disorders. You will find information on child and adolescent psychiatry, fact sheets for parents and caregivers, AACAP membership, current research, practice guidelines, managed care information, awards and fellowship descriptions, meeting information, and much more.

Association for Behavioral and Cognitive Therapies
305 7th Avenue, 16th Fl. New York, NY 10001
Phone: (212) 647-1890
Fax: (212) 647-1865
www.aabt.org
This is an organization which provides information to professionals and the public about cognitive and behavioral therapies.

Child & Adolescent Bipolar Foundation (CABF)
1000 Skokie Blvd., Suite 570,
Wilmette, IL 60091
Phone: (847)256-8525
www.bpkids.org
This is an organization whose goal is to educate families, clinicians and the public about bipolar disorder in children. They offer information about support groups and other resources to families,

advocate for patients with bipolar disorder and encourage and support research on pediatric bipolar disorder.

Kids Health
The Nemours Foundation
1600 Rockland Road
Wilmington, DE 19803
Phone: (302) 651-4046
www.kidshealth.org
This is an organization which provides information to parents, children and teens about a variety of medical conditions including depression and teen suicide. There is information targeted to the education of each of these groups.

Parents Med Guide
www.parentsmedguide.org
Information complied by the American Academy of Child and Adolescent Psychiatry and the American Psychiatric Association for parents and physicians about childhood depression and treatment options which was developed in response to increasing concern about suicidal thoughts among children and teens who are prescribed antidepressant medications. These guides have been endorsed by multiple different professional organizations.

Red Flags
MHA of Summit County
P.O. Box 630
Phone: (330) 923-0688
Phone: (800) 991-1311
Fax: (330) 923-7573
www.redflags.org
Red Flags is a school-based prevention program to help students, parents and school staff members recognize and respond to signs of depression and related mental illness

Yellow Ribbon International Suicide Prevention Program
PO Box 644
Westminster, CO 80036-0633
Phone: (303)429-3530
Fax: (303)426-4496
www.yellowribbon.org
Email: ask4help@yellowribbon.org
This is an organization which offers online help for teens and parents, as well as resources and support group information. They offer information for professionals as well as teens and families about suicide prevention as well as resources for survivors of suicide.

School Psychiatry Program & MADI Resource Center
www.Schoolpsychiatry.org
This is a website which provides information about a variety of mental health conditions to parents, teachers, students and clinicians. This site provides basic information about illnesses as well as a comprehensive list of screening tools to assess for psychiatric illnesses. This website includes links to publishing companies that make a wide variety of screening tools including the Child Behavior Checklist, the Beck Depression Inventory and the Children's Depression Inventory.

U.S. Food and Drug Administration (FDA)
5600 Fishers Lane
Rockville, MD 20857-0001
Phone: 888-INFO-FDA (888-463-6332)
www.fda.gov
The latest information on the use of antidepressants in children and adolescents can be found at the FDA Web site.

National Institute of Mental Health (NIMH)
5600 Fishers Lane, Room 7C-02
Rockville, MD 20857
Phone: (301) 443-4513
E-mail: nimhinfo@nih.gov
www.nimh.nih.gov/nimhhome/index.cfm
NIMH's mission is to reduce the burden of mental illness and behavioral disorders through research on mind, brain, and behavior. This site contains information for the public and professional community.

CHAPTER 80

CONVERSION REACTION

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Conversion reaction and functional somatic complaints, which consist of apparent physical symptoms without underlying physical etiology, are seen relatively commonly in pediatric psychiatry consultation. Evaluating, diagnosing, and treating possible conversion reaction is a complex and challenging task. Multidisciplinary techniques of evaluation and intervention are necessary, culminating in a structured and carefully designed treatment plan that includes informational, activity, cognitive, and behavioral components. Clinical experience and research evidence suggests this approach to assessing and treating conversion reaction offers the best potential for remission of symptoms.

It is relatively common for children to report physical symptoms for which no organic etiology can be found. In many cases, these functional somatic complaints mimic a possible disease (eg, symptoms of infectious disease, such as muscle aches and abdominal pain) and may resolve after "treatment" with antibiotics or other medicines. However, a small percentage of functional somatic complaints persist or evolve into more severe and impairing conditions, which continue to evade physical explanation. These persistent, disabling, apparent physical symptoms with no physical origin carry various labels, including somatoform disorder, conversion reaction, and hysteria. The latter two labels were popularized by psychological theories (including psychoanalysis) in the late nineteenth and early twentieth centuries. They reflect the belief that physical symptoms without organic cause could occur as a result of repressed conflicts that expressed themselves indirectly through a physical symptom instead of psychological distress.

Although some early theories hypothesized that a hysterical personality or conversion of internal psychological conflict led to all functional somatic complaints, more modern theories allow for several possible causes. In addition to intrapsychic conflict and personality characteristics, other possible causes of functional somatic complaints include external stressors, social-familial systems (including social learning and structural family factors), cognitive belief systems, and classical conditioning. Any one or a combination of these causes could lead to apparent physical symptoms in the absence of an organic process, as described below:

- External stressors may cause functional somatic complaints by leading to psychological and physiologic hyperarousal. The individual who feels overwhelmed by these stresses may avoid the environment and focus on his or her own well-being. The combination of hyperarousal and a focus on well-being may lead the individual to interpret minor somatic problems (which may be normal physiologic responses to stress) as intense and disabling.
- Characteristics of the family environment or the broader social environment can exacerbate stress or increase the attention given to somatic symptoms. Stresses within the family structure may create internal anxiety and a focus on somatic issues as a way of diverting attention from family conflict or as a way of maintaining an enmeshed relationship between one parent and the child. Social learning may cause conversion reaction when a child is exposed to frequent examples and reminders of illness in the family environment. Children are both suggestible and prone to imitation, which makes them likely to internalize the things they observe. Children raised in illness-focused families, for example, learn to scan their bodies for problems and focus on symptoms when they occur.

- The belief system of the child may contribute to the development of functional somatic complaints in several ways. For example, the child may be prone to attribute bodily sensations to symptoms of illness rather than to other causes because of a belief that normal sensations are signs of illness. Additionally, the child may have a distorted interpretation of minor illness symptoms as catastrophic. Beliefs about individual vulnerability to illness and about appropriate responses to possible illness sensations will also heavily influence the child's experience of bodily sensations. Symptoms of depression or anxiety are frequently comorbid with functional somatic complaints, and the negative beliefs that accompany depression and anxiety can lead the child to make pessimistic attributions about ambiguous internal sensations.
- Classical conditioning is a form of learning in which a normal physical response (eg, a reflex or bodily sensation) becomes associated with a formerly neutral stimulus because of some past experience. Children who develop functional somatic complaints because of classical conditioning have had some organic physical condition or symptoms that became associated with some aspect of their daily routine. However, even when the organic condition resolves, the association of the symptoms with their daily routine persists. For example, a child who experienced repeated vomiting in school over a period of days as a result of a gastrointestinal (GI) condition later returned to school (after treatment of the condition) but continued vomiting. In that case, vomiting had become associated with the school environment.

Isolated, minor functional somatic complaints are relatively common in outpatient pediatric practices, and more severe or persistent conversion reactions are seen with some frequency in pediatric hospitals as well. In a recent 1-year period at our children's hospital, 29 of 214 (14%) psychiatry consults requested by pediatric services were for physical problems thought to be caused or exacerbated by psychological factors; 19 of 214 (9%) were subsequently diagnosed with probable somatoform or conversion reaction. In a 3-year period in the mid-1990s at our site, almost 20% of consultation referrals received a diagnosis of either *psychological factors affecting medical condition* or *conversion disorder*. Hence, functional somatic complaints account for a relatively high percentage of psychiatric problems seen in pediatric settings.

As the understanding of the multifaceted etiology of functional somatic complaints has improved, the diagnostic nomenclature that categorizes these symptoms has also evolved. Clusters of apparent physical symptoms with no organic etiology are categorized as *somatoform disorders* within the current diagnostic system for mental disorders. Somatoform disorders are further subdivided into several specific diagnostic areas: *conversion disorder* consists of symptoms or deficits in motor or sensory functioning in the absence of sufficient physiologic cause; *pain disorder* is characterized by pain sensations in the absence of a somatic explanation for the type, location, or intensity of pain; s*omatization disorder* involves multiple physical symptoms across several organ systems (GI, sexual, neurologic, and pain symptoms); and *hypochondriasis* is the belief that one has a specific, serious disease despite medical evidence to the contrary. *Undifferentiated somatoform disorder* is diagnosed for longstanding (greater than 6 months) functional somatic symptoms that do not fit another somatoform disorder diagnosis. Finally, *body dysmorphic disorder* is characterized by distress and an excessive focus on an imagined physical defect. The term "conversion reaction" usually refers to the loss or abnormality of some motor or sensory function and is, therefore, most synonymous with the current category of conversion disorder. However, many cases of pain disorder, somatization disorder, and undifferentiated somatoform disorder also involve sensory-motor abnormalities and, therefore, also fall into the spectrum of conversion reactions. Of all of the types of somatoform disorders, conversion reactions are most likely to require neurologic evaluation and management because they involve sensory-motor symptomatology; hence, the remainder of this chapter focuses specifically on conversion reactions.

Evaluation and Diagnosis

The most common presentation of conversion reaction is as an apparent neurologic abnormality. Ambulation or gait problems, paralysis, sensory loss, dizziness, and apparent seizures (pseudoseizures) appear to be some of the most frequent complaints. Conversion reaction may also often take the form of GI complaints, typically abdominal pain, nausea, and vomiting.

Pseudoseizures are one of the more common manifestations of conversion disorder and, at times, one of the more difficult to diagnose and treat. Even experienced observers may not be able to distinguish pseudoseizures from epileptic seizures after witnessing an episode. The episodes may consist of staring and unresponsiveness, trembling of the extremities, or fluctuating, arrhythmic tonic and clonic movements. Features in the history that suggest pseudoseizures include episodes occurring only before witnesses, episodes that never interrupt play, and a lack of postictal confusion after apparent tonic-clonic seizures. The precipitation of episodes by suggestion and certain seizure manifestations, such as irregular nonphysiologic progression of clonic movements, partial retention of consciousness during a generalized episode, and abrupt recovery, also indicate possible pseudoseizures. Other seizure characteristics that tend to be more common

in pseudoseizures than in true epileptic seizures are situation-specificity of symptoms, gradual onset, closed eyelids, seizure duration > 2 minutes, and presence of a pupillary light reflex. Conversely, the initiation of a seizure during sleep, urinary incontinence, and biting of the side of the tongue are more characteristic of true epileptic seizures than of pseudoseizures. Although these characteristics do tend to differentiate groups of patients with true epileptic seizures and pseudoseizures, there is not a single specific observational feature that definitively distinguishes the two in the individual patient. Hence, professionals should be careful not to draw firm conclusions from observational features of the symptoms. Diagnosis may also be complicated by the presence of true epileptic seizures and pseudoseizures in the same child, an association found in approximately 15 to 30% of cases.

The evaluation of a possible conversion reaction begins with a thorough medical work-up. Historical research and clinical experience had indicated that as many as one fourth to one-third of children initially diagnosed with conversion disorder may later be found to have an organic illness. However, more recent evidence suggests far lower error rates (< 5–10%) in specialty clinics using modern medical and psychiatric evaluation techniques. Regardless of the specific error rate, it appears that the accuracy of conversion reaction diagnosis is improving but that some error remains a risk. Because of the known presence of some error in conversion reaction diagnosis, as well as the fact that evaluation often shows possible components of both organic and psychological etiology (especially for conditions such as pseudoseizures), the risk of some organic involvement should always be carefully evaluated with a thorough medical examination and follow-up.

When pseudoseizures are suspected, a video electroencephalogram (EEG) to record the episode is essential. The absence of a rise in plasma prolactin after a seizure is suggestive evidence but not proof of a pseudoseizure. If an episode is captured on video EEG, a distinction can be made between epileptic and nonepileptic seizures. Some nonepileptic events are found to be paroxysmal movement disorder, parasomnias, gastroesophageal reflux, inattention, or mannerisms. Others are behavioral. Pseudoseizures may be due to conversion disorder or panic attacks. Factitious disorder by proxy, in which an adult induces (or fabricates) the apparent seizures in a child, is another possibility. In a series of cases from the Cleveland Clinic, one-third of the children with pseudoseizures and conversion disorder had comorbid major mood disorder.

After the medical evaluation, psychiatric evaluation for conversion reaction can provide important insight into the characteristics and possible causes of the disorder. In addition to the standard components of a psychiatric diagnostic interview (history of present illness; background information with medical, developmental, family, social, and academic histories; mental status exam; etc), focused attention to characteristics commonly associated with conversion reaction should be part of the evaluation. When investigating these characteristics, it is important to remember that no single characteristic or cause is universally seen in conversion reaction. Furthermore, many of the common features of conversion reactions are sometimes seen in children with known organic etiology. With these caveats in mind, the following characteristics are seen with some frequency in conversion reaction and, therefore, should be covered in the psychiatric evaluation:

- Recent stressors, particularly at school or home
- Family trauma, neglect, conflict, or separation
- Social or peer problems
- Defensiveness about psychiatric symptomatology or psychological cause for the disorder
- Family fixation on illness issues
- Presence of an illness model in a family member or other individual with whom the child is familiar (including an earlier illness of the child in some cases)
- Secondary gain for the physical symptoms, including avoidance of an unpleasant situation
- Past history of somatic complaints
- Excessive focus on internal physical sensations and possible symptoms
- Individual beliefs about health, illness, and the meaning of possible physical symptoms.
- Apparent and inappropriate comfort (or lack of upset) over symptoms ("belle indifference")

In the specific case of PNES, for example, family stressors (such as family conflict or loss) may be present in as many as half of cases. Other reports cite abuse and/or traumatic injury (especially head injury) as relatively common in the histories of children with PNES, occurring in as many as one-third to one-half of some reported samples. However, no single stressor or etiological event is present in all (or even in a large majority of) cases of PNES.

Despite the presence of belle indifference in some children with conversion reaction, other children and families (probably a majority) with conversion reaction are very distressed by the symptoms. Hence, psychiatric evaluation should also include attention to psychological distress and possible reactions of the child and family to that distress. Considerable anxiety is frequently present. Families and children who present as defensive, angry, and even hostile about the diagnostic possibility of a conversion disorder are often reacting to their anxiety that some serious physical illness has been missed. Depression is possible when the child or family feels misunderstood or abandoned by the nonpsychiatric medical establishment. These symptoms should be evaluated and managed as though the conversion

reaction is itself a stressor. In addition to standard psychiatric examination, psychological testing may be warranted to obtain more extensive information about the personality, level of distress, cognitive or learning ability, or other psychiatric symptoms of an individual with a possible conversion reaction. However, no psychological test profile is typical of or unique to the individual with a conversion reaction. Personality tests, such as the Minnesota Multiphasic Personality Inventory (MMPI) for adolescents and adults or the Personality Inventory for Youth (PIY) for children and adolescents, may help the evaluator to more fully understand personality factors involved in conversion and other symptoms. Symptom checklists and rating scales such as the Behavior Assessment System for Children (BASC) can warn of other symptoms and level of distress. Although these instruments can be of great help in comprehensively understanding the patient, they are generally not considered essential to every evaluation of a conversion reaction.

A common diagnostic misunderstanding of conversion reactions is the belief that the symptoms are intentionally produced by the child. As with all somatoform disorders conversion reactions are not intentionally produced; the patient believes that the symptoms are actual physical problems. Stated simply, the patient believes the symptoms to be "real," and the implication that these apparent physical sensations may be a result of psychological rather than physical processes is, therefore, initially hard to believe for many patients.

Treatment

Although clinical observations and follow-up studies indicate that some proportion of conversion reactions remit without active treatment, outcome studies and the debilitating functional impact of conversion reaction argue in favor of aggressive treatment. Placebo and wait-list controlled studies suggest that between 10 and 50% of somatoform disorders improve in the absence of active treatment, but follow-up studies of actively treated conversion disorder groups have shown improvement rates > 50% and as high as 80 to 100% over a 1-year period. Early diagnosis and good premorbid adjustment predicts favorable outcome. On the other hand, studies show rates of mood and anxiety disorders as high as 25 to 35% in children and adolescents with conversion reaction, even after their conversion symptoms are successfully treated.

Many treatments have been tried to address conversion reaction, including medication, psychoanalysis, psychotherapy, play therapy, hypnosis, family therapy, and inpatient psychiatric hospitalization. However, only medication and some components of psychotherapy have been supported in outcome research. In the medication arena, tricyclic antidepressants have received the most research attention and empiric support, although most of this research has been conducted with adults. Studies typically report that between 50 and 75% of patients (usually adults) with somatoform disorders improve significantly when treated with tricyclic antidepressants, compared with 30% of those taking placebo. Because double-blind, placebo-controlled trials have not shown tricyclic antidepressants to be more effective than placebo for depression in children, caution must be exercised when using these drugs to treat conversion reaction in childhood. Compared with improvement rates seen with use of tricyclics, improvement rates are somewhat lower and there is less consistent support for selective serotonin reuptake inhibitors, unless clear depressive symptoms are present. Additionally, topiramate and Saint-John's-wort have been used in samples of adults, with some preliminary positive results.

Effective psychotherapeutic approaches to treating conversion reaction and somatoform disorders integrate cognitive, behavioral, rehabilitation, and case management components into a unified medical-psychological intervention. In randomized, controlled studies, treatment plans using some or all of these components have been found to reduce symptoms of somatoform disorders in samples of adolescents and adults; reviews suggest that between 30 and 75% of samples report clinically significant improvement, with some studies showing superiority to placebo. Effect sizes (compared with wait-list or placebo) are usually mode rate and typically fall into the 0.5 to 1.0 range. Studies specifically focusing on conversion disorder in children are sparse but suggest that the medical-psychological intervention is effective in this age group as well. One of the most well-defined (although early in development) medical-psychological interventions for children with conversion reactions (as well as other disorders that reduce functional independence) is the Children's Health and Illness Recovery Program (CHIRP). Although CHIRP has not been validated in clinical trials, it involves the use of a comprehensive set of established medical-psychological interventions and has shown promise in clinical settings. The components of an integrated medical psychological treatment, which have been described by several authors, are summarized in Table 80-1.

Treatment using an integrated medical-psychological model begins with a comprehensive medical evaluation, with involvement of psychiatric consultation as soon as conversion reaction appears to be a possible diagnosis. When this evaluation is complete, members of all involved disciplines should meet with the family for a conference, during which the family is provided with a complete explanation of findings, diagnosis (including a full explanation of conversion disorder), and plans for treatment. This meeting is essential for enlisting the family's active participation in the treatment of the conversion reaction as well as for educating the family

TABLE 80-1. Multidisciplinary, Multimodal Intervention for Conversion Reaction

1. Comprehensive medical and psychiatric evaluations
2. Multidisciplinary meeting (all disciplines involved in evaluation, coordinated by attending service) with family
3. Reassure family of continued involvement of all relevant medical disciplines (evaluation and treatment by other medical disciplines will not be changed because of conversion reaction diagnosis and involvement of psychiatry)
4. Set clear goals for treatment
5. Begin cognitive therapy
   a. Stress identification and management
   b. Problem and emotion focused coping
   c. Independent functioning
   d. Educate family about illness stress, coping, and functional independence
6. Begin activity therapies
   a. Physical or occupational therapy
   b. Sleep hygiene (if needed): clearly defined bedtime and waking times and routines
7. Begin scheduling therapies
   a. Set a clear school day schedule (introduce gradually if full return is not possible)
   b. Set a clear morning and evening schedule
8. Set rules of illness behavior
9. Set environmental behavioral contingencies to reduce illness behavior
   a. Reward healthy behavior and activity
   b. Prevent/reduce avoidance by illness complaints
   c. Expose child gradually to conditions that have been associated with illness
10. Regular outpatient meetings with psychotherapist to implement plan and address resistance and other psychological challenges

about the nature of a somatoform or conversion disorder. It is important at this meeting to convey to the family that the symptoms are real (in the sense that they are experienced as bona fide by the child) and that a multidisciplinary approach (not an exclusively psychological approach) is being taken in their management. Family confusion about findings, concerns about missed diagnoses, suggestions for medical testing, and hypotheses about physical causes can best be addressed by a representative of the specific discipline in question (eg, neurology about a neurologic complaint or test). In the case of pseudoseizures, for example, an explanation of the difference between epileptic seizures and pseudoseizures (with review of video EEG results as needed) is often very helpful, particularly in cases of children who have both seizures and pseudoseizures. In these cases, families often need reassurance (and explanation) that treatment for the pseudoseizures will not adversely affect treatment for the epileptic seizures.

Involvement of all disciplines at this meeting also prevents splitting, which can occur when the family attempts to enlist the support of one physician (or group of physicians) against another. The family should be reassured at this meeting that the diagnosis of a conversion reaction will not change the involvement of the various disciplines currently working with the child; physicians will continue or end their evaluations and ongoing monitoring as they would have whether conversion reaction were diagnosed or not. This communication often reassures families who fear that the implementation of a conversion disorder treatment plan might mean that a possible undiagnosed serious physical disorder would not receive any further monitoring or evaluation. Ongoing monitoring of the child's symptoms by appropriate medical services continues to be warranted, even after implementation of the treatment plan.

To implement the remainder of the treatment plan for a conversion reaction, the child and family meet regularly with a psychotherapist. Working with the family, the psychotherapist defines the details of the intervention and encourages adherence to the components of the intervention. If more intensive family or individual intervention is needed for adherence or to address problems, psychotherapy directed at those family or individual characteristics may be needed. Initially, however, the psychotherapist focuses on structuring the conversion reaction intervention as described below.

The actual interventions for conversion disorder begin with setting concrete goals for improvement in symptoms and in day-to-day functioning. Emphasis is placed on functional improvement and realistic management of symptoms, using a rehabilitation approach, as opposed to the belief in a quick cure. Typically, a good starting point is a discussion of what aspects of daily life have been adversely affected and what can be done to improve them.

Next, several components of therapy are put into place, including cognitive therapy interventions, gradual exposure to increased activity and functioning, and implementation of a schedule. Cognitive therapy addresses beliefs, attributions, and automatic stress responses that exacerbate or maintain conversion symptoms. Children are encouraged to understand how their beliefs contribute to illness attributions and fears, and inaccurate or maladaptive beliefs are challenged. For example, the belief that leg pain signals a weakness and inability to walk may be challenged by suggesting alternative reasons and implications of the pain. Illness anxiety, which is often rooted in catastrophic beliefs about one's health, may also be a target of intervention by discussing past illness experiences and how these experiences have created anxiety that may not be appropriate in the present situation. Coping skills are frequently taught to give the child some sense of control over beliefs, attributions, attention to physical symptoms, and somatic states. Such skills may include self-talk, relaxation training, distraction, biofeedback, and self-hypnosis. Evidence indicates, for example, that hypnosis for symptom control and self-exploration results in significant improvement in conversion symptoms in adults, compared with wait-list control subjects. For younger children and children with less insight, play techniques must be used to explain cognitive concepts and to practice coping skills in a more concrete and repetitive fashion.

Activity and scheduling interventions aim to return the child to an adequate (ideally normal) level of daily physical activity. To achieve this goal, physical or occupational therapy is initiated as soon as possible, and the child's daily schedule (including sleep–wake schedule, which is often disrupted by the child's symptoms) is adjusted to include regular activities. Increases in activity level in the context of a daily schedule promote feelings of physical well-being, improve physical functioning, desensitize the child to environmental cues that may have been associated with illness, and provide distraction from physical symptoms.

To address factors maintaining illness behavior, rules and contingencies are set regarding the child's physical symptoms. First, rules of illness behavior are defined in a meeting with the child and family. Repeated complaints of the same symptoms are defined as nonfunctional (they do not communicate any new information to others), so they are discouraged. For example, the child may have one defined time of day (eg, a half-hour in the evening) to make these repeated complaints. Otherwise, they are ignored. Illness complaints that are new (including changes in illness complaints) or functional (can be addressed with some acceptable treatment in the environment, such as asking for medicine for a headache) may be directed once to appropriate caretakers at any time. Family discussion of or focus on illness (including pessimism about treatment and physical status) is strongly discouraged. Setting these boundaries around illness complaints prevents them from becoming a pervasive focus of the child's and family's life. Similar rules are set up with the physicians and with the school to allow an appropriate response to the child's physical symptoms while not reinforcing symptoms or encouraging a somatic focus. It is important that these rules reassure the child and family that appropriate help and support will be available when symptoms occur. However, limits are placed on access to the medical system (or other support systems) when such access would not be helpful or would be inappropriately reinforcing the physical symptoms.

Environmental contingencies are designed to encourage healthy behavior and activity while not allowing illness to be used to escape or avoid unpleasant activity. Rewards (including privileges and access to favored activities) should be set for achievement of activity goals, and (within reason) the child should not be allowed to avoid unpleasant events by making illness complaints. In the case of classically conditioned illness complaints, the child should be exposed gradually to situations that appear to have been associated with sensations of illness. For example, a child who associates the smell and taste of food with nausea (as sometimes can occur following certain GI illnesses or treatments that cause nausea) should be gradually exposed to food, with increasing requirements for food intake and exposure.

Throughout the intervention, regular meetings with the psychotherapist are essential. These meetings are typically used to implement cognitive therapy interventions, address problems, refine details of the plan, answer questions, set up contingencies, and encourage adherence to the intervention. If the intervention appears to be ineffective (or inadequate) because of resistance, severe or persistent symptoms, or more significant psychopathology, additional adjunctive treatments, such as family therapy and more intensive psychotherapy, may be necessary. In extremely severe or resistant cases, treatment plans may have to be implemented in a highly structured environment, such as an inpatient hospital setting. Inpatient treatment for conversion reaction follows the same goals and interventions of the medical-psychological model, but in a more intensive and structured way. A "level system" is often used to define access to privileges, with few privileges at the beginning levels and increasing sets of privileges (phone use, access to peers or family, access to favored activities, freedom to leave the room or unit, etc) at higher levels that are achieved as symptoms and functioning improve. Levels and privileges are also contingent on active participation in the treatment plan. Physical and psychological therapies are more intensive, occurring daily or multiple times a day, and the child is expected to complete coping work (such as lessons in a coping workbook) between therapy sessions. Inpatient treatment is frequently used to achieve rapid improvement of severe or resistant symptoms, with outpatient follow-up after discharge.

Suggested Readings

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Practitioner and Patient Resources

American Academy of Child and Adolescent Psychiatry (AACAP)
3615 Wisconsin Avenue NW
Washington, DC 20016-3007
Phone: (202) 966-7300
http://www.aacap.org
This Web site is designed to serve AACAP members as well as parents and families. Information is provided as a public service to aid in the understanding and treatment of the developmental, behavioral, and mental disorders that affect an estimated 7 to 12 million children and adolescents at any given time in the United States.

American Psychiatric Association
1000 Wilson Boulevard, Suite 1825
Arlington, VA 22209-3901
Phone: (703) 907-7300
E-mail: apa@psych.org
http://www.psych.org/
The American Psychiatric Association is a medical specialty society recognized worldwide. Its over 35,000 U.S. and international member physicians work together to ensure humane care and effective treatment for all persons with mental disorders.

American Psychological Association (APA)
750 First Street NE
Washington, DC 20002-4242
Phone: (202) 336-5700
E-mail: public.affairs@apa.org
http://www.apa.org/
The American Psychological Association is a scientific and professional organization that represents psychology in the United States. With more than 150,000 members, it is the largest association of psychologists worldwide.

CHAPTER 81

NEUROFIBROMATOSIS

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Neurofibromatosis types 1 and 2 are distinct autosomal dominant disorders that are associated with the formation of multiple tumors. Diagnostic criteria and approaches to management are provided.

"Neurofibromatosis" is a term that encompasses two distinct disorders referred to as neurofibromatosis 1 (NF1) and neurofibromatosis 2 (NF2). Both are dominantly transmitted genetic disorders characterized by the occurrence of multiple benign tumors of the peripheral nerve sheath (neurofibromas in NF1 and schwannomas in NF2). NF1 includes nontumor manifestations, such as skeletal dysplasias and learning disabilities and includes a risk of malignancy. The hallmark lesion of NF2 is the vestibular schwannoma, but schwannomas may also occur along other cranial nerves and peripheral nerves, and other tumors, such as meningiomas, ependymomas, and gliomas, may occur. Current management focuses on clinical diagnosis and early detection of treatable complications. The genes for both NF1 and NF2 have been identified, however, which is leading to insights into pathogenesis that are beginning to suggest new methods of diagnosis and treatment. Recently, a third disorder has been added to the list of neurofibromatoses. Referred to as "schwannomatosis," the sole manifestation is multiple schwannomas but not vestibular schwannomas. Schwannomatosis usually occurs as a sporadic trait, though dominant transmission can occur. The responsible gene has not been identified.

NF1

Background

NF1 is one of the most common single gene disorders to affect the nervous system. It occurs in about 1:4,000 individuals worldwide, without racial or ethnic predilection. It is an autosomal dominant trait with complete penetrance and variable expression. Approximately, 50% of cases occur sporadically due to new mutation. The gene is located on chromosome 17 and encodes a protein referred to as "neurofibromin."

Diagnosis

NF1 is diagnosed on the basis of clinical criteria (Table 81-1 and Figure 81-1). Multiple café-au-lait macules are the most common presenting sign. Café-au-lait macules usually appear within the early weeks of life and may increase in number over the first 2 years of life. At least six macules measuring 5 mm before puberty and 15 mm after puberty are required to fulfill a diagnostic criterion for NF1. Café-au-lait macules do not mark the location of future NF1 complications, and their overall number does not correlate with the severity of the disorder. Skin-fold freckles are usually the next sign to appear, usually between ages 3 and 5 years. Eventually, there may be widespread freckling and diffuse hyperpigmentation. Neurofibromas represent benign tumors of the nerve sheath, consisting principally of Schwann cells and fibroblasts. Dermal neurofibromas may protrude from the surface of the skin or be recessed in the deep subcutaneous tissues. Internal neurofibromas may

TABLE 81-1. Diagnostic Criteria for NF1. An Individual who Fulfills Two or More Criteria can be Diagnosed as Having NF1

1. Six or more café-au-lait macules larger than 5 mm before puberty or 15 mm after puberty.
2. Freckles within skin folds, such as axillae or groins.
3. Two or more neurofibromas or one plexiform neurofibroma.
4. Two or more iris Lisch nodules.
5. Optic glioma.
6. Characteristic skeletal dysplasia, such as tibial dysplasia or sphenoid dysplasia.
7. Affected first-degree relative.

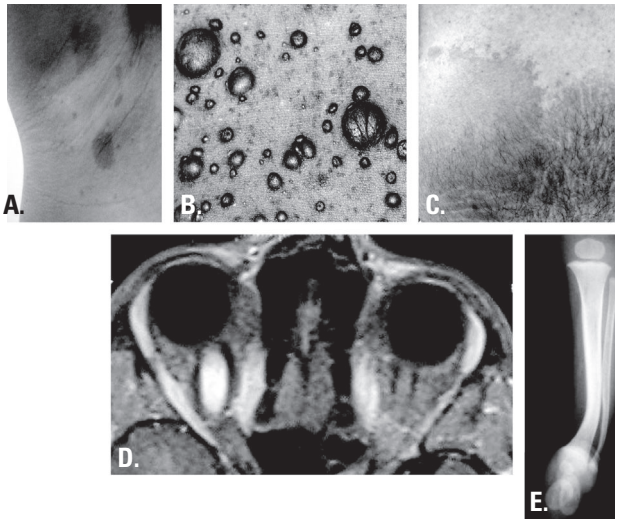

FIGURE 81-1. Characteristic lesions of NF1. (A) Café-au-lait macules and axillary freckles; (B) multiple skin neurofibromas; (C) Hyperpigmentation overlying plexiform neurofibroma; (D) Orbital optic glioma (left side); (E) x-ray showing tibial dysplasia.

occur anywhere in the body. Plexiform neurofibromas grow along nerves and may involve multiple branches of a major nerve and cause soft-tissue hypertrophy. Dermal neurofibromas usually do not appear before puberty, but plexiform neurofibromas usually are congenital and may be associated with an overlying cutaneous hyperpigmentation. Iris Lisch nodules are melanocytic hamartomas that are highly specific for NF1. They usually appear after age 6 years and do not affect vision. Optic glioma occurs in approximately 15% of affected children and may involve the optic nerve, chiasm, or both. Most are clinically silent and do not require treatment (see Section "Treatment"). Characteristic skeletal dysplasia includes tibial dysplasia, clinically manifest as lower leg bowing, and orbital dysplasia, including defect of the greater sphenoid wing associated with trigeminal plexiform neurofibroma. Finally, if a parent, sibling, or offspring fulfills diagnostic criteria, the diagnosis can be made in a child who otherwise fulfills one criterion. Macrocephaly and learning disability occur commonly in children with NF1 but do not have sufficient specificity to be diagnostic criteria.

Evaluation

A child suspected of being affected with NF1 should have a thorough skin examination, looking for café-au-lait macules, skin-fold freckles, and neurofibromas. It is not necessary to use the Wood's lamp to see café-au-lait macules since the diagnostic criterion applies to ordinary room lighting. There are rare families in which multiple café-au-lait macules occur as an autosomal dominant trait without other signs of NF1, which is why multiple café-au-lait macules alone are not sufficient to diagnosis NF. A slit-lamp examination should be performed by an experienced ophthalmologist to search for Lisch nodules. There has been much debate surrounding the use of brain magnetic resonance imaging (MRI) in the diagnosis and management of NF1. MRI may reveal foci of enhanced T2 signal intensity in the basal ganglia, brain stem, and cerebellum, but similar lesions may be seen in unaffected individuals. MRI may also reveal optic glioma, but the finding of an asymptomatic optic glioma does not i clinical management since most do not require treatment. MRI in young children requires sedation, and findings may cause anxiety without changing management. MRI is, therefore, best used to investigate signs or symptoms rather than as a means of establishing a diagnosis of NF1.

Molecular testing to detect the NF1 mutation is available on a clinical basis (<http://www.genetests.org>). Testing can be used to confirm a diagnosis in an individual who presents with a single diagnostic feature (such as a child with multiple café-au-lait spots) or with an atypical presentation suggestive of NF1. It can also be used as a basis for prenatal diagnosis. With the exception of a severe phenotype in those with deletions of the entire NF1 gene, genetic testing does not predict the specific phenotypic features or severity. Some individuals display signs of NF1, including café-au-macules, skin-fold freckles, and even neurofibromas, in a restricted region of the body. This is so-called "segmental NF," which appears to be due to somatic mosaicism for an NF1 mutation.

Treatment

There is no definitive cure for NF1. Management is, therefore, limited to surveillance for treatable complications and anticipatory guidance. Children with NF1 should be followed at least annually by a physician who is familiar with the disorder, who will examine for neurofibromas, skeletal dysplasia (including scoliosis), and neurological function. An annual ophthalmologic examination should also be performed to look for signs of optic glioma. Growth and blood pressure should be monitored. Parents should be counseled about the potential for learning disabilities, and developmental assessment should be done for children who show signs of learning difficulty. The severity of NF1 varies widely, making it difficult to predict specific complications. Affected individuals and family members should be counseled that many of the severe complications are rare, and some, such as tibial dysplasia or plexiform neurofibroma, are congenital. Also, the severity of NF1 is often overstated in medical and lay publications.

Pigmantary Features

Café-au-lait macules and skin-fold freckles may pose a cosmetic problem for some individuals. They tend to fade

in adulthood. Laser treatment has been used to remove café-au-lait macules, although the long-term efficacy of such treatment has not been studied.

Neurofibromas

Dermal neurofibromas can appear at any time but most often begin during puberty. Women often notice the growth of new neurofibromas during pregnancy. The number of neurofibromas an individual will develop over a lifetime is unpredictable. Most develop at least some neurofibromas, but the occurrence of thousands of neurofibromas covering the entire body is relatively unusual. Individual neurofibromas may be removed by plastic surgery or by laser treatment.

Plexiform neurofibromas are usually congenital and often grow rapidly in the early years of life. Some are associated with soft-tissue hypertrophy leading to overgrowth of part of the body. Severe cosmetic deformity may occur, particularly for plexiform neurofibromas involving the face. Surgical resection is the only current means of management, but this is limited by the fact that plexiform neurofibromas may invade surrounding tissues, making complete resection impossible and regrowth after surgery likely. Clinical trials are beginning to test new drug treatments for plexiform neurofibromas (see below).

Neurofibromas are usually not painful but can compress nerves, leading to weakness, sensory loss, and pain. Radicular pain may occur from compression of a nerve root, and neurofibromas may invade the spinal canal and compress the cord. Surgical resection is the only available treatment. The clinician should be alert to the presence of a large patch of hyperpigmentation over the spine, which may indicate a plexiform neurofibroma involving nerve roots near the spine.

Optic Glioma

As noted, optic gliomas are common in children with NF1 but often grow without causing symptoms. Children should be monitored for visual acuity, visual fields, and signs of precocious puberty. Orbital optic gliomas can also cause proptosis and interfere with extraocular movements. The peak age for progression of optic glioma is 4 to 6 years. In the past, radiation therapy was the standard treatment for symptomatic optic gliomas, but complications, including endocrinopathy and vascular stenosis, have led to avoidance of radiation treatment in young children. Currently, chemotherapy, usually with vincristine and carboplatin, is used as a first-line treatment. Treatment should be reserved for tumors that are symptomatic and clearly progressive. Asymptomatic tumors found incidentally by MRI can be monitored; increase in size by MRI is not sufficient to trigger treatment if signs or symptoms of visual impairment are not present. Precocious puberty can be managed by hormonal treatment.

Malignancy

The lifetime risk of malignancy in NF1 is about 5% (over the 25% lifetime risk of cancer in the general population). Malignant tumors include gliomas (in addition to optic gliomas), sarcomas (especially malignant peripheral nerve sheath tumors [MPNST]), and leukemia (especially non-lymphocytic leukemia). Patients (and parents of young children) should be advised to be alert to unexplained pain, sudden growth of a neurofibroma, or change in consistency of a tumor from soft to firm. Most MPNST in NF1 arise within plexiform neurofibromas. There are no distinctive imaging characteristics that reliably distinguish benign from malignant lesions, and biopsy may miss the malignant component. Positron emission tomography scanning with FDG-glucose may be helpful in identification of a malignant component. Treatment of MPNST is best accomplished by resection; radiation and chemotherapy have not been demonstrated to increase survival.

Skeletal Dysplasia

Tibial dysplasia occurs as a congenital lesion and can be recognized clinically. The leg is usually placed in a clamshell brace to avoid fracture. If fracture occurs, healing can be very difficult to achieve and may require multiple orthopedic procedures, including bone grafts. Orbital dysplasia is treated surgically, though treatment is often deferred until adolescence after facial growth is complete and the plexiform neurofibroma has stopped growing. Scoliosis may occur in childhood or adolescence and can be associated with a dystrophic vertebra, usually in the thoracic region. Severe curves ($> 40^{o}$) usually require surgery.

Vascular

Hypertension may be a consequence of renal artery stenosis. Stenosis of other vessels can lead to cerebrovascular occlusion and moyamoya syndrome. Arterial dissection may occur, with consequent hemorrhage. Other causes of hypertension are essential hypertension and pheochromocytoma.

Endocrine

Precocious puberty usually occurs in association with optic glioma. Children with NF1 often grow more slowly than predicted from familial height.

Learning Disability

The frequency of learning disability in NF1 is about 50%. Some children have severe developmental delay with

onset in the first year of life, but more commonly, more subtle learning disabilities are present. Children may have hypotonia, delayed motor milestones, and poor coordination. Attention deficit, with or without hyperactivity, may occur and respond to the same treatments as are used in the general population, including stimulant medication. There is no learning disability pattern that is specific to NF1. Children with learning problems should be evaluated to determine areas of need and provided appropriate help.

Genetic Counseling

An affected individual has a 50% chance of passing an *NF1* gene mutation to any offspring. Severity can be variable even within a family. Parents of a sporadically affected child have a low risk of recurrence, barring the rare occurrence of germ line mosaicism.

Discussion

The *NF1* gene product, neurofibromin, appears to function by regulating the activity of RAS, a protein involved in the control of cell proliferation and differentiation in response to extracellular signals. Loss of *NF1* function is believed to lead to increased activity of RAS, producing hyperproliferation of Schwann cells, which in turn probably recruit the growth of fibroblasts by secretion of cytokines. Clinical trials have been initiated with several agents, including inhibitors of components of the RAS signaling pathway and other agents, such as angiogenesis inhibitors. It is hoped that increased understanding of the pathogenesis of NF1 will gradually lead to the development of new approaches to treatment that will prevent or reverse many of the complications of the disorder.

NF2

Background

NF2 is an autosomal dominant trait with a population frequency of about 1:40,000. The responsible gene is located on chromosome 22 and encodes a protein referred to as "merlin" or "schwannomin."

Diagnosis

Diagnostic criteria are set forth in Table 81-2. The hallmark feature is the occurrence of bilateral vestibular schwannomas. These may not occur until adulthood, however, making diagnosis difficult in a young child who may present with one of the other tumors of NF2 or cataract. A presumptive diagnosis may be established in a person with unilateral vestibular schwannoma or multiple meningiomas and of the other NF2-associated tumors or posterior subcapsular cataract. NF2 should be considered in any individual aged 30 years or less who presents with a vestibular schwannoma or meningioma.

Evaluation

An individual suspected as having NF2 should be evaluated for vestibular schwannoma. Audiology may reveal high-frequency hearing loss, and auditory brain stem evoked responses may be abnormal. MRI is the standard test to identify vestibular schwannomas, however, and may also reveal other NF2-related tumors. Molecular diagnostic testing available on a clinical basis; laboratories are listed in the GeneTests database (<http://www.genetests.org>).

Management

The management of NF2 is currently limited to surveillance for treatable complications and counseling. There is a wide range of variable expression, with some individuals having early onset and rapid progression of tumors, whereas others may have milder disease. To some extent, these differences may breed true within families and correlate with specific types of *NF2* gene mutations.

Vestibular Schwannoma

Vestibular schwannomas usually become symptomatic after the first decade but can occur in childhood. Presenting symptoms include loss of balance, vertigo, tinnitus, and hearing loss. Tumors are monitored by audiology, brain stem auditory evoked response testing, and MRI. Treatment options include surgery and stereotactic radiation therapy. The decision to treat is a complex algorithm that includes consideration of whether bilateral tumors are present, degree of preservation of hearing, and presence of associated symptoms, such as facial nerve palsy.

Other Tumors

Schwannomas may occur along other cranial nerves, especially the fifth nerve. Spinal nerve root tumors may cause radicular symptoms or compress the spinal cord. They occur commonly and are detected by MRI. It is not clear, however, that screening spinal MRIs are helpful in the absence of signs or symptoms. Schwannomas may also occur along peripheral nerves, including cutaneous nerves, where they may appear as plaques in the skin. Schwann cell overgrowth in peripheral nerves can cause a neuropathy. Multiple meningiomas can be responsible for

TABLE 81-2. Diagnostic Criteria for NF2

Bilateral vestibular schwannomas or first-degree relative with NF2 and unilateral vestibular schwannoma under age 30 or any two of the following:
Meningioma
Schwannoma of other cranial or peripheral nerve
Ependymoma
Glioma
Posterior subcapsular cataract or cortical wedge opacity

major morbidity. Often they are not accessible to surgical resection, and effective nonsurgical treatments are not currently available. Epenymomas and gliomas may occur within the brain or spinal cord. Often these are asymptomatic; symptomatic tumors require surgical resection.

Cataract

Presenile posterior subcapsular cataract and cortical wedge opacity occur more commonly in NF2 than the general population. These lesions can be identified in children with the disorder, providing a means of early diagnosis. Cataracts may be asymptomatic but should be monitored by an ophthalmologist and treated surgically as needed.

Discussion

The *NF2* gene encodes a cytoskeletal protein. Tumors have mutations of both *NF2* alleles: one inherited and one acquired. *NF2* is, therefore, a tumor suppressor gene. The mechanism whereby loss of *NF2* function leads to formation of tumors is unknown, however. A mouse model for *NF2* has been developed, and it is hoped that further study of the pathogenetic mechanisms will lead to the development of new approaches to treatment.

Suggested Readings

Dow G, Biggs N, Evans G, et al. Spinal tumors in neurofibromatosis type 2. Is emerging knowledge of genotype predictive of natural history? J Neurosurg Spine 2005;2:574–9.

Ferner RE. Neurofibromatosis 1. Eur J Hum Genet 2006.

Gutmann DH, Aylsworth A, Carey JC, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA 1997; 278:51–7.

Huson SM, Harper PS, Compston DA. Von Recklinghausen neurofibromatosis. A clinical and population study in South-East Wales. Brain 1988;111(Pt 6):1355–81.

MacCollin M, Chiocca EA, Evans DG, et al. Diagnostic criteria for schwannomatosis. Neurology 2005;64:1838–45.

Moffat DA, Quaranta N, Baguley DM, et al. Management strategies in neurofibromatosis type 2. Eur Arch Otorhinolaryngol 2003;260:12–8.

Practitioner and Patient Resources

Information for patients and families can be obtained from the following sources:

Children's Tumor Foundation
95 Pine Street, 16th floor
New York, NY 10005
Phone 212-344-6633
Fax 212-747-0004
E-mail: info@ctf.org
<http://www.ctf.org>

Neurofibromatosis, Inc.
PO Box 18246
Minneapolis, MN 55418
Phone 301-918-4600
E-mail: nfinfo@nfinc.org
<http://www.nfinc.org>

Understanding NF1
<http://www.understandingnf1.org>

Chapter 82

Tuberous Sclerosis Complex

Paolo Curatolo, MD

Tuberous sclerosis complex is an autosomal dominantly inherited disorder characterized by widespread hamartomas in a great number of organs in the human body, including the brain, heart, skin, eyes, kidney, lung, and liver. Epilepsy, learning disability, and autism are the most common neurologic symptoms.

Tuberous sclerosis complex (TSC) is a genetically determined, variably expressed, multisystem disorder that may affect any human organ with well circumscribed, benign, noninvasive lesions. The skin, brain, retina, heart, kidney, and lung are the organs more often involved. This devastating disorder resulting from mutations in one of two genes (*TSC1* and *TSC2*) affects as many as 1 in 5,800 live births. The importance of central nervous system (CNS) involvement in TSC is emphasized by the fact that the condition has retained its name for over a century. "Tuberous sclerosis of the cerebral convolutions" is the term used by Bourneville (1880) to describe the unique and distinctive cerebral pathology that he found in a patient with seizures and mental subnormality. The majority of patients identified as having the disorder experience symptoms referable to the CNS. Even in subjects without neurologic symptoms, CNS lesions are present in all brains studied. CNS abnormalities, therefore, remain the hallmark of TSC and its most common and clinically serious manifestations.

Molecular Genetics

TSC results from mutations in *TSC1*, the gene on chromosome 9q34, and *TSC2*, the gene on chromosome 16p13. Frequent loss of heterozygosis for alleles in 16p13.3 and rare loss in 9q34 has been found in hamartomas from TSC patients, indicating that a second somatic mutation may be required to produce the TSC phenotype at the cellular level. These findings are consistent with the *TSC1* and the *TSC2* acting as growth suppressor genes.

The characterization of the *TSC1* and *TSC2* genes is summarized in Table 82-1.

The mutations observed in *TSC1* consist of small deletions, small insertions, and point mutations. The majority of mutations are likely to inactivate protein function, and these findings support the hypothesis that *TSC1* functions as a tumour suppressor gene. At the moment, about 1,000 different mutations in both TSC genes are known. There is an equal distribution of mutations between *TSC1* and *TSC2* among familial cases, while among sporadic cases, TSC2 mutations are much more frequent than TSC1 mutations. The wide range of tissues in which TSC associated hamartomas develop implies a fundamental role for both TSC genes in regulating cell proliferation and differentiation.

The Tuberin-Hamartin complex acts as an inhibitor of the kinase mammalian target of rapamycin, an important element in a signaling pathway involved in the control of cell growth and proliferation, controlled by the protein-kinase Akt.

Diagnostic Criteria

Criteria for diagnosing of TSC are divided into two groups, major and minor, and re listed in Table 82-2. The diagnoses of TSC is established when two major features or one major plus two minor features can be demonstrated.

At the time of initial diagnosis, diagnostic studies are commonly performed to either confirm the presence of TSC or to evaluate presenting symptoms such as seizures or cardiac dysfunction. In addition, it is often useful to establish a baseline assessment in areas that could develop complications later. Unless specific areas of concern are identified with these initial studies, following testings are aimed toward areas with a high risk of dysfunction and to lesions that can be possibly treated.

Moreover, at the time of initial presentation, the majority of the patients with TSC experience magnetic resonance

TABLE 82-1. Characterization of the TSC1 and TSC2 genes

	TSC1	TSC2
Localization	9q34	16p13.3
Structure	23 exons—8.6 kb transcript; alternate splicing in the 5′ UTR	41 exons—5.5 kb transcript; exons 25, 26, and 31 alternatively spliced
Mutations	Small truncating mutations	Large deletions/rearrangements, small truncating mutations, missense mutations
Occurrence	10–15% of sporadic cases	70% of sporadic cases
Phenotype	?less mental impairment	?more likely to be mentally retarded; contiguous gene deletion syndrome with PKD1
LOH in hamartomas	Rare	Frequent
Product	Hamartin	Tuberin
Function(s)	?regulates cell adhesion through interaction with ezrin and rho?; regulator/modulator of tuber in activity	GTPase activating protein?; role in the cell cycle
Subcellular localization	Cytoplasmic, ?cortical	Cytoplasmic, ?Golgi associated
Animal models	Knockout mice under development	Eker rat knockout mice drosophila (gigas)

LOH = loss of heterozygosity; TSC = tuberous sclerosis complex.

imaging (MRI) to search for additional evidence of TSC already suspected on the basis of other signs. The number, size, and perhaps the location of the dysplastic cortical lesions detected by MRI tend to correlate with the severity of the clinical neurologic dysfunction. Electroencephalography (EEG) is useful when the initial presentation includes epileptic seizures. Nevertheless, children who never manifested seizures and are not suspected of having epileptic seizures generally do not need to undergo baseline EEG.

Usually, adolescents and adults have a greater chance of developing symptomatic renal angiomyolipomas (AMLs) than children, but it sometimes happens even in childhood.

TABLE 82-2. Revised Clinical Diagnostic Criteria for Tuberous Sclerosis Complex (Adapted from Roach et al, 1998)

Major Features	Minor Features
Facial angiofibromas or forehead plaque pits in dental enamel	Multiple, randomly distributed
Nontraumatic ungula or periungual fibroma	Hamartomatous rectal polyps
Hypomelanotic macules (three or more)	Bone cysts
Shagreen patch (connective tissue nevus) migration lines	Cerebral white matter radial
Multiple retinal nodular hamartomas	Gingival fibromas
Cortical tuber	Nonrenal hamartoma
Subependymal nodule	Retinal achromic patch
Subependymal giant cell astrocytoma	"Confetti" skin lesions
Cardiac rhabdomyoma, single or multiple	Multiple renal cysts
Lymphangiomyomatosis and/or renal angiomyolipoma	

For each patient, renal ultrasonography is carried out at the time of diagnosis. Furthermore, cardiac arrhythmias occasionally occur even in patients with TSC who do not have a demonstrable cardiac rhabdomyoma. An arrhythmia can be present at birth or develop later. Wolff-Parkinson-White syndrome appears to be the most commonly noted arrhythmia in patients with TSC. Therefore, a baseline study must be performed at the time of diagnosis. Echocardiography may reveal one or more cardiac rhabdomyomas in more than 50% of the younger individuals with TSC. However, these cardiac tumours are more innocuous than they might seem as they tend to involute over the years, often disappearing completely by adulthood. Moreover, the most rapid reduction in lesion size occurs during the first three years of life, a period after which rhabdomyomas tend to change less dramatically.

Each patient affected by TSC should have an accurate ophthalmic examination at the time of diagnosis. Children usually do not suffer from facial angiofibromas or ungual fibromas at the time of initial diagnosis, and typical hypomelanotic macules can be early recognized by most clinicians who are knowledgeable about TSC. Generally, a dermatologic examination might be important when the skin lesions are atypical or when the diagnosis of TSC is uncertain.

A scrupulous age-appropriate screening for behavioral cognitive and neurodevelopmental dysfunction at the time of diagnosis should also been performed. Unfortunately, children with apparently normal initial testing and developmental milestones can still suffer milder deficits that interfere with their learning. It is advisable that each child is reassessed around the time school begins, even if no abnormalities were detected by the previous screenings. Children with abnormal behavior or cognitive function should be periodically retested, and reevaluation is also appropriate when there is a significant change in behavioral or cognitive function. Newly diagnosed adolescents or young adults with

a well-established pattern of completely normal social and cognitive function as determined by educational achievement sometimes do not require formal testing.

Gene characterization could ultimately identify patients at a greater or lesser risk of particular complications. Moreover, further diagnostic studies could be performed selectively on individuals at greatest risk for certain specific complications, thereby decreasing the number of useless investigations.

Clinical Features

Clinical features of TSC are most commonly observed in the brain, skin, kidneys, heart, eyes, and lungs. The physical findings can vary greatly since TSC can affect different organ systems in different ways at different times in the individual's life. Most of the findings traditionally regarded as among the most specific for TSC become apparent only in late childhood, limiting the usefulness for early diagnosis in infants.

Neurologic Manifestations

Eighty-five percent of patients with TSC experience complications associated with the CNS. These manifestations, which include cognitive impairment, behavioural problems, autism, and epilepsy, are a direct result of the cytoarchitectural derangements produced by TSC on the developing nervous system. Both supratentorial and infratentorial brain lesions can be identified on neuroimaging. The most common are located in the supratentorial compartment and are composed of cortical tubers, subependymal nodules (SENs), and subependymal giant cell astrocytomas (SEGAs).

Cortical tubers are variable in size and usually multiple in number. They occur most often at the grey–white junction and are seen as low-density lesions on computed tomography (CT) scanning and high signal intensity lesions on T2-weighted fluid attenuated inversion recovery sequences on MRI. However, MRI scans characteristically show these lesions as hyperintense on T1-weighted and hypointense on T2-weighted images. They can be noted in the cerebellum as well as in the cerebrum. There appears to be no particular lobar predilection or specific clinical correlation in terms of anatomic location. It has been demonstrated that greater numbers of tubers correlate with greater cognitive/behavioral impairments. The cortex overlying a tuber may itself be dysplastic, with regions of pachygyria or polymicrogyria. Histologically, tubers are composed of a proliferation of both glial and neuronal cells with dysplastic cells of mixed lineage (giant cells). These cellular components align themselves in an irregular lamination and aberrant columnar orientation.

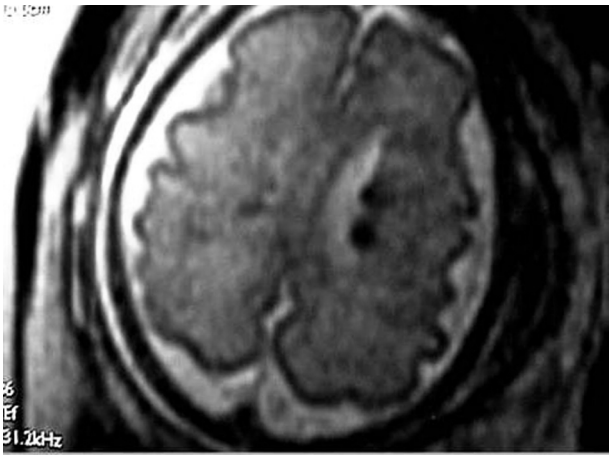

FIGURE 82-1. Axial fetal magnetic resonance imaging at 27 weeks of gestation showing multiple subependymal nodules and tubers.

SENs are hamartomas that are typically seen in the subependymal wall of the lateral ventricles, mainly at the foramina of Monro. Some nodules protrude into the ventricular cavity. SENs develop during the fetal life are found in the great majority of patients with TSC and are usually asymptomatic Figure 82-1. However, growth of these lesions at the foramen of Monro may determine a blockage of the cerebral fluid circulation, resulting in progressive lateral ventricular dilatation and intracranial hypertension.

The progressive growth of enhancing lesions at the foramen of Monro in a patient with TSC strongly suggests that it is a SEGA Figure 82-2.

Rapamycin, a commercially available immunosuppressant can induce regression of SEGA associated with TSC and might offer an alternative option to surgical treatment of these lesions.

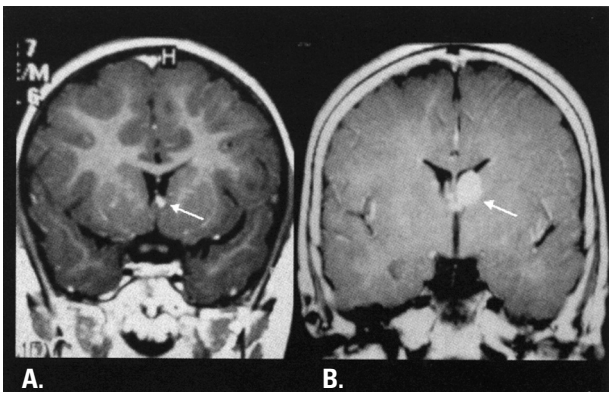

FIGURE 82-2. Progressive growth of an enhancing lesion at the foramen of Monro in a tuberous sclerosis complex patient. Coronal T1-weighted image with Gadolinium (A) shows a small enhancing lesion; marked growth in the three-year follow-up (B).

Epilepsy is the most common presenting symptom of TSC and affecting 80 to 90% of patients. Epilepsy in TSC often begins during the first year of life and, in most cases, in the very first month. The high incidence of infantile spasms and hypsarrhythmia has long been emphasized, but it is now clear that infantile spasms in infants with TSC are clinically and electroencephalographically different from classical spasms and hypsarrhythmia of West syndrome. In the same child, focal seizures may precede, coexist with, or evolve into infantile spasms. Subtle focal seizures, such as unilateral tonic or clonic phenomena mainly localized in the face or limbs, and other seizures with subtle lateralizing features, such as tonic eye deviation, head turning, and unilateral grimacing can occur but may be missed by the parents until the third or fourth month of life.

Focal or multifocal epileptiform abnormalities may be found when an EEG is performed between the neonatal period and the development of the infantile spasms. Nonrapid eye movement sleep is associated with increased epileptiform activity. Multifocal and focal abnormalities tend to generalize and bursts of more synchronous polyspikes, and waves separated by sudden voltage attenuation become evident, resembling a hypsarrhythmia.

As maturation progresses, the modified hypsarrhythmic pattern tends to disappear and interictal EEG recordings tend to exhibit focal spikes or slowing, with transitional stages from discrete foci to multifocal discharges. During sleep, the EEG is characterized by multifocal abnormalities associated with bursts of bilateral and more synchronous slow spike-waves, with a pattern similar to that seen in Lennox-Gastaut syndrome Figure 83-3.

Although treatment with adrenocorticotropic hormone can be effective, vigabatrin has been the drug of choice in the treatment of infantile spasms associated with TSC. A clinical response is often observed after 1 to 2 doses, and this response is dose-independent. Vigabatrin is generally well tolerated. In recent years, converging evidence has been produced on the association between concentric narrowing of the visual field and vigabatrin treatment. The use of the electroretinogram is the most sensitive measure of the retinal toxicity.

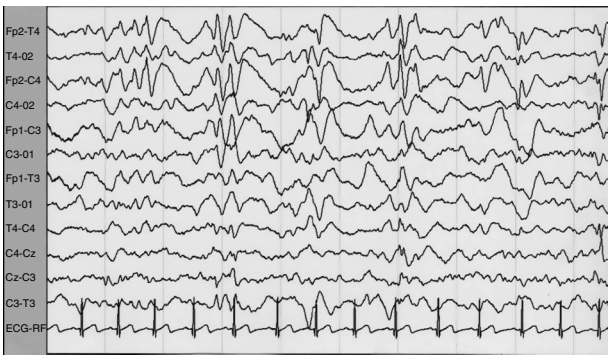

FIGURE 82-3. Interictal electroencephalography showing apparently generalized abnormalities in 4-year-old child with intractable frontal lobe seizures.

Patients with TSC and epilepsy have been considered surgical candidates for tuber resection when a dominant tuber is identified as the primary epileptic zone. Because intractability of seizures induces a high rate of cognitive deficit, interventions aimed at reducing seizure frequency can prevent significant morbidity. The identification of a primary epileptic tuber, however, can be difficult. The use of video encephalographic monitoring in concert with MRI, single photon emission CT, and positron emission tomography has improved the yield of a primary epileptic tuber focus.

The recently proposed technique of multistage surgery may offer an option to complicated patients with multiple epileptogenic tubers in distant brain regions. This multistage surgical approach has been useful in identifying both primary and secondary epileptogenic zones in TSC patients with multiple tubers.

Cognitive impairment ranging from learning disability to severe mental retardation occurs in approximately 60% of patients. Virtually, all mentally retarded patients with TSC have concomitant epilepsy. However, up to one-third of all TSC patients with epilepsy have normal cognition. Both intractable epilepsy and infantile spasms independently increase the risk of greater cognitive impairment. Another 25 to 50% of patients with TSC may also have autism. The co-occurrence of TSC and autism is well recognized, although no definite reason has been determined for the association. The majority of reported TSC children with autism spectrum disorders have experienced infantile spasms and are mentally retarded.

Attention deficit hyperactivity disorder and related behaviors are also seen in about 50% of children with TSC, particularly in those with severe disabilities. Self-injurious behaviours, aggressive outbursts, and temper tantrums are commonly observed in children with TSC with severe disabilities.

In older children, adolescents, and adults, anxiety and mood-related disorders become increasingly prevalent. Anxiety and mood symptoms are seen in individuals with and without global cognitive difficulties and can be very debilitating to higher functioning young people and adults.

Sleep disorders, such as night waking, prolonged sleep latency, and seizure-related sleep problems, are considered one of the most common behavioral manifestations in children with TSC. Prolonged sleep latency and frequent awakenings due to epileptic seizures need to be differentiated using polysomnography.

Nonneurologic Manifestations

Cardiovascular Manifestations

Cardiovascular manifestations of TSC are the predominant findings in the fetus and newborn infant. Cardiac rhabdomyomas are congenitally acquired tumors. Despite being typically multiple in number, they are infrequently symptomatic. Prenatally, they may manifest as fetal arrhythmia, fetal nonimmune hydrops, or fetal death. Postnatally, rhabdomyomas can be found as isolated tumors. Approximately 51 to 86% of patients so identified will ultimately be diagnosed with TSC. These tumors usually are 3 to 25 mm in diameter, although extremely large lesions have been reported. They are most commonly located within the ventricles and more often within the walls rather than the septum Figure 82-4. In a small percentage of patients, supraventricular tachycardia secondary to Wolff-Parkinson-White syndrome or another ventricular preexcitation syndrome can be associated with these septal lesions. If large enough, the lesions may obstruct cardiac outflow or be a nidus for cardio-embolic disease. Most often, however, the lesions regress over time with early complete regression evident by 6 years of age. Intracranial aneurysms in patients with TSC have been identified in a small number of patients. The internal carotid artery, however, has been affected in 60% of those cases reported, which is an increased incidence compared with the general population. Isolated patients have been reported with aortic aneurysms within the thorax and abdomen.

Dermatologic Manifestations

The most prevalent manifestation of TSC is the hypomelanotic macule. It is often referred to as a hypopigmented macule or "ash leaf" spot when it takes on the characteristic pyramidal shape with a rounded bottom and pointed end Figure 82-5. The hypopigmented macules are best seen under ultraviolet light (Wood's lamp). In the general population, 4.7% of unaffected individuals have been found to have one or two hypopigmented macules. Therefore, three or more are considered clinically significant and have been noted in at least 96% of patients with TSC. The location of the macules has no diagnostic connotation. However, when on the scalp or the skin under the eyebrows, the overlying hair may also turn white (poliosis). There can be abnormal pseudomotor function in addition to diminished sweat volume produced in the overlying macule. This has been postulated to be due to abnormal postganglionic sympathetic innervation. Facial angiofibromas (adenoma sebaceum) are another distinctive dermatologic hallmark of TSC. These are hamartomatous nodules of vascular and connective tissue seen in a butterfly pattern over the malar eminences and nasal labial folds of the face Figure 82-6. They generally appear when a child is around 3 to 4 years of age, lending a ruddy appearance to the cheek, and then develop a more roughened cobblestone appearance thereafter.

Estimated frequency is about 50 to 75% of patients with TSC. These can also be seen in patients with multiple endocrine neoplasia type I patients. Another fairly common dermatologic feature of TSC is the shagreen patch Figure 82-7. These patches are connective tissue nevi generally located at the lumbosacral flank, but they can also occur scattered across the trunk or upper legs. They are usually evident by 10 years of age with an irregular border, a raised, roughened surface, and normally pigmented skin color. These are noted in about 15 to 30% of patients with TSC. They can rarely be inherited as an isolated dominant trait. Ungual fibromas are an additional connective tissue hamartoma adjacent to or underneath nail beds. They are

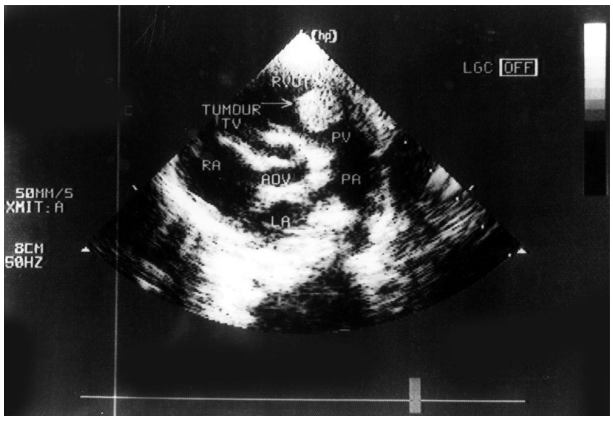

FIGURE 82-4. Echocardiography showing an hyperechoic rhabdomyoma.

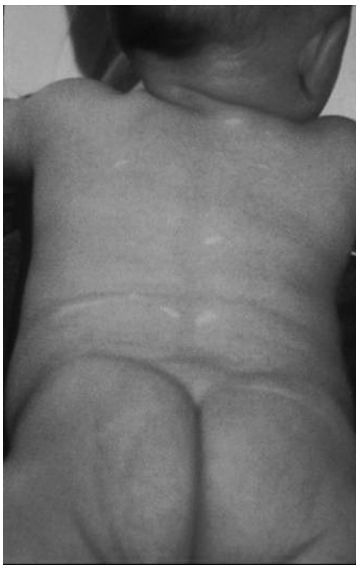

FIGURE 82-5. Hypomelanotic macules.

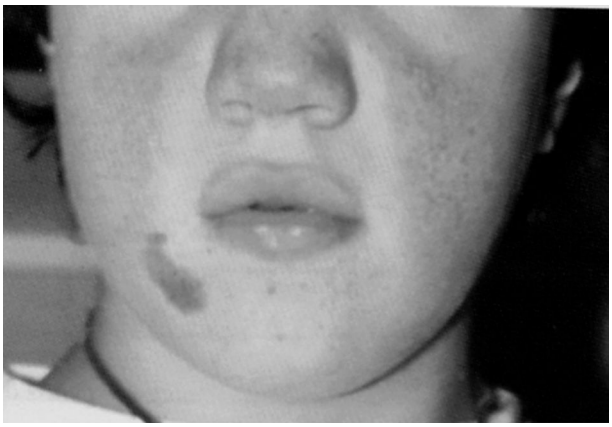

FIGURE 82-6. Facial angio miofibromas.

generally seen in the toes to a greater extent than the fingers and more often in girls. When at the base of the nail, they may produce a groove in the nail as an indirect sign. Rarely, they can be induced by nail bed trauma. Less frequent features of TSC include forehead fibrous (collagen) plaques, molluscum fibrosum pendulum (skin tags), and multiple 2 to 3 mm hypopigmented macules over the legs referred to as confetti lesions.

Renal Manifestations

Renal involvement in TSC is noted in approximately 50% of patients with TSC. It may produce AMLs, renal cysts, renal cell carcinoma, oncocytoma, perirenal cysts, and polycystic kidneys. The frequency of mortality and morbidity from renal lesions is second only to that associated with the CNS.

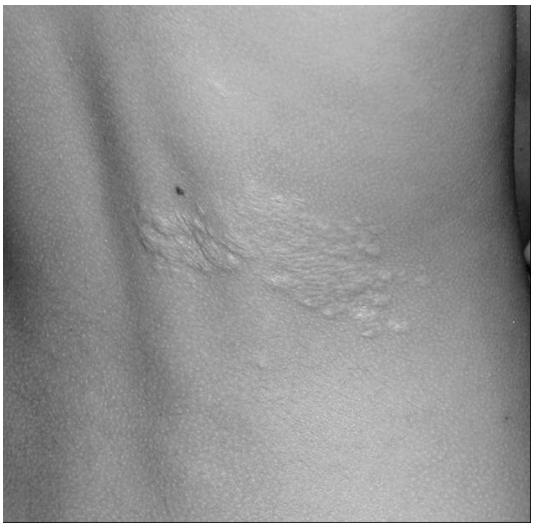

FIGURE 82-7. Shagreen patch.

The most common renal lesion is the AML. AMLs account for 75% of lesions seen in the kidneys. They often are evident by the time a patient is 6 to 10 years old and increase in size and number over the patient's lifetime. Ninety percent of patients with TSC have multiple lesions and 80% have bilateral lesions. Concomitant renal cysts are noted in another 20 to 40%. AMLs are composed of vascular tissue, smooth muscle, and fat. The blood vessels within an AML have no internal elastic laminae, and the smooth muscle is replaced by dense, fibrous connective tissue, making vessels more prone to rupture. Approximately one-half of all AMLs have smooth muscle cells that stain positive for progesterone receptors. These are nearly all from women younger than 50 years of age and are not found in men. Periodic surveillance (every 6 months) with renal ultrasound or CT scanning is suggested for asymptomatic lesions 4 cm or larger. Symptomatic lesions may require intervention with embolization or surgery. Renal cysts are seen in 20% of patients with TSC who manifest renal disease. These are typically multiple in numbers and are unique histologically when compared with those associated with other cystic kidney diseases as they are composed of hypertrophic, eosinophilic epithelial cells. Ninety percent of the cysts are multiple and 80% are bilateral with a female preponderance. In some patients, renal cysts regress over time, whereas in others, they increase in size and number. Compared with AMLs, these cysts are more likely to produce renal insufficiency and hypertension. If TSC is caused by a large deletion of *TSC2*, then polycystic kidney disease may be present. This is due to the fact that *TSC2* lies adjacent to *PKD1* on chromosome 16 and will result in a large contiguous gene deletion syndrome.

Rarely, renal cell carcinoma can be identified in patients with TSC. This more often occurs in conjunction with AML, with an incidence of approximately 2.5 to 4%.

Retinal Manifestations

The lesions confined to the retina may be difficult to identify without pupillary dilation and direct ophthalmoscopy. The retinal hamartoma is typically seen adjacent to the optic nerve emanating forward, with a tapioca surface appearance. The lesion is referred to as a "mulberry lesion" and is composed of glial-astrocytic fibers. These lesions, which generally do not cause visual disturbances, should be evident by 2 years of age and are considered congenital even if they are not apparent at birth. Even if they are not present early in childhood, they will develop later in life. Initially, these lesions may be translucent. After several years, they often calcify Figure 82-8. They may be seen in 75% of patients with TSC and can be bilateral in up to 50% of patients. Less commonly, an achromic patch can be seen in the retina similar to the hypopigmented macules seen on the skin.

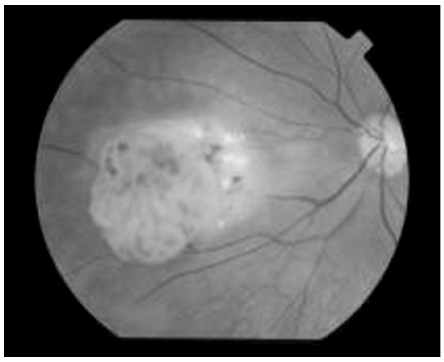

FIGURE 82-8. Retinal hamartoma.

Pulmonary Manifestations

The primary pulmonary lesion in TSC is lymphangioleiomyomatosis (LAM) of the lung. This affects less than 1% of patients with TSC and manifests only in women. At first, this is an asymptomatic lesion that develops over the teenage to young adulthood years. Spontaneous pneumothorax, shortness of breath, and hemoptysis herald the symptomatic onset. Cystic interstitial lung disease due to hyperplasia of interstitial smooth muscle cells also develops. Cystic lung disease can be seen with chest CT. This is recommended in all young women with TSC who are 18 years of age and older. LAM is a progressive disorder of the lung requiring lung transplantation. Without transplantation, one-half to two-thirds of the patients die within 5 years of the onset of symptoms. Even after lung transplantation, LAM may recur if it is associated with AML of the kidneys. There is a propensity for AML cells to migrate through the bloodstream and metastasize within the lung, producing recurrent LAM. An additional distinct lung disease seen in both men and women with TSC is multifocal micronodular pneumocyte hyperplasia. This is a benign condition producing small cysts due to hypertrophy of type II pneumocytes.

Clinical Management

Long-term surveillance testing should be directed toward lesions which are frequent, which can be treated if early identified, and which have a significant risk of dysfunction or death. A surveillance protocol based on the natural history of TSC provides some practical basis for driving follow-up tests. Any effort should be made to minimize costly testing of asymptomatic patients and to maximize the likelihood of early identification of a treatable lesion. The guidelines that follow Table 82-3. are designed for long-term clinical management of an asymptomatic patient whose diagnosis is perfectly assured.

TABLE 82-3. Testing Recommendations (Adapted from Roach et al, 1999)

Assessment	Initial Testing	Repeat Testing
Neurodevelopmental testing	At diagnosis and at school entry	As clinically indicated
Ophthalmic examination	At diagnosis	As clinically indicated
Electroencephalography	At diagnosis	As clinically indicated
Electrocardiography	At diagnosis	As clinically indicated
Echocardiography	If cardiac symptoms occur	If cardiac dysfunction occurs
Renal ultrasonography	At diagnosis	Every 1–3 years
Chest computed tomography	At adulthood (women only)	If pulmonary dysfunction occurs
Cranial MRI	At diagnosis	Children/adolescent: every 1–3 years

MRI = magnetic resonance imaging.

CNS

Children should undergo periodic cranial imaging with either CT or MRI scans every 1 to 3 years, depending on the level of clinical suspicion in each child. In general, there is a greater likelihood for children to develop SEGAs than for adults. Usually, the need for EEG is dictated by the clinical features and response of seizures to antiepileptic drugs. As a rule, EEG is not required for adults with TSC who do not have epileptic seizures. However, since seizures are not regularly clinically obvious, EEG should always be considered in the evaluation of a patient with an unexplained decline of cognitive or behavioral function in which epileptic seizures are suspected. During early infancy, the seizure pattern can change rapidly, and sometimes, it might be indispensable to repeat the studies at frequent intervals of time.

A number of neurodevelopmental and behavioral dysfunction patterns occur as a result of TSC. Contrarily to mental retardation, which is a classic and common feature of TSC, learning disabilities, autism, attention deficits, and other difficulties are probably underrecognized. The children that suffer such problems can benefit from early recognition, specific education, and treatment plans. Formal cognitive testing is not necessary for adolescents and adults with well-established patterns of normal social and cognitive function. When a patient is diagnosed with TSC in infancy or early childhood, testing should be repeated around the time the child enters school. Older children, instead, should be reassessed periodically in response to educational or behavioral concerns.

Kidney

During the first decade of life, the number and size of the renal AMLs tend to increase, but large renal AMLs are more likely to cause symptoms than smaller lesions. It is

therefore wise to monitor more closely patients with large tumors. Renal ultrasonography should be generally undertaken every 1 to 3 years. How frequently the patient is tested depends mostly on the degree of concern for him and on the results of previous examinations. Regardless of age, patients who have large renal lesions or lesions that seem to have grown substantially should have more frequent follow-up examinations. MRI might be necessary for these patients to define with greater precision the extent of the kidney disease.

Heart

Cardiac rhabdomyomas tend to regress over time and can disappear altogether by adulthood. The majority of the patients with TSC who have a cardiac rhabdomyoma remain asymptomatic. Continuous cardiac evaluations are not required and even unnecessary for most a symptomatic patients with TSC. However, some patients may occasionally develop arrhythmias during adolescence or adulthood. A cardiologist should follow all those patients who have new symptoms that might indicate cardiac dysfunction and those with previous symptoms, benefiting from periodic studies to evaluate heart function.

Lungs

Pulmonary disease (LAM) due to TSC is uncommon, especially in children and in men. In the rare cases in which it occurs, it is suffered almost exclusively by women. The average age of onset is 32 to 34 years. The best method to use to understand pulmonary abnormalities of TSC is the chest CT scan. Women should undergo chest CT scans at least once on reaching adulthood. If pulmonary symptoms should develop, this test should be repeated.

Retina

Repeated ophthalmologic evaluations are usually unnecessary, unless there is some specific reason for concern.

Skin

Facial angiofibromas can have major consequences for some patients. Laser therapy is one way in which skin tumor growth can be limited, even though the treatments often need to be repeated periodically as the lesions tend to regrow gradually after the treatment is over. Ungual fibromas sometimes cause severe problems, which can be effectively treated.

Suggested Readings

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Chapter 83

Sturge-Weber Syndrome

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An estimated 5,000 individuals the United States have Sturge-Weber syndrome (SWS), the third most common neurocutaneous disorder. SWS is typically characterized by the presence of a cutaneous vascular malformation on the face, an ipsilateral leptomeningeal angiomatosis, and glaucoma. Early diagnosis is essential for assessing and managing associated complications.

Sturge-Weber syndrome (SWS) is a sporadic disorder thought to be caused by a somatic mutation, but the genes remain unidentified. An early embryonic vascular plexus malformation arising within the cephalic mesenchyme between the epidermis (neuroectoderm) and the telencephalic vesicle may account for the abnormalities of the skin, leptomeninges, eyes, and cortex. It is presumed that interference at approximately 5 to 8 weeks of gestation with the development of vascular drainage of these areas subsequently affects the face, eyes, leptomeninges, and brain. Currently, the only treatment for SWS is symptomatic.

Diagnosis

Three in 1,000 children are born with a cutaneous vascular malformation or port wine stain (PWS). However, only 8% of individuals with a PWS actually have an associated leptomeningeal angiomatosis or glaucoma. Children with a PWS in the first branch of the trigeminal nerve have an increased risk for SWS of about 25%. In children with glaucoma or new-onset seizures, one should carefully inspect the eyelid, because pinpoint vascular anomalies can be difficult to detect in some children. The risk of SWS increases to 33% when the PWS affects the first branches of the trigeminal nerve bilaterally. The vast majority of children with SWS have a unilateral PWS with ipsilateral brain and eye involvement.

When a child is born with a PWS covering the V1 distribution, he or she should have a contrast-enhanced magnetic resonance imaging (MRI) scan of the brain to screen for the presence of leptomeningeal angiomatosis. However, the MRI can be falsely negative in infants who are shown at a later date to have SWS. Calcifications are often best visualized on computed tomography (CT) scans, but they may not be present in infancy. In addition, the child should have complete dermatologic, neurologic, and ophthalmologic evaluations.

SWS Variants

In 1992, Roach categorized SWS variants into three types:

- Type I: individual has a facial PWS, leptomeningeal angioma, and may have glaucoma
- Type II: individual has a facial PWS, no leptomeningeal angioma, and may have glaucoma
- Type III: individual has leptomeningeal angiomatosis, no facial PWS, and, rarely, glaucoma

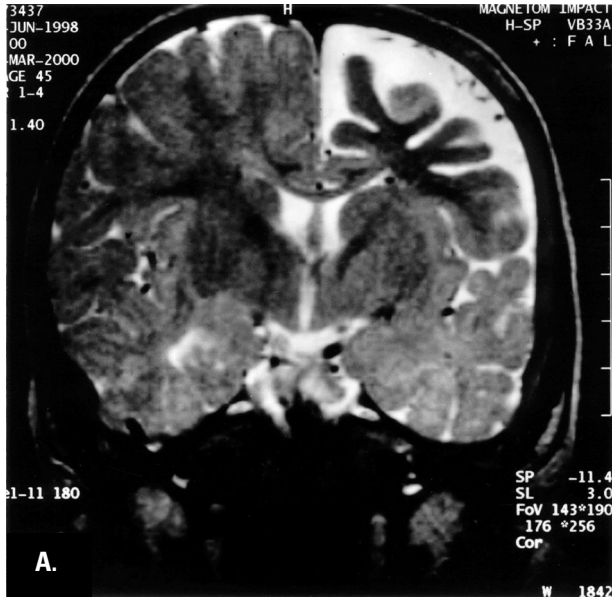
Neurodiagnostics

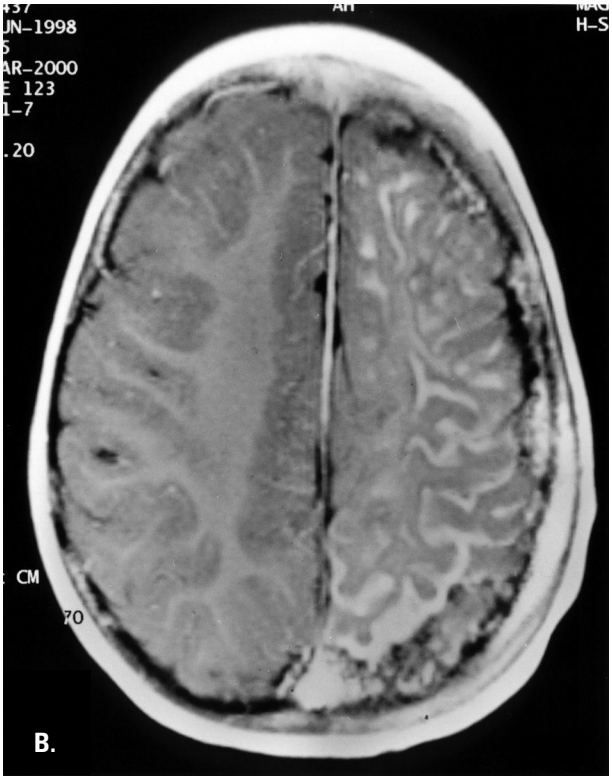
The leptomeningeal angiomatosis is associated with impaired cerebral blood flow. The thin-walled and narrow veins are inadequate to drain cortical blood. Tortuous and enlarged transmedullary veins develop, presumably to serve as alternate venous drainage pathways. The ipsilateral choroid plexus becomes engorged. The venous microcirculatory status probably causes ischemic brain injury, seizures,

headache, neurobehavioral abnormalities, and neurologic deterioration. As neuronal loss progresses, calcification is noted in the brain. Therefore, the features most often seen in imaging studies are the enhancement of the leptomeningeal angioma, enlarged transmedullary veins, choroids plexus hypertrophy, white matter abnormalities (perhaps secondary to ischemia), atrophy, and calcification.

Children with PWS in the V1 distribution should have the following imaging studies completed: a noncontrast-enhanced computed tomography (CT) scan and a contrast-enhanced MRI scan of the head. The only longitudinal study reported in children with SWS reported progression of central nervous system (CNS) abnormalities in a minority of cases. Thus, one should be cautious about the implication of normal imaging because children may ultimately be shown to have uni-hemispheric or bi-hemispheric disease. The MRI with contrast is ideal to define the vascular anatomy characteristic of SWS (Figure 83-1).

Other imaging studies that may prove helpful in selected cases are single photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance spectroscopy (MRS), and perfusion CT or magnetic resonance (MR) studies. PET, SPECT, and MRS imaging studies may show abnormalities that extend well beyond





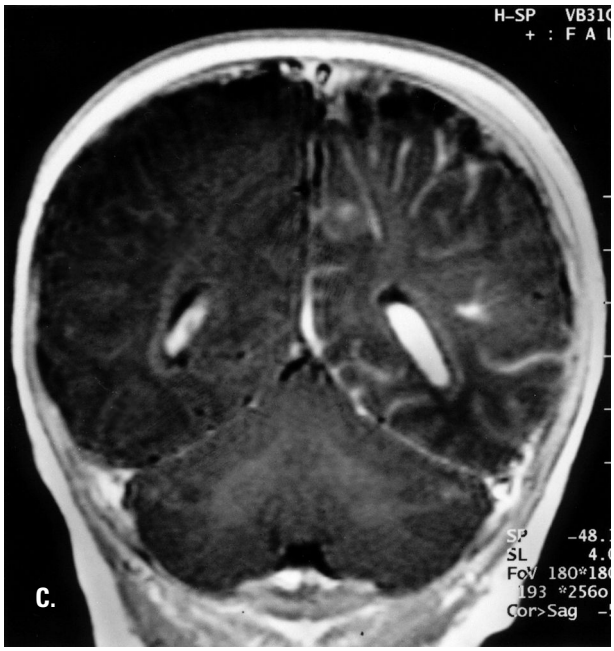


FIGURE 83-1. *A,* Coronal T_2-weighted magnetic resonance imaging (MRI) scan showing left hemisphere atrophy and prominent subarachnoid space. *B,* Axial gadolinium-enhanced MRI reveals atrophy and prominently enhancing leptomeningeal angiomatosis. *C,* Coronal gadolinium-enhanced MRI also shows prominent left choroid plexus.

what is expected from CT or MRI data. Information is much more limited on the value of perfusion CT or MR imaging in SWS. Not surprisingly, brain regions that are hypoperfused or hypometabolic have decreased levels of neuronal *N*-acetylaspartate. Metabolic imaging studies are useful adjuncts when structural imaging studies are negative in suspected cases. However, SPECT, PET, and MRS are not "standard" imaging studies and should be obtained selectively.

Although the disorder can be associated with progressive cerebral hypoperfusion, hypometabolism, atrophy, and calcifications, repeated neuroimaging is not required, unless one is evaluating a patient's candidacy for epilepsy surgery because of intractable epilepsy. Caregivers are understandingly curious about the evolution of CNS lesions, but to date, there is little evidence that radiologic changes are related to clinical features or prognosis. An electroencephalogram (EEG) is routinely obtained in patients with SWS and epilepsy. Typically, there is slowing ipsilateral to the cerebral involvement, with associated spikes and sharp waves. During episodes of transient, stroke-like episodes, however, the EEG frequently shows slowing without active epileptiform activity (see below). Although status epilepticus is usually considered at the top of the differential diagnosis in patients with SWS and sudden hemiparesis, nonepileptic stroke-like episodes are usually to blame.

Cutaneous Malformations

All children with a PWS should have a full dermatologic evaluation. The PWS ranges from light pink to dark purple and is actually caused by an excess of capillaries underneath the affected skin (capillary vascular malformation).

The current treatment of PWS is laser treatment, most often using a pulsed dye laser. Caregivers report insurance denials for laser treatment on the basis that "stains are cosmetic problems." However, treatment is encouraged for reasons that extend beyond cosmetic issues. For example, children with a large PWS are more likely to have social and behavioral issues. Untreated, over time PWS will frequently develop hypertrophy of the tissue, blebbing and cobblestoning which can, depending on location, impair vision, speech or the airway and result in bleeding. Multiple treatments are required to remove or significantly lighten a PWS. Because a PWS grows as the child grows and often becomes hyperpigmented and nodular, fewer treatments are required if started in early infancy. Results with modern lasers are excellent, and it is often difficult to detect the PWS years later.

Ophthalmologic Complications

When the PWS involves the eyelid, vascular abnormalities of the conjunctiva, episclera, retina, and choroid may occur. Patients with the most severe anomalies in conjunctival and episcleral vessels are at greatest risk of glaucoma, and overall, 30 to 70% of patients with SWS will develop glaucoma. As with intracranial involvement, the presence of a cutaneous vascular malformation in the distribution of the ophthalmic division of the trigeminal nerve increases the probability of glaucoma. Glaucoma is diagnosed in infancy in most children with SWS, but 40% of patients develop the complication as adolescents or in adult years. Therefore, a neonate with a PWS over the V1 distribution should have an ophthalmologic evaluation as soon as possible. Follow-up screenings every 3 months for the first year, semiannually the second year, and annually thereafter will detect increased intraocular pressure. Rarely, a child will present with buphthalmos due to this increased pressure. Most commonly, the eye affected will be ipsilateral to the PWS. Occasionally, the glaucoma and buphthalmos are bilateral.

Medical and surgical treatment for glaucoma in SWS is very challenging and chronic. For many patients, management requires β-blockers, carbonic anhydrase drops, and multiple surgeries. Table 83-1 shows the recommended treatments for common SWS complications.

Forty percent of SWS patients have choroidal hemangiomas, which in children typically do not require treatment. However, choroid thickening may cause vision loss and require laser photocoagulation for retinal detachment later in adolescence or adulthood. Ongoing ophthalmologic care is essential to current management of SWS.

Neurologic Manifestations

A child with a facial PWS should have a full neurologic evaluation, although neurologic findings, such as frank hemiparesis, are rarely apparent in the first few years of life. Clues of mild motor dysfunction include early handedness (< 12 months) or left-handedness in children with leptomeningeal angiomas affecting left hemisphere function.

Epilepsy

The most common neurologic complication of SWS is epilepsy. Approximately 80% of individuals with SWS have epilepsy, with partial seizures being the most common seizure type. Unfortunately, many children with SWS do not receive the diagnosis until after they develop seizures, delaying appropriate assessment and management of associated complications.

Although 75% of seizures occur by the first birthday, adults with SWS can develop new-onset seizures. Fever and infection may trigger the onset of seizures in many children with SWS, so parents should treat fevers and maintain proper hydration to minimize these risk factors.

Although daily antiepileptic drugs (AEDs) are not recommended in the management of febrile seizures or after the first unprovoked seizure in the general population,

TABLE 83-1. Recommended Treatments for Associated Complications in Sturge-Weber Syndrome

Therapy	Glaucoma	Partial Epilepsy[†]	Headache and Migraine[‡]	Stroke-Like Episodes	Neurobehavior
1st choice	β-blocker drops	Chronic: Carbamazepine Oxcarbazepine Acute: Diastat	Ibuprofen	Aspirin 3–5 mg/kg/d[§]	Methylphenidate
2nd choice	Adrenergic drops or carbonic anhydrase drops	Chronic: valproate, leviteracitam Topiramate Acute: Lorazepam Phenytoin Phenobarbital	Abortive therapy with sumatriptan Zofran, phenergan or Compazine for vomiting	N/A	Clonidine
Other options	Trabeculectomy*	Epilepsy surgery	Preventive therapy with propranolol or nortriptyline valproate Topamax	N/A	Dextroamphetamine, Risperdal

*If drops fail, consider trabeculectomy. Surgery is associated with a high risk of complications because of elevated episcleral venous pressure from the hemangioma.

[†]Children with SWS may have generalized seizures or infantile spasms, but partial epilepsy (with or without secondary generalization) is most prevalent.

[‡]Approximately one-third of children with SWS meet diagnostic criteria for migraine. Management in SWS is similar to management of common migraine not associated with SWS.

[§]Anecdotal evidence suggests that children with SWS receiving aspirin therapy (antiplatelet dose) have fewer stroke-like episodes.

the authors recommend the use of oxcarbazepine or extended-release carbamazepine at onset of febrile seizures or first unprovoked seizures in children with SWS. Given the tenuous nature of the cerebral circulatory status in SWS and the associated energy demands of recurrent seizures, the authors believe that the benefits of AEDs probably outweigh the risks of starting AEDs in children with SWS and concurrent unrelated febrile seizures or first unprovoked seizures. The evidence is that approximately one-half of patients with SWS can achieve complete seizure control. It is essential to increase the dose for weight gain as control can be lost if adequate AED doses are not maintained in the moderate to high range. Rarely, children may develop infantile spasms and require use of steroids or vigabatrin (or topiramate or zonisamide) rather than carbamazepine. Except for intravenous management of seizures in SWS, phenobarbital and phenytoin are no longer recommended for use in children with SWS. However, if intravenous phenobarbital has been necessary to achieve seizure control, it is slowly tapered orally over several months and replaced with a different AED. If seizures recur in children with SWS receiving carbamazepine, we add topiramate, with the ultimate goal of providing seizure control with monotherapy topiramate. Leviteracitam, valproate, or clonazepam are excellent alternatives to topiramate. Abortive therapy with rectal diazepam is recommended for seizures of 5 minutes or more in duration. As with managing epilepsy in all children, the track record and side effect profile (including potential serious adverse events) must be considered in every case and therapy must be individualized (See Chapter 26,"Recurrent Seizures"). The authors are not aware of any published studies on use of the ketogenic diet or vagal nerve stimulator in SWS.

Epilepsy surgery should be considered very carefully in patients with frequent, debilitating seizures in whom antiepileptic drugs have been ineffective. Because a long-term longitudinal study has yet to be completed in SWS, there are no good data to suggest that early onset of seizures has prognostic value. One of our patients with seizures in early infancy has been seizure-free for more than 20 years. This is an important point because the dogma has been that hemispherectomy should be considered in children with early-onset seizures caused by SWS. In our opinion, it is not possible to predict who will have intractable epilepsy, and surgery candidacy is no different than it is for other conditions associated with intractable epilepsy. Kossoff and colleagues (2002) examined the natural history of 32 SWS patients who underwent hemispherectomy and found that age at onset of seizures did not predict seizure freedom. In fact, an older age at surgery correlated with an improved outcome. We recommend a trial of two or more AEDs for over six months before considering surgical management. Surgical guidelines published for SWS can be found in the Suggested Readings section.

Stroke-Like Episodes

Transient deficits in motor, visual, and cognitive function are under-recognized as a complication of SWS. These episodes last hours to days and are regularly thought to be epileptic rather than stroke-like in nature. Importantly, in contrast to status epilepticus, EEGs obtained during attacks show slowing over the affected hemisphere, with

little in the way of spikes or sharp waves. In addition, although seizures frequently accompany stroke-like episodes, they typically follow the onset of motor deficits rather than precede them, as in a Todd's paralysis. Because stroke-like episodes are associated with seizures, their true frequency has not been fully appreciated. Stroke-like episodes should be aggressively managed with hydration, rectal diazepam, and intravenous fosphenytoin or phenobarbital to reduce the risk or occurrence and severity of associated seizures. Although it has been speculated that such events result from either venous microcirculatory stasis or thrombotic occlusion of larger veins, imaging studies (eg, MR venography) are usually unrevealing. There are no reported studies on the safety or efficacy of clot-busting agents for stroke-like episodes in SWS.

The most important implication of a thrombotic mechanism for neurologic deterioration in SWS is the potential for antiplatelet drugs to prevent neurologic deterioration associated with these events. Patients with stroke-like episodes have a gradual improvement in motor function over days to weeks, although careful motor testing often shows permanent motor and sensory deficits. Anecdotal reports and retrospective studies show that aspirin is beneficial, but no randomized, controlled clinical trials have been completed in SWS. The authors prescribe aspirin (3–5 mg/kg/d) in children with SWS after a first stroke-like episode. Because of the known association between Reye's syndrome, natural varicella, and influenza, patients should have received varicella immunization; yearly immunization for influenza is also recommended. Because the risks of aspirin are relatively benign when compared with the neurologic effects of SWS, many caregivers invite its use before stroke-like episodes are problematic. To adequately treat the transient stroke-like episodes and progressive hemiparesis, occupational and physical therapy are beneficial.

Cognitive and Behavioral Issues

Developmental delay, learning disabilities, and mental retardation are often seen in children with SWS, more so in those who have seizures (although the relative contribution of epilepsy to neurobehavioral problems is unknown). Children with SWS also have an increased risk for having emotional and behavioral difficulties, including attention-deficit hyperactivity disorder (ADHD). Poor school performance associated with one or more of the above problems have been a major concern of parents. In our experience, most individuals with SWS require neuropsychological assessment of intellectual and academic skills, social skills, and mood to guide educational interventions. School performance of children with SWS can improve dramatically with judicious use of medication to manage inattention, impulsivity (see Chapter 41, "Current Pharmacotherapy for Attention-Deficit Hyperactivity Disorder"), and depression (see Chapter 79, "Childhood Depression").

Headache

Severe headaches and migraines are more frequent in SWS than in the general population. Severe headaches may precede the stroke-like episodes and have also been related temporally to seizure clusters. The temporal relation between migraine-like headache, recurrent seizures, and hemiparesis in SWS is consistent with observations in animal models that dural stimulation causes distention of cranial vessels, stimulation of trigeminal afferents, and the release of vasoactive peptides at nerve terminals. Hypothetically, the leptomeningeal angioma may predispose children to neuronal hyperexcitability that accounts for migraine. Refer to Chapter 16, "Current Pharmacotherapy for Pediatric Migraine" for recommended abortive and preventive therapies for migraine. However, the safety, toxicity, or efficacy of antimigraine medication has not been studied in SWS. However, data from a recent study conducted by one of the co-authors (AMC) showed that prophylactic medications for headache are probably underutilized in patients with SWS. Patients reported very frequent headaches and safe and effective use of triptans as abortive therapy.

Education

A multidisciplinary approach is recommended when educating caregivers on the diagnosis and prognosis of SWS. The neurologist, ophthalmologist, dermatologist, and other appropriate professionals should all take time to carefully explain each affected organ system and possible complications so that caregivers have a complete understanding of the entire disorder. For example, there may be an increased incidence of growth hormone deficiency in children and adults with SWS It is imperative that caregivers be able to recognize the possible complications so that they are treated quickly and effectively to minimize further damage.

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Thomas-Sohl KA, Vaslow DF, Maria BL. Sturge-Weber syndrome: a review. J Child Neurol 2004. [In press]

Practitioner and Patient Resources

The Sturge-Weber Foundation
P.O. Box 418
Mount Freedom, NJ 07970-0418
Phone: (973) 895-4445 or 800-627-5482
Fax: (973) 895-4846
E-mail: swf@sturge-weber.com
http://www.sturge-weber.com
The Sturge-Weber Foundation is the most complete resource and the "first stop" for families of children with SWS.

Bodensteiner J, Roach FS, editors. Sturge-Weber syndrome. Mount Freedom (NJ): The Sturge-Weber Foundation; 1999. p 1–95. An authoritative text on SWS, containing extensive lists of organizations and Web sites that will assist families, teachers, and health professionals.

The John Hopkins-Kennedy Kreiger Institute Sturge-Weber Syndrome Center (JHKKISWSC)
http://www.neuro.jhmi.edu/HopkinsSWSCenter/index.htm
The JHKKISWSC has a cadre of expert physicians and health care professionals in a variety of disciplines—neurology, ophthalmology, dermatology, neuroradiology, and rehabilitation medicine and physical, occupational, and speech and language therapy—with the express goals of providing a comprehensive diagnostic evaluation and patient and family education, and maximizing patient function. The JHKKISWSC is the only such center in the United States.

CHAPTER 84

HYPOMELANOSIS OF ITO

FELINA KOSTOVA, BS

BERNARD L. MARIA, MD, MBA

The diagnosis of hypomelanosis of Ito (HI) is appropriate in individuals with hypopigmented skin lesions on the trunk and limbs following the lines of Blaschko. HI was originally named incontinentia pigmenti achromians in 1952 by Ito because the nonrandom streaks, whorls, and patches seen in HI are often described as the "negative pattern" of the hyperpigmented skin lesions in the disorder incontinentia pigmenti. Ito first described the disorder as a cutaneous syndrome, but it now seems clear that 33 to 94% of individuals have associated neurologic, ophthalmologic, and other complications.

Mental retardation and seizures are characteristically associated with central nervous system (CNS) involvement in HI, but there is extreme variability in the severity of disease. Recent evidence convincingly suggests that HI is not a discrete disorder as originally believed but instead is a nonspecific pigmentary disorder caused by chromosomal mosaicism. HI almost always occurs sporadically, and it seems to be caused by a de novo mutation in early embryogenesis. Although HI is often considered the fourth most common neurocutaneous syndrome, its incidence is very rare, with only 1 affected individual in every 600 to 1,000 new patients in a pediatric neurology service.

Diagnosis

The diagnosis is made in most individuals within the first two years year of life because of the hypopigmentation of their skin, caused by a decreased number melanocytes, with melanosomes of decreased quantity and size in the basal layer of the epidermis. Though this is present at birth in most cases, it can be acquired at up to two years. As in tuberous sclerosis, early diagnosis is enhanced by using a Wood's lamp when evaluating children with new onset seizures; the bilateral or unilateral hypopigmented whorls, streaks, and patches are usually found on the trunk and limbs. These lesions follow the lines of Blaschko, swirling around the trunk and down the arms or legs.

Clinical Features

All affected individuals have the hypopigmented skin lesions (Figure 84-1). A significant number of affected individuals also show CNS involvement, most frequently mental retardation and seizures. In a study of 76 cases in 1998, Pascual-Castroviejo and colleagues reported 57% of patients had an intelligence quotient (IQ) score < 70 and 40% had an IQ < 50. In addition, 49% suffered from seizures, with generalized tonic-clonic seizures being the

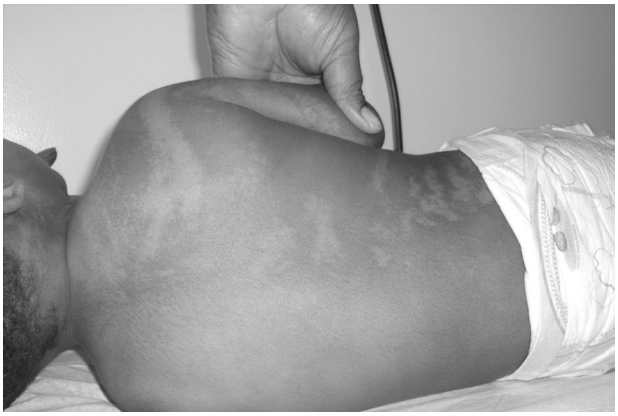

Figure 84-1. Note unilateral hypopigmented streaks and patches on the neck, trunk, and arm in a child with Hypomelanosis of Ito.

most common. Partial seizures, infantile spasms, and myoclonic seizures were also observed. Other significant neurologic complications included hypotonia, macrocephaly, microcephaly, speech delay, autistic behaviors, and expressive language disabilities. Skin manifestations include café-au-lait spots, cutis marmorata, angiomatous nevi, nevus of Ota, Mongolian blue spots, hypohidrosis of hypopigmented areas, and morphea. Hair, tooth, and nail abnormalities can also be seen.

Ophthalmologic abnormalities include strabismus, nystagmus, congenital cataracts, and various other nonspecific findings. A number of dental and craniofacial abnormalities such as abnormal number, size, shape or spacing of the teeth, and macrocephaly, low set ears, small nose, and orbital hypertelorism have been reported in HI patients.

Some patients have limb asymmetries, scoliosis, pectus anomalies, and foot deformities. Cardiac, kidney, liver, and genital abnormalities, as well as benign and malignant tumors, have also been reported to a lesser extent. However, with such a small number of reported cases and high variability in clinical expression, it is difficult to definitely state the true prevalence of associated problems. There are no reported studies of the natural history of disease in HI.

Evaluation

Thorough dermatologic, neurologic, and ophthalmologic examinations are extremely important given the heterogeneity and potential severity of HI. Chromosomal analysis of blood, skin fibroblasts, or epidermal keratinocytes or melanocytes is warranted to detect mosaicism or other chromosomal anomalies. For suspected complications, patients may need to be referred to specialists such as an orthopedist, nephrologist, cardiologist, endocrinologist, and dentist. Radiographic examination may be needed to study musculoskeletal abnormalities. Electrocardiograms (ECGs) are required for patients suspected of having cardiac abnormalities. It has also been suggested that all patients be screened using renal functional and structural tests.

Magnetic resonance imaging (MRIs) and electroencephalograms (EEGs) are justified to characterize structural and neurophysiologic abnormalities upon clinical manifestations. White matter abnormalities are commonly found in MRIs of HI patients. In a 1996 study by Ruggieri and colleagues, MRI findings included increased signal abnormalities in the parietal periventricular and subcortical white matter of both hemispheres in T2-weighted images. These white matter anomalies are similar to those found in other neurocutaneous syndromes. Several studies report gray matter heterotopias in HI patients, which may suggest that the etiology of associated seizure is caused by a defect in neuronal migration. EEGs can show focal discharges and slowing, but there has been no consistent finding in HI patients.

A report by Rafay et al. suggests that HI, like other neurocutaneous syndromes, may be linked with moyamoya disease, a cerebrovascular disease. Because of this potential link, they recommend considering angiography (MRA) in children with HI and focal neurologic abnormalities.

Genetics of HI

In earlier literature and case reviews, many modes of inheritance were proposed but none have been proved. Recent publications have supported the idea that HI is a phenotype of chromosomal mosaicism. In almost all reported cases, HI occurs sporadically. Karyotype analysis of blood, skin fibroblasts, epidermal keratinocytes, or melanocytes has shown that many patients have chromosomal mosaicism. Yet, there is no consistent pattern, as mosaicism has been found in both autosomal and sex chromosomes. Sporadic X: autosome translocations involving Xp11 have also been found in some girls suffering from HI symptoms. Some authors believe this translocation causes a functional disomy. Although some individuals' karyotypes have appeared normal, mosaicism may exist at the molecular level or minor abnormalities may have gone undetected. Until the genetics of HI are further delineated, physicians should offer families genetic counseling. In addition, when parents of an affected child are considering additional pregnancies, a chromosomal analysis of the affected child or the parents is warranted to confirm that the risk of having another affected child is extremely low.

Differential Diagnosis

HI can be difficult to diagnose but careful examination can differentiate it from similar disorders. The fourth stage of *incontinentia pigmenti* (IP) can often be confused with HI because of the presence of linear hypopigmented skin lesions. However, hypopigmentation in HI is not preceded by inflammatory, bullous skin lesions, as in IP. A more common neurocutaneous disorder, *tuberous sclerosis*, is characterized by multiple hypomelanotic, ash leaf-shaped lesions. *Nevus depigmentosus* is a cutaneous disorder with localized, nonlinear congenital lesions without any of the associated extracutaneous symptoms seen in HI. *Vitiligo* is a pigment disorder caused by the absence of melanocytes, producing decreased pigmentation in patches of skin. The lesions do not follow the lines of Blaschko and may appear well after birth. The extracutaneous symptoms associated with HI are not commonly seen.

Treatment

Treatment for HI is symptomatic. The skin lesions require no special treatment, and individuals do not have to take extra precautions with sun exposure. For individuals without additional neurologic manifestations, an annual follow-up appointment is recommended. The hypopigmented lesions tend to darken with time.

Children with HI and neurologic complications will benefit from special education services. Dentists can frequently treat abnormalities of the teeth. Surgery, corrective glasses, vision therapy, and medication may help some of the ophthalmologic conditions seen in HI.

Patients suffering from seizures may benefit from antiepileptic drugs. Valproate, carbamazepine, and phenytoin are first-line therapies in the treatment of generalized tonic clonic seizures. First choice drugs for partial seizures include oxcarbazepine, carbamazepine, phenytoin, primidone, phenobartital, and valproate. Treatment of infantile spasms. Almost 30% of patients with HI have refractory epilepsy. Placantonakis and colleagues report success with neurosurgical intervention by resection of the epileptogenic cortex in two HI patients with intractable epilepsy.

Prognosis

There is extreme variation in the clinical features expressed in patients with HI. There are no published series on the natural history of the disease, so it is difficult to precisely state the prognosis. As many as 70% of affected individuals in reported series have isolated cutaneous abnormalities. However, because of ascertainment bias in clinical series, the true prevalence of brain disease is unknown. A minority suffers from mental retardation and seizures and may depend on another person for self-care. Parents should be reassured that this is rare and that most severe complications are detected early in life.

Summary

HI is a rare neurocutaneous disorder most likely caused by chromosomal mosaicism. HI patients may suffer from numerous clinical manifestations, but the expression of the disease is highly variable. There is no systemic treatment for the disorder, except for symptom management. It is hoped that further investigation into the genetics of HI will lead to a more tailored approach to treatment.

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Practitioner and Patient Resources

HITS (UK) Family Support Network
Saskatchewan
99 Great Cambridge Rd
London, Intl N17 7LN
United Kingdom
Phone: (44) 7940 114943
Fax: (44) 208 352 1824
E-mail: tgrant@hitsuk.freeserve.co.uk
http://www.e-fervour.com/hits
HITS (UK) aims to support families by letter, E-mail, telephone, Internet chat group, monthly live Internet chats, and 3 newsletters per year and by bringing families together at events to reduce the sense of isolation often felt.

Epilepsy Foundation
4351 Garden City Drive
Landover, MD 20785
Phone: (301) 459-3700, 800-332-1000, or 800-332-2070 (TDD)
Fax: (301) 577-2684
E-mail: postmaster@efa.org
http://www.epilepsyfoundation.org
The Epilepsy Foundation ensures that people with seizures are able to participate in all life experiences and will prevent, control, and cure epilepsy through research, education, advocacy, and services.

CHAPTER 85

BRAINSTEM AND CEREBELLAR MALFORMATIONS

MICHAEL S. SALMAN, MB BS, MSc, MRCP, PhD

BERNARD L. MARIA, MD, MBA

In this chapter, the current management of developmental disorders of the brainstem and cerebellum are discussed. These include Chiari malformations (CM), Dandy-Walker malformation (DWM), Joubert syndrome (JS), and pontocerebellar hypoplasia (PCH). In addition, rarer disorders will be briefly described.

The hindbrain is made up of the brainstem and cerebellum and occupies the posterior cranial fossa. Information to the cerebellum from the spinal cord, cerebral cortex, and vestibular system is conveyed via afferent axons arranged in three white matter bundles: the superior, middle, and inferior cerebellar peduncles. Efferent axons, originating mainly from the deep cerebellar nuclei, transfer information from the cerebellum to the cerebral cortex and spine via the superior and inferior cerebellar peduncles. The brainstem, made up of the midbrain, pons, and medulla oblongata, is connected to the cerebellum by these peduncles.

The term *cerebellum* is derived from Latin, meaning small brain. The ratio of weight or volume of the cerebellum to the cerebrum is only about 10%. However, the number of cerebellar neurons is in the same order of magnitude as the number of neurons in the cerebral cortex ($\sim 10^{11}$).

The cerebellum is made up of many lobules, sublobules, and folia that develop at different time points during embryogenesis from the caudal parts of the mesencephalon and rhombencephalon, starting at about 5 weeks' gestation and finishing several months after birth. The cerebellum comprises two cerebellar hemispheres and the vermis, a midline structure that is separated from the cerebellar hemispheres on either side by the paramedian sulcus. The vermis and its lateral hemispheric expansions contain 10 lobules that are designated by Roman numerals I to X.

Information from the spinal cord, cerebral cortex, and brainstem is conveyed to the cerebellum via afferent axons arranged in three white matter bundles: the superior, middle, and inferior cerebellar peduncles. Efferent axons, originating mainly from the deep cerebellar nuclei, transfer information from the cerebellum to the cerebral cortex and spine via the superior and inferior cerebellar peduncles.

Developmental malformations of the brainstem and cerebellum have diverse etiologies; for example, mechanical compression of the cerebellum secondary to a small posterior fossa in Chiari malformation (CM) type II or genetic mutations in Joubert's syndrome (JS).

Classification of Brainstem and Cerebellar Malformations

Anatomic classification of hindbrain malformation provides a practical way of investigating affected children. Cerebellar malformations may be associated with other brain and systemic involvement, or they can be isolated. Unilateral cerebellar malformations are usually caused by pre-, peri-, or postnatal insults, such as hemorrhage in one cerebellar hemisphere, rather than a genetic syndrome. Bilateral cerebellar malformations can involve the vermis mainly, the cerebellar hemispheres, or the entire cerebellum. Malformations of the cerebellum may be associated with pontine hypoplasia of greater extent than the secondary pontine hypoplasia associated with retrograde wallerian degeneration of the cerebellum. Some of the more common disorders in these categories are discussed below.

Malformations That Mainly Involve the Midline Cerebellum

Chiari Malformations

Chiari malformations (CM) are the most common congenital malformations of the hindbrain. The classification proposed by the Austrian physician, Hans Chiari in 1891 and 1896, is in common use today.

CM Type I

The cerebellar tonsils are bilateral masses with an oval shape and lying close to the vermis. They are the hemispheric extension of vermis lobule IX, the uvula. In CM type I, the tonsils herniate down foramen magnum into the cervical spinal canal. Malsegmentation of the neural elements of the cervicomedullary junction and developmental abnormalities of the bony elements of the skull base, which cause a small posterior fossa, have been implicated in the pathogenesis of CM type I. These changes result in crowding of hindbrain structures.

Subjects with CM type I are often asymptomatic in early childhood and usually present in late childhood and early adolescence with cerebellar ataxia, neck pain, and throbbing frontal or occipital headache that worsens on exercise, coughing, sneezing, or straining. Other symptoms and signs are related to brainstem compression, such as diplopia, nystagmus, decreased gag, vertigo, and tinnitus, or to secondary obstructive hydrocephalus. Syringohydromyelia, a fluid-filled cyst within the spinal cord, is commonly associated with CM type I and presents with upper extremity sensory deficit or weakness. Leg weakness and hyperreflexia have also been reported. Although few studies have reported that greater magnitude of tonsillar herniation, usually > 5 mm below foramen magnum, is associated with more likelihood of being symptomatic, this finding has not been widely replicated.

CM type I is usually an isolated and sporadic disease but may be associated with other neurologic diseases, for example craniosynostosis or Klippel-Trénaunay-Weber syndrome.

Magnetic resonance imaging (MRI) of the brain and cervical spinal cord is essential to look for tonsillar herniation, syringomyelia, and hydrocephalus in children suspected of having CM type I. Management of symptomatic patients with CM type I is by suboccipital decompressive surgery. Syringospinal shunting or syringocisternostomy is recommended for clinically progressive and symptomatic syringohydromyelia.

CM Type II

CM type II is seen in children with spina bifida (SB), a defect in neural tube closure that occurs in approximately 1 to 2 per 1,000 births in North America. Spina bifida myelomeningocele is the most common defect of caudal neural tube closure that is congruent with survival. Its birth prevalence is about 0.5 to 1 per 1,000. It continues to be an important and prevalent disorder despite a marginal decrease in incidence brought about by antenatal ultrasound screening and detection programs, together with the prophylactic preconception and first trimester supplementation of folate for women planning to have children.

Several theories have been proposed to explain CM type II in SB. The most widely accepted theory proposes that crowding of a small posterior fossa is responsible for CM type II. The small size of the posterior fossa is caused by a cerebrospinal fluid (CSF) leak through the myelomeningocele. According to this hypothesis, this leak prevents distension of the embryonic ventricular system through the pressure generated from CSF build-up.

The hindbrain anatomic deformity is characteristic. The brainstem is stretched inferiorly and narrowed in the anteroposterior diameter, often lying at the foramen magnum or in the cervical spinal canal. The cervical spinal cord and the medulla are displaced inferiorly forming, in some, a cervicomedullary kink. The inferior part of the cerebellar vermis often herniates down, forming a tongue of tissue posterior to the medulla that usually extends down to the C2 or C4 level (Figure 85-1). The cerebellum wraps around the brainstem and is indented rostrally by the tentorium and caudally by the foramen magnum or by the posterior arch of C1.

The superior part of the cerebellar vermis is shifted upward. On sagittal brain MRI, the tectum appears like a beak (see Figure 85-1). Other anomalies associated with CM type II include dysplasia of the tentorium and cerebellar dysplasia.

Although CM type II is considered to be a midline deformity of the hindbrain, small cerebellar volume, weight, and cell content in CM type II have been reported in many studies. The small cerebellar size is likely to be due to mechanical compression secondary to crowding of the posterior fossa. The cerebellar loss affects the cerebellar hemisphere asymmetrically and usually spares the vermis. The midsagittal surface area of the vermis was recently reported to be enlarged on MRI. This enlargement involved all the vermis lobules and could not be blamed on inferior vermis herniation alone. The midsagittal enlargement is likely caused by compression Mechanical compression may be exacerbated by hydrocephalus, which occurs in 85 to 90% of children with SB. Outlet obstruction of the fourth ventricle and aqueduct stenosis cause hydrocephalus.

Symptoms of brainstem compression, cognitive deficits (especially lower performance intelligence quotient [IQ] in comparison with verbal IQ), and upper limb skeletal motor abnormalities occur commonly in children with CM type II. This may be related to hindbrain malformation, primary

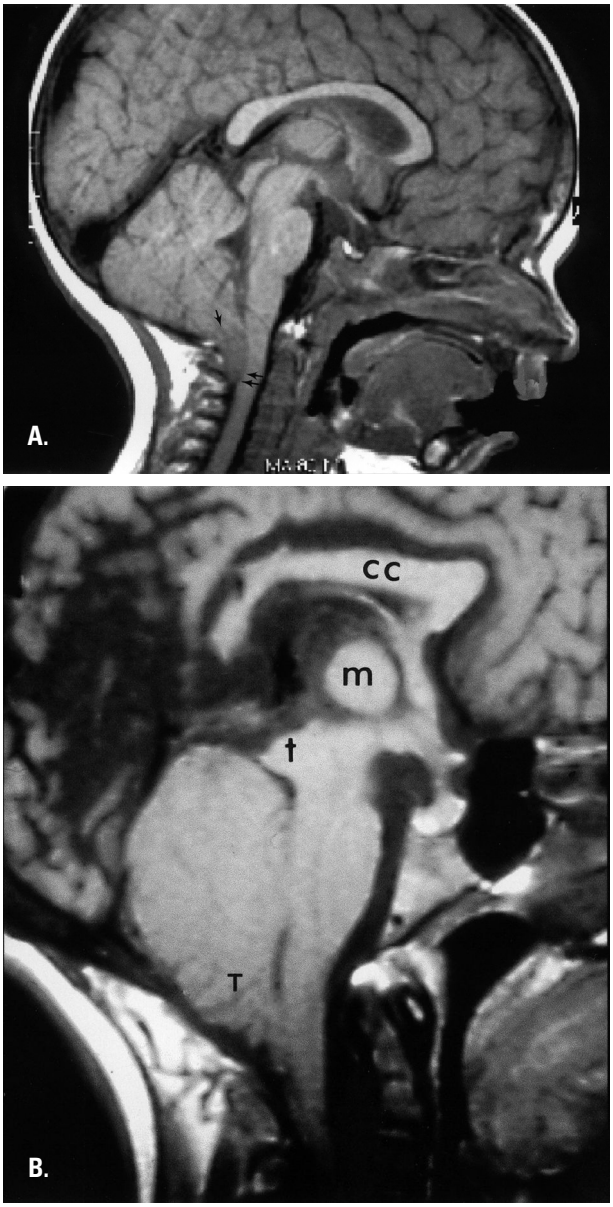

FIGURE 85-1. Chiari malformation (CM). *A,* T_1-weighted midline section illustrating a CM type I. CM type I is characterized by tonsillar ectopia (*arrow*) and low position of the cervicomedullary junction (*double arrow*). The foramen magnum is typically enlarged but to a lesser extent than occurs in the CM type II. Impaction of the cerebellar tonsils and cervicomedullary cord within the confines of the foramen magnum can contribute to the formation of a cervical syrinx (not evident in this CM type I example). *B,* T_1-weighted midline section illustrating a CM type II. In the CM type II, there is often more pronounced downward cerebellar tonsillar ectopia, but a multitude of additional cranial anomalies are present. CM type II is invariably associated with an overt, or at least occult, lumbar dysraphic disorder. Included among the usually associated cranial abnormalities (and present in this illustration) are anomalies of the incisural region—widened tentorial hiatus, hypoplastic caudal corpus callosum (cc), midline cystic spaces, trigone dilation-colpocephaly, tectal peaking (t), and enlargement of the massa intermedia (m). Not shown are other typical finding of spinal cord syrinx, cortical dysplasia, and lumbar dysraphism.

neuronal abnormalities (eg, the associated neuronal migration defects), secondary effects of hydrocephalus, agenesis or hypogenesis of the corpus callosum, and syringohydrobulbia or syringohydromyelia, which occur in about 50% of subjects with CM type II.

Management of SB and CM type II is multidisciplinary and is aimed at addressing the cognitive, motor, and renal complications. Early closure of the myelomeningocele is recommended soon after birth, followed by insertion of a ventriculoperitoneal CSF shunt when hydrocephalus develops, which is usually in the first few week of life in most affected neonates. Surgical decompression of the posterior fossa is recommended for symptoms of brainstem compression, such as bulbar palsy, apnea, or stridor. Interestingly, recent reports have demonstrated a reduction or prenatal resolution of CM type II after primary repair of the spinal defect in utero.

CM Types III and IV

CM type III is rare and usually lethal. There is a cervical encephalocele with protrusion of the cerebellum through the defect. In CM type IV, there is cerebellar hypoplasia. This type is no longer considered part of CMs.

Dandy-Walker Malformation

Dandy-Walker malformation (DWM), originally described by Sutton in 1887, is a triad of cystic dilation of the fourth ventricle, hypoplasia of the cerebellar vermis, and hydrocephalus. Other features include enlarged posterior fossa and elevation of the lateral venous sinuses and the tentorium (Figure 85-2). The origin of these anomalies is unknown, but atresia of the foramina of Magendie and Luschka was suggested in the past. However, more recently, developmental arrest in hindbrain formation has been proposed. DWM, together with Dandy-Walker variant and mega cisterna magna, constitute the Dandy-Walker complex, a continuum of developmental anomalies of the cerebellum and other brain regions. DWM is a sporadic disorder in most cases. Its etiology is heterogeneous and includes chromosomal abnormalities, single gene disorders, and teratogen exposure.

DWM can be detected on prenatal ultrasonography, but it usually presents in early infancy with macrocephaly, symptoms and signs of raised intracranial pressure secondary to hydrocephalus, and cerebellar ataxia. Cognitive and developmental delay are presenting features in late infancy in about one-third of affected children and may be severe depending on the presence of seizures. In addition, there may be hearing and visual impairments, associated central nervous malformations (such as neuronal migration defects and agenesis of the corpus callosum), and chronic hydrocephalus. Extracranial congenital anomalies are common, including polydactyly, syndactyly, hemangioma, cardiac abnormalities, and skeletal dysplasia.

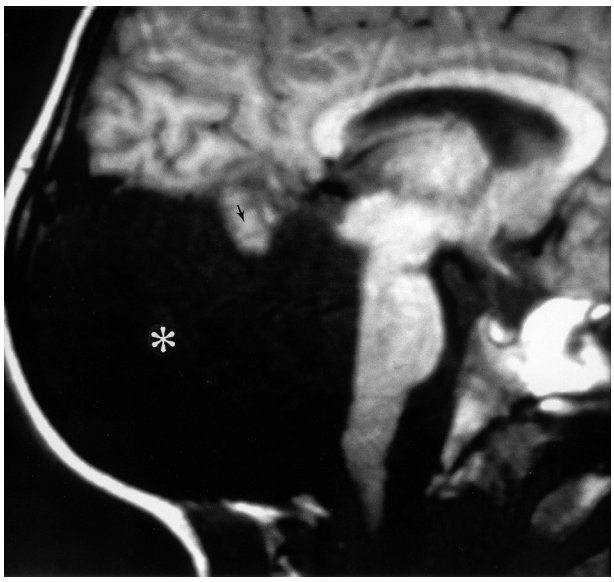

FIGURE 85-2. T1-weighted midline section illustrating a Dandy-Walker anomaly. Dandy-Walker malformation is characterized by dilation of the fourth ventricle producing a posterior fossa cyst (*). The brainstem may be displaced but is otherwise not abnormally formed. The vermis and cerebellar hemispheres, on the other hand, will not only be hypoplastic (small in size) but may be abnormally developed (dysplastic) as well. Such is the case in this illustration, where the vermis (*arrow*) is both small in size and incompletely formed.

MRI is the imaging technique of choice for the diagnosis of DWM. Associated brain anomalies and extracranial manifestations should be evaluated before the diagnostic assessment is completed. Management of DWM is multidisciplinary and addresses the commonly associated cognitive deficits and motor complications. Surgical management of DWM includes ventriculoperitoneal or cystoperitoneal shunting, or both. Complications of shunting include obstruction, which may be life threatening, infection, overshunting, shunt migration, and disconnection. Shunting has been attempted in utero with some success in some centers. Early diagnosis and aggressive therapy has improved survival of children with DWM in the past 2 decades to 80 to 90% at age 10 years.

PHACE Syndrome

This syndrome is characterized by the association of posterior fossa malformations, most commonly the DWM; hemangiomas, usually facial but may be subglottic or intracranial; arterial anomalies (for example, aneurysmal blood vessels); coarctation of the aorta and/or cardiac defects; and eye abnormalities, predominantly anterior segment abnormalities.

Other Cystic Malformations

Arachnoid Cysts

Arachnoid cysts account for the majority of posterior fossa cysts. They may present as a retrocerebellar pouch that does not communicate with the fourth ventricle. Ventriculomegaly is common, and shunting is recommended.

Mega Cisterna Magna

The cisterna magna occupies the vallecula, which is a space inferior and dorsal to the vermis. Mega cisterna magna consists of an enlarged posterior fossa, secondary to an enlarged cisterna magna. The fourth ventricle and the cerebellum are normal. It communicates with the fourth ventricle and subarachnoid space and does not produce hydrocephalus. Mild scalloping of the inner table of the occipital bone is commonly seen. No specific treatment is required and many consider it a normal variant when it is present as an isolated finding.

Persisting Blake's Pouch

There is no communication between this cyst and the subarachnoid space; therefore, obstruction to CSF flow occurs and hydrocephalus develops. Shunting is recommended and allows the expansion of the compressed cerebellum.

Syndromes with Cerebellar Vermis Hypoplasia

Joubert Syndrome

JS is an autosomal recessive disorder characterized by hypotonia, ataxia, episodic apnea and hyperpnea (especially in the neonatal period, that may be life threatening), global developmental delay, ocular motor apraxia (defined as the inability to move the eyes on command and manifesting as head thrusts), saccadic initiation failure, and impaired smooth pursuit tracking. Other features include progressive retinal dysplasia, coloboma, nystagmus, strabismus, congenital heart disease, microcystic renal disease, liver fibrosis, polydactyly, tongue protrusion, and soft tissue tumors of the tongue. Sleep disorders are encountered and may be problematic. Linkage has been established in JS and JS-related disorders to many chromosomes (eg, 9q 34.3, 11p 11.2-q 12.3, 6q 23.3, 2q 13, and 12q 21.32) suggesting significant genetic heterogeneity. Diagnosis of JS is supported by the finding of the molar tooth sign on axial MRI through the malformed pontomesencephalic junction (isthmus). This sign consists of deepening of the interpeduncular fossa, thick and straight superior cerebellar peduncles, and hypoplastic vermis (Figure 85-3). The molar tooth sign is highly suggestive but not pathognomonic for JS and has been described in other

syndromes of vermis hypoplasia. The vermis is hypoplastic or dysplastic, the caudal midbrain tegmentum is elongated, and the caudal medulla is dysplastic, which may explain the breathing abnormalities.

Management is multidisciplinary and supportive. Cardiorespiratory monitoring may be indicated in some neonates and infants. Sleep studies may be helpful in characterizing associated sleeping disorders. Annual electroretinography, renal ultrasonography, blood electrolytes, and liver function tests are also indicated to monitor disease progression. Physical, occupational, and speech therapies are recommended. Severe behavioral problems in JS can be treated by behavior management techniques and drug therapy.

Oral-Facial-Digital Syndrome Type IV

This is an autosomal recessive disorder with digital and facial anomalies, vermis hypoplasia, abnormal breathing pattern, abnormal eye movements, and hypotonia.

Arima Syndrome

Arima syndrome (cerebro-oculo-hepato-renal syndrome) is an autosomal recessive disorder and has similar features to JS. However, the abnormalities are more severe and death in infancy is common. The renal abnormalities are consistent with cystic dysplastic kidneys, which presents with renal failure early in life.

Senior-Loken Syndrome

This syndrome consists of vermis hypoplasia, retinopathy, and juvenile-onset nephronophthisis. Nephronophthisis causes chronic renal failure in children.

COACH Syndrome

This syndrome consists of cerebellar vermis hypoplasia, oligophrenia (developmental delay), congenital ataxia, coloboma, and hepatic fibrosis. Nephronophthisis is also a common feature of this syndrome. Abnormal breathing pattern and ocular motor abnormalities may also be associated.

Cerebellar Vermis Dysgenesis

Tectocerebellar Dysraphia

The dysgenetic vermis is associated with occipital encephalocele. Dorsal traction of the brainstem results in ventrolateral displacement of the hypoplastic cerebellar hemispheres and fusion of the tectum.

Rhomboencephalosynapsis

The absent or small vermis is associated with fusion of the cerebellar hemispheres, cerebellar peduncles, thalami, or dentate nuclei. Additional supratentorial abnormalities may be present. Many patients have hydrocephalus or ventriculomegaly. Clinical findings are variable and range from normal cognitive and language development to mental retardation, epilepsy, and spasticity. Management is supportive.

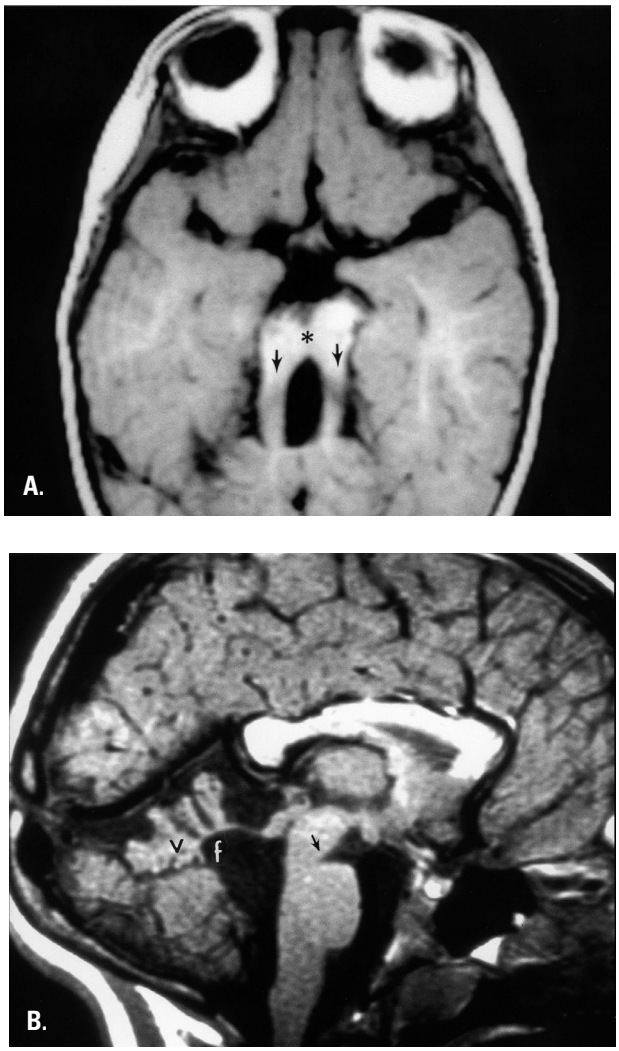

FIGURE 85-3. Joubert's syndrome. *A,* Molar tooth sign on axial T_1-weighted section through the superior cerebellar peduncles. Joubert's syndrome is characterized by two features in particular: enlarged superior cerebellar peduncles that do not decussate in the isthmus portion of the brainstem and cerebellar vermis dysplasia. This axial section illustrates the thickened superior cerebellar peduncles (*arrows*). Since they do not decussate, (*) isthmus is then reduced and the interpeduncular fossa is secondarily enlarged. *B,* Sagittal, T_1-weighted sequences. Vermis (v) dysplasia become evident. Notice the reduced vermis volume and the almost "picket fence" appearance of the dysplastic vermis lobules. The fastigium (f) of the fourth ventricle projects more rostral. Notice also the deep posterior portion of the interpeduncular fossa (*arrow*), reflecting the failure of the superior cerebellar peduncles to decussate in the midline of the isthmus.

Lhermitte-Duclos Disease

This is a dysplastic gangliocytoma of the cerebellum with thick folia that causes focal enlargement of the cerebellum. The disease presents with macrocephaly, seizures, and cerebellar deficits.

Hypoplasia of the Cerebellar Hemispheres

Many factors can cause hypoplasia of the cerebellar hemispheres, including drugs such as phenytoin, infection with cytomegalovirus, ionizing radiation during pregnancy, and genetic defects (eg, trisomies 21, 18, and 13; Smith-Lemli-Opitz syndrome; Marinesco-Sjögren syndrome, which is associated with congenital cataract; fragile X syndrome; Walker-Warburg syndrome; and hypomelanosis of Ito).

Pontocerebellar Hypoplasias

Congenital Disorders of Glycosylation Type IA

Dysmorphic features, failure to thrive, hepatopathy, developmental delay, seizures, retinopathy, deafness, demyelinating neuropathy, hypotonia, ataxia, and stroke-like episodes in association with pontocerebellar hypoplasia (PCH) are the main features of this disease. The deficient enzyme is phosphomannomutase. Diagnosis is confirmed by the presence of abnormal pattern of glycosylation of serum transferrin and other glycoproteins on isoelectric focusing.

PCH Type 1

This disease comprises anterior horn cell degeneration in association with PCH. It presents soon after birth with hypotonia, respiratory distress, and severe weakness of muscles or later in infancy with hypotonia, feeding difficulties, and developmental delay. Recently, retinal dystrophy has been described in two siblings with this disease.

PCH Type 2

Features of this disorder include extrapyramidal dyskinesia, seizures, developmental delay, and acquired microcephaly in association with PCH. Treatment is supportive. The dyskinesia may be dopa-responsive.

Other causes of Pontocerebellar Hypoplasias

PCH may be found in other disorders, including congenital muscle dystrophy, mitochondrial cytopathies, chromosomal abnormalities, teratogen exposure, congenital CMV infection, 3-methylglutaconic aciduria, PEHO syndrome (progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy), autosomal recessive cerebellar hypoplasia in the Hutterite population, lissencephaly with cerebellar hypoplasia, and PCH types 3, 4, or 5.

Brainstem Malformations

Isolated brainstem malformations are rare. Möbius syndrome is well known among brainstem nuclear agenesis syndromes. It is characterized by congenital facial diplegia caused by aplasia of the facial nerve nuclei. Other features include bilateral sixth cranial nerve palsy (the eyes are unable to move laterally even with oculocephalic head maneuver), palatal and lingual palsy, deafness, deficiency of the pectoral muscles, and extremities defects (syndactyly, missing or extra digits). Management is multidisciplinary and includes a neurologist, plastic surgeon, speech, and occupational therapists.

Duane Anomaly

Duane anomaly results from partial agenesis of the abducens motor neurons with aberrant innervation of the lateral rectus muscle by oculomotor nerve fibers. It is characterized by inability to abduct the eye, palpebral fissure narrowing and globe retraction on attempted adduction. No treatment is usually indicated.

Congenital Fibrosis of the Extraocular Muscles

There is absence or abnormal development of motor neurons in the oculomotor nucleus usually, though other extraocular motor nuclei may be involved. Other isolated brainstem malformations are very rare. In midbrain and upper pons agenesis, the cerebellum may be hypoplastic and death occurs soon after birth.

Conclusion

The cerebellum is crucial for coordinating novel and skilled voluntary movement, including eye movements, as well as for control of motor tone, posture, and gait. In addition, the cerebellum is involved in motor learning and in diverse cognitive, language, and behavioral functions. Physicians should, therefore, be aware of the diverse symptoms, signs, and disabilities caused by cerebellar malformations. This will facilitate the earlier diagnosis and management of these disorders.

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Suggested Readings

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Practitioner and Patient Resources

National Organization for Rare Disorders (NORD)
P.O. Box 8923
New Fairfield, CT 06812-8923
E-mail: orphan@rarediseases.org
http://www.rarediseases.org
NORD is a federation of more than 140 not-for-profit voluntary health organizations serving people with rare disorders and disabilities.
NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service.

National Institute of Neurologic Disorders and Stroke (NINDS)
31 Center Drive, MSC 2540
Building 31, Rm 8806
Bethesda, MD 20832
Phone: (301) 496-5751 or 800-352-9424
http://www.ninds.nih.gov
"The nation's leading supporter of biomedical research on disorders of the brain and nervous system," the NINDS conducts research on the causes, prevention, diagnosis, and treatment of neurologic disorders and stroke and supports basic research in related scientific areas.

CHAPTER 86

ACQUIRED DEMYELINATION OF THE CENTRAL NERVOUS SYSTEM

BRENDA L. BANWELL, MD

Acquired inflammatory demyelination of the central nervous system (CNS) may occur as a monophasic illness or as a component of a chronic disease such as multiple sclerosis (MS). This chapter focuses on treatment of acute demyelinating attacks and management of specific symptoms and on long-term immunomodulatory therapies.

Acute demyelination of the central nervous system (CNS) is associated with immune-cell targeting of white matter, leading to dysfunction of the neurologic processes subserved by the affected white matter pathways. Individual patients may experience clinical symptoms referable to dysfunction of a single white matter pathway or multiple deficits due to simultaneous demyelination of multiple sites in the brain, optic nerves, or spinal cord.

Many children with acute CNS demyelination experience a single episode (monophasic disease) or transiently recurrent, but ultimately self-limited disease (recurrent and multiphasic acute disseminated encephalomyelitis). However, some children will experience recurrent episodes of demyelination over time, leading to a diagnosis of multiple sclerosis (MS). This chapter discusses manifestations of acute demyelination, treatment of acute attacks and specific symptoms, and chronic immunomodulatory therapies.

Clinical Phenotypes

General Comments

Distinction between the various demyelinating presentations, and even between different demyelinating disease phenotypes, currently rests largely on clinical definitions. An international working group has proposed specific clinical definitions for acquired demyelination in children. Recently, the presence in serum of IgG antibodies directed against the aquaporin 4 molecule has been specifically associated with the clinical disease known as neuromyelitis optica (NMO). Serum antibodies directed against myelin oligodendrogial (MOG) protein have been detected in some patients with acute disseminated encephalomyelitis (ADEM), suggesting that the future characterization of demyelinating disease phenotypes may involve both clinical and biological assessments.

Optic Neuritis

Optic neuritis (ON), due to demyelination of the optic nerve (s), presents with acute visual loss of one or both eyes (simultaneously or sequentially), in the presence of at least two of: impairment of color vision, pain with ocular movement, afferent pupillary defect, disc pallor, abnormal visual evoked potentials, or central or centrocecal field defect. The prognosis for visual recovery is generally excellent with approximately 80% of children recovering to better than 20/100 vision in the affected eye. In a recent study of 36 children with acute ON, 12 (36%) experienced recurrent demyelinating attacks leading to a diagnosis of MS within 2 years, and one child was diagnosed with NMO. The presence of clinically-silent white matter lesions or findings on neurological examination distinct from the optic nerves was highly predictive of MS outcome. None of the children with a normal brain MRI have been diagnosed with MS to date. However, as recurrent

attacks leading to the diagnosis of MS may occur more than 10 years after an initial episode of ON in childhood, the negative predictive accuracy of normal brain MRI can only be evaluated after many years of observation.

Transverse Myelitis (TM)

A recent international panel defined transverse myelitis (TM) as bilateral sensory or motor dysfunction localized to the spinal cord, a defined sensory level, and magnetic resonance imaging (MRI) or myelography exclusion of spinal compression, plus one of the following: (1) cerebrospinal fluid (CSF) pleocytosis or increased immunoglobulin (Ig) G index or (2) gadolinium-enhancement of cord, progressing to maximal deficit between 4 hours and 21 days after symptom onset. Bladder and bowel dysfunction may also occur and must be managed acutely.

Neuromyelitis Optica (Devic Disease)

Devic disease is characterized by acute, severe transverse myelitis and bilateral optic neuritis occurring simultaneously or sequentially (within 2 years, but often within weeks). Symptoms may occur as a monophasic syndrome (ie, no further attacks after the initial ON and TM) or may be associated with multiple relapses of ON and TM. A key distinguishing feature from typical MS is that clinical and MRI evidence of white matter involvement in the brain is absent. The spinal cord involvement in Devic syndrome is also distinct, in that it involves multiple, contiguous spinal cord segments (longitudinally-extensive transverse myelitis, LETM) in contrast to the small, partially transverse lesions characteristic of MS. While initial clinical criteria for NMO stipulated that lesions in the brain MRI must be absent, more recent modified criteria allow the presence of lesions provided that they are not in a pattern typical of MS. Serum NMO IgG antibodies are present in 73% of adults with relapsing NMO, as compared to approximately 5% of patients with MS. NMO is a more severe demyelinating disease than MS, with a 20% mortality and 50% of surviving patients developing paraparesis or blindness within 5 years of onset. Children with NMO may have milder disease, although larger studies are required. Pathological studies demonstrate a severe necrotizing myelopathy, distinct from the typical pathological features of transverse myelitis in MS patients.

Devic syndrome has been reported in children and seems to have a more favorable prognosis. In the pediatric series, however, ON and TM occurred within 8 weeks of each other, a factor that was also associated with a better clinical outcome in a series of adult Devic syndrome patients.

Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is the most controversial of the demyelinating phenotypes. Clearly defined clinical criteria for ADEM have not been established. The classic description of ADEM includes polysymptomatic demyelination with at least two of the following: fever, encephalopathy, meningismus, and headache. ADEM may be associated with a history of viral illness or vaccination within 2 weeks of symptom onset. ADEM after measles infection was particularly severe. Effective measles vaccination programs have led to fewer cases of severe ADEM. MRI typically demonstrates bilateral, asymmetric white and gray matter lesions. However, MRI cannot be used to confirm a specific diagnosis of ADEM and cannot distinguish an attack of ADEM from the first attack of MS. Application of the term *ADEM* varies among clinicians. In some centers, the presence of multiple white matter lesions alone is used to confer the diagnosis of ADEM, irrespective of the clinical symptoms. This has resulted in considerable clinical heterogeneity in published ADEM series and may contribute to the variable outcomes reported.

ADEM is classically considered to be a monophasic disease. However, some children with ADEM experience recurrent neurologic symptoms. Recurrence of the same symptoms as the initial event, typically during taper of corticosteroids, is considered an incomplete response to therapy rather than a new event. However, some children develop new symptoms (clinically and associated with radiologic evidence of new areas of demyelination). If these relapses occur in close proximity to the original symptoms the term *multiphasic ADEM* has been applied. Children who experience a single relapse, with subsequent resolution of white matter lesions on MRI, have been diagnosed with *biphasic ADEM*. Recurrent demyelinating attacks, well separated in time from the initial ADEM episode and associated with evidence of involvement of previously uninvolved white matter pathways, leads to a diagnosis of MS. However, there remains considerable controversy regarding the diagnosis of MS in children for whom the first demyelinating attack was considered to be ADEM. Longitudinal studies of carefully characterized ADEM patients are required to truly determine MS risk in this population.

Polysymptomatic Demyelination

The presence of neurologic deficits referable to multiple sites within the CNS, but without symptoms of encephalopathy, fever, or meningismus, is termed *polysymptomatic demyelination*.

Monosymptomatic Demyelination

Clinical symptoms referable to discreet neurologic pathways other than the optic nerve or spinal cord may also be the presenting feature of CNS demyelination. Children may present with hemisensory or hemimotor

deficits, cerebellar symptoms, or with symptoms referable to a discrete brainstem lesion (ie, intranuclear ophthalmoplegia). Monosymptomatic demyelination (including ON) is now referred to as a *clinically isolated syndrome* in the adult demyelinating disease literature.

Multiple Sclerosis

MS is a chronic autoimmune inflammatory and neurodegenerative disorder of the CNS. MS is defined by recurrent attacks of inflammatory demyelination, separated in time by more than 30 days and involving separate CNS white matter pathways. Recently proposed diagnostic criteria for MS now incorporate MRI as a means of confirming dissemination of demyelinating lesions within the CNS and for recognition of emergence of new (clinically silent) lesions over time. Clinical symptoms must persist for more than 24 hours to constitute a clinical "attack." All attacks must be clearly distinct from acute infection. Separate from acute attack symptoms, MS patients may also suffer profound physical and cognitive fatigue, emotional lability, depression, and cognitive decline. Over time, patients may develop permanent physical disability, spasticity, tremor, or bladder dysfunction.

Although MS is typically considered a disease that affects young adults, at least 5% of all MS patients present prior to their 16th birthday. The number of children diagnosed with MS has increased in recent years, likely owing to improved diagnostic awareness among pediatric health care practitioners and to MRI confirmation of active white matter disease. However, numerous barriers remain to the diagnosis of MS in children. Many pediatricians are unfamiliar with MS or do not believe MS occurs in childhood, many children who recover from an inciting demyelinating event are not followed in a systematic manner and thus the significance of their second attack is not fully appreciated, and MRI criteria for the diagnosis of MS in children have yet to be established.

The clinical course of MS is variable. More than 80% of adult MS patients and more than 95% of all pediatric MS patients have a course of MS initially characterized by relapses (MS attacks) and remissions (partial or complete resolution of relapse symptoms). Over time, the vast majority of adult patients with *relapsing-remitting MS* (RRMS) begin to accrue disability between attacks, a phase of the disease known as *secondary progressive MS* (SPMS). Retrospective, longitudinal studies of pediatric-onset MS patients indicate that 50% of patients will progress to SPMS after 23 years of disease. *Primary progressive MS*, in which patients experience progressive disability from onset, without discrete clinical relapses, is exceptionally rare in children.

MRI in childhood MS

MRI diagnostic criteria specific for pediatric MS are under development, as the MRI criteria developed for MS in adults do not apply as well in children. The typical MRI appearance of MS in children consists of multiple white matter lesions, often with a predilection for the periventricular white matter and corpus callosum-similar to findings in adult MS. Younger children with MS tend to have a greater likelihood for less well-defined lesions and a greater preponderance for lesions in the brainstem or cerebellar white matter. Although bilateral, ill-defined white matter lesions and lesions in the deep grey nuclei are characteristic for ADEM, these features can also be seen in children ultimately diagnosed with MS. In a study of children with acute demyelination, the sole presence of well-defined lesions, and lesions perpendicular to the long axis of the corpus callosum were found to be highly specific (100%), but relatively less sensitive (34%) for MS in children. A detailed study of white matter lesion distribution in pediatric MS, and proposed MRI criteria for MS in children is in progress.

Differential Diagnoses of CNS Demyelination

One of the key tenets of MS diagnosis or the diagnosis of an initial demyelinating attack is that other etiologies be excluded. The clinical signs and symptoms of CNS typically peak for a few days or, occasionally, even for a few weeks. This is a helpful distinction from acute vascular syndromes, hemorrhage (posttraumatic, vascular malformations, tumor-related), or acute intoxication, in which deficits peak within 24 hours. Gradual neurologic deterioration, over weeks to months, is more typical of leukodystrophies (adrenoleukodystrophy, metachromatic leukodystrophy, late-onset Krabbe's disease), juvenile Alexander disease (which can have MRI features very similar to MS), CNS malignancy, mitochondrial disease (although intermittent deficits can also occur, and thus mitochondrial disease must always be considered), and nutritional deficiency (ie, vitamin B_{12}). As mentioned previously, the primary progressive form of MS, in which deficits progress over months, is exceptionally rare in children. The advent of MRI has greatly improved the diagnostic evaluation of CNS demyelination. MRI appearance of mitochondrial disorders, leukodystrophies, malignancies, and vascular disorders are well described.

The main disorders included in the differential of acute CNS demyelination include viral infection, CNS vasculitis, neurosarcoid (rare), and vitamin B_{12} deficiency (in patients with dorsal column or spinal cord symptoms or with macrocytic anemia). Mitochondrial disease must always be considered, particularly if there is a history of short stature, diabetes, deafness, or myopathy in the patient or family. CNS vasculitis, particularly systemic lupus erythematosus (SLE), can mimic CNS demyelination. Signs of systemic

illness, cognitive change, and headache would prompt specific consideration of vasculitis. Serum autoimmune markers (double-stranded deoxyribonucleic acid [DNA], antinuclear antigen, and erythrocyte sedimentation rate) and magnetic resonance (MR) angiography are performed for all children in whom this diagnosis is entertained. All children with acute demyelination seen in our institution are investigated with a comprehensive viral serology, Lyme serology, West Nile virus serology (seasonal), angiotensin-converting enzyme level, serum and CSF lactate, MR spectroscopy for brain lactate, chest radiography, and serum B_{12} levels (when indicated). Spinal fluid analysis for infection should be performed on all children with fever or encephalopathy but is more controversial for evaluation of otherwise well-appearing children with monosymptomatic demyelination. CSF oligoclonal bands, present in over 90% of adult MS patients, can be transiently present in children with ADEM and can be absent in children with confirmed MS. Further studies are needed to clarify the diagnostic utility of CSF oligoclonal bands in pediatric demyelination.

Management of Acute Demyelination

Figure 86-1 outlines a proposed treatment algorithm for acute symptomatic demyelination. Initiation of the algorithm should only be instituted for children in whom demyelinating symptoms are so severe they interfere with daily function. Mild symptoms do not require acute medical therapy.

Corticosteroids

The putative mechanism of action and rationale for corticosteroid therapy in acute demyelination have been reviewed. In brief, corticosteroids act at the cellular level through the glucocorticoid steroid receptor, leading to upregulation and repression of messenger ribonucleic acid (mRNA) transcription of antiinflammatory and proinflammatory genes, respectively. Corticosteroids also act at the endothelial cell membrane to reduce permeability of the blood-brain barrier (BBB) to immune cells, mediated by steroid-induced reduction in leukocyte receptors. This effect is seen clinically by a reduction in gadolinium enhancement of demyelinating lesions in steroid-treated patients. Steroids also reduce the total circulating lymphocyte population, as well as the circulating levels of the harmful cytokines and chemokines secreted by activated lymphocytes. Thus, corticosteroid therapy affects numerous aspects of the immunologic cascade involved in the pathogenesis of an acute demyelinating episode.

The efficacy of corticosteroids in the treatment of demyelination is well recognized clinically. However, there are few placebo-controlled corticosteroid trials. The Optic Neuritis Treatment Trial (ONTT) randomly assigned adult patients to placebo, low-dose oral prednisone, or intravenous methylprednisolone (IVMP). Patients treated with IVMP improved more quickly than did those who took oral prednisone or placebo, although visual function at 1 year was similar for all three groups. The benefit in terms of quality of life of the patients was not specifically addressed in this study. Clinical experience dictates that rapid recovery of vision has enormous benefit to the patient's ability to pursue normal daily activities. IVMP has also been shown to hasten clinical recovery from other demyelinating phenotypes. Several studies have confirmed the short-term benefit of IVMP and high-dose oral prednisone.

There are no published trials on the use of corticosteroids in pediatric demyelination. IVMP is widely used to treat children with acute demyelinating syndromes, as reflected in several published series in which treatment is mentioned. The treatment algorithm presented in Figure 86-1 is based on our experience in treating more than 130 children with acute demyelination in the past 4 years.

Clinical Care Model for Children with MS

We employ a comprehensive, multidisciplinary model of care in our Pediatric MS Clinic. Our clinic is staffed by a pediatric neurologist, two MS-certified nurses, a social worker, a pediatric neuro-physiotherapist, a clinic coordinator, two child psychiatrists, and a pediatric neuro-ophthalmologist. The clinic is linked with the local chapter of the MS Society of Canada, and patients and families are provided printed material and on-line literature relating to pediatric MS.

Nursing Care for Children with MS

Nurses play an integral role in the education and psychosocial support of children with MS and their families. At diagnosis, they provide families with information about MS, treatment options and resources to help them understand the impact this disease will have on their lives, to aid them in making informed decisions about treatment and to promote coping and adaptation. Once a family decides on treatment with a disease modifying therapy, nurses teach injection techniques, discuss ways to help the child cope with the injections and review strategies for managing side effects. They also address adherence issues that can be particularly challenging with adolescents.

Linking families with resources that help them understand and cope with MS is another important nursing role. The National MS Society and the MS Society of Canada facilitate the *Young Persons with MS Network* that offers numerous educational and support services for this population (http://www.mssociety.ca/en/help/YoungPersonsMS.htm;http://www.nationalmssociety.org)

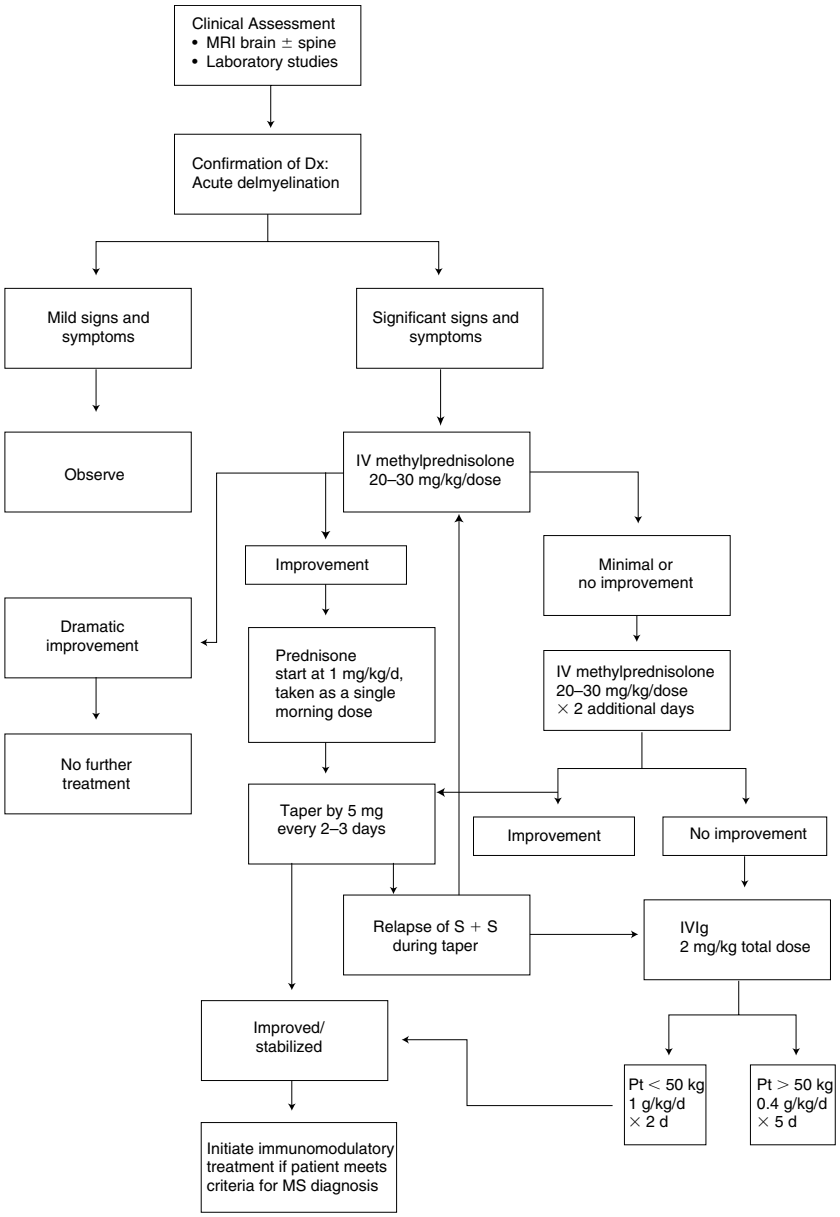

FIGURE 86-1. Once the diagnosis of acute CNS demyelination is confirmed, treatment is initiated for those children in whom symptoms are of a severity sufficient to interfere with function. Treatment is initiated with high dose intravenous methylprednisolone (IVMP) for three days. If symptoms resolve completely, no further therapy (and no prednisone taper) is required. Children with incomplete resolution of symptoms should receive two further days of IVMP. Oral prednisone, starting at 1 mg/kg given as a single morning dose is then initiated. The dose of prednisone is then reduced after three days by 5 mg Q3days until discontinued (ie: taper over 14 to 21 days). Children must be closely monitored, and the speed of prednisone modified if necessary. Children who fail to respond to IVMP, or those who experience clinical recurrence of symptoms during prednisone taper should either receive a second course of IVMP or should be offered IVIg. IVIg is given at high dose, 2 grams/kg divided over two days (small children) or over five days (children over 40 to 50 kg). In our experience, low dose IVIg is ineffective.

Nurses also identify the need for referral to other psychosocial supports such as social work, psychology and psychiatry. Because fatigue, cognitive deficits and physical disability are problems associated with MS that impact on school attendance and performance, nursing staff work with school personnel to educate them on these issues and advocate for resources that promote successful integration and academic achievement. In light of the chronic and uncertain nature of MS and the changing needs of the developing child, nurses provide ongoing education and support around understanding MS, symptom management, coping with relapses, treatment adherence and school issues.

Immunoglobulin

A proportion of children with acute demyelination will either fail to respond to IVMP or will demonstrate reemergence of their demyelinating symptoms upon reduction of corticosteroid therapy. The risks of prolonged corticosteroid therapy (reduced somatic growth, osteopenia, hyperglycemia, hypertension, acne, etc) are of significant concern. Several case reports and small case series have suggested a role for intravenous immunoglobulin (IVIg) for these children. Our experience with IVIg has been similarly favorable. IVIg is given at a dose of 2 gm/kg, in divided doses, as indicated in Figure 86-1.

The mechanisms of action of IVIg are not fully understood. In general, IVIg is thought to bind circulating antibodies, thus preventing them from entering the CNS. IVIg binds complement components, inhibiting tissue damage, inhibits B cell production of antibodies, interacts with the mechanisms of action of macrophages, and may inhibit the production of pro-inflammatory cytokines. A recent meta-analysis in which four trials of IVIg were analyzed demonstrated that IVIg significantly reduced the annual number of MS relapses and raised the proportion of relapse-free patients, compared with placebo. A largescale IVIg trial in adult MS is currently under way. We have used IVIg in select pediatric MS patients. In our clinic, IVIg is used to stabilize children with very frequent relapses, usually as an adjunct to their MS-targeted immunomodulatory therapy.

Physical and Occupational Therapy

Rehabilitation is a key component of any acute neurologic injury. Active range-of-movement exercises are important for children with severe hemi- or paraparesis to reduce the risk of secondary complications such as contractures, disuse atrophy, or skin breakdown. Children with incomplete recovery or those with a prolonged recovery phase will benefit from exercises dedicated to reduce spasticity, improve strength and coordination, and increase early mobilization.

Management of Multiple Sclerosis

Figure 86-2 outlines a proposed treatment overview for pediatric MS. This is meant as a general guideline only. As the vast majority of children with MS have relapsing remitting disease, treatments discussed will focus on this type of MS only. Primary progressive MS therapy in children is extremely rare, and treatments for these children are individualized.

The Pediatric MS Clinic at the Hospital for Sick Children uses a comprehensive, multidisciplinary model of care. The clinic is staffed by a pediatric neurologist, two MS-certified nurses, a social worker, a pediatric neuro- physiotherapist, a clinic coordinator, two child psychiatrists, and a pediatric neuro-ophthalmologist. The clinic is linked with the local chapter of the MS Society of Canada, and patients and families are provided printed material and online literature relating to pediatric MS.

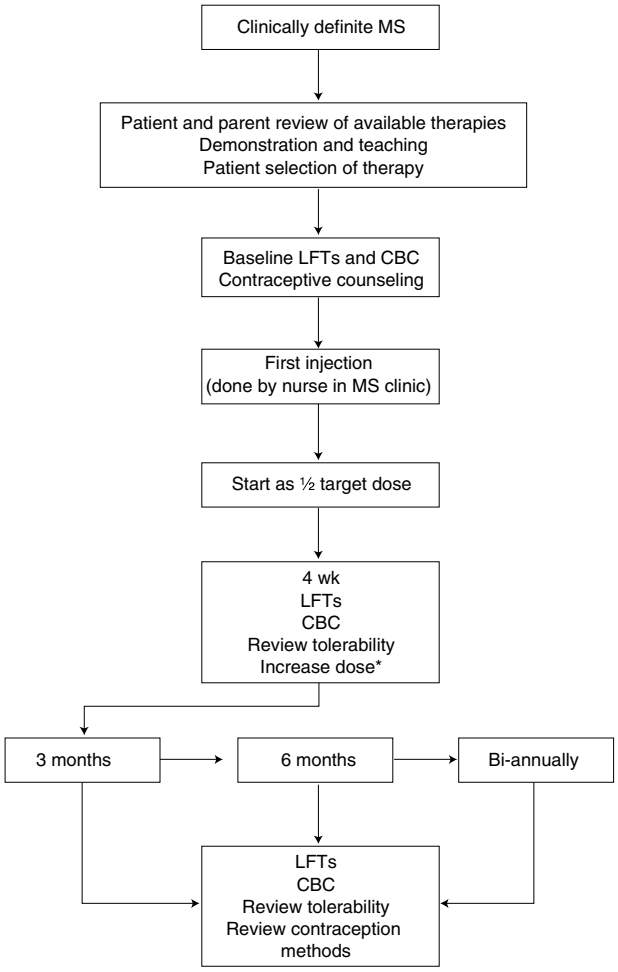

FIGURE 86-2. The model used at the Pediatric Multiple Sclerosis (MS) Clinic at The Hospital for Sick Children for the initiation of immunomodulatory therapy. Liver function test (LFT) abnormalities do occur in children receiving interferons and must be closely monitored. *Escalation of dose should only occur if liver indices are normal, and once the patient is tolerating their current interferon dose. Glatiramer acetate is given at full dose (20 mg/d subcutaneous) from initiation of therapy. LFT abnormalities are not a reported side effect of glatiramer acetate. CBC = complete blood count.

Disease-Modifying Therapies

Interferons and Glatiramer Acetate

The development of disease-modifying therapies for MS has led to a significant change in MS care. Table 86-1 outlines dosage and mode of administration for each of the four approved medications.

TABLE 86-1. Immunomodulatory Therapies in Multiple Sclerosis

Medication	Trade Name	Dose	Route	Frequency
Interferon β-1a	Avonex®	30 μg	IM	Once weekly
Interferon β-1a	Rebif®	22 or 44 μg	SQ	3 times weekly
Interferon β-1b	Betaseron®	8 mIU	SQ	Every other day
Glatiramer acetate	Copaxone®	20 mg	SQ	Daily

The presumed mechanisms of action of interferons and glatiramer acetate (GA) differ, but both act to reduce CNS inflammation. Interferons decrease syntheses within the immune system of requisite costimulatory molecules, proinflammatory cytokines, and other pro-inflammatory mechanisms leading to inhibition of reactive T cells. Interferons also inhibit trafficking of T cells across the blood-brain barrier. GA, a random polymer, acts as a molecular "decoy." GA is engulfed by antigen-presenting cells, leading to presentation of GA-specific antigens and subsequent GA-specific T cells. These GA-specific T cells favor the more antiinflammatory Th2 T cell subtype, rather than the pro-inflammatory Th1 phenotype. Furthermore, the GA-specific T cells may further suppress autoimmunity by acting through a mechanism known as "bystander suppression."

Detailed reviews of the disease-modifying therapies have recently been published. All reduce the frequency of annual clinical relapses by 29 to 34%. Interferon β-1a (Avonex® and Rebif®) has been shown to reduce the progression of disability. All four medications have shown a reduction in inflammatory activity as assessed by gadolinium enhancement on MRI, and interferon β-1a (Avonex®) has been shown to reduce the rate of brain atrophy.

Side effects of interferons include flu-like symptoms, elevation in serum of hepatic transaminases, menstrual irregularities, reduction in white blood cell count, and injection-site reactions. The flu-like side effects are usually mild and respond well to administration of acetaminophen or ibuprofen. For some patients, however, the flu-like side effects limit tolerability. GA does not lead to the flu-like side effects of the interferons but is associated with injection site reactions and with a self-limited systemic reaction characterized by an unpleasant flushing-sensation, dyspnea, palpitations, and anxiety.

Initiation of therapy with interferon β-1a at the time of a first demyelinating event delayed conversion to MS in adult patients at high risk for MS (on the basis of MRI findings). Recent studies also suggest that initiation of disease-modifying therapies as early as possible after confirmation of MS diagnosis leads to improved long-term outcome (as measured by reduced physical disability) compared with untreated natural history cohorts. Interferon β-1a (Avonex®) has also been shown to have a beneficial effect on cognitive outcome in adult MS patients.

The available literature on the use of interferons and GA in pediatric MS patients is restricted to tolerability data in isolated small case series or single case reports. Use of these agents in children requires a carefully structured patient care model. The fact that the disease-modifying agents are administered via injection poses a challenge for all MS patients but is a particular challenge for young children. In our clinic, we spend a great deal of time educating children and their parents about the treatment options and involve the child or adolescent in the choice of therapy. Injections are demonstrated by the use of a puppet, which also allows the parent (or adolescent if self-injection is planned) to practice injection techniques.

We use an arbitrary method to determine the dose of interferons on the basis of the child's weight relative to a normal adult female body weight (ie, a 30 kg child is 50% of a normal 60 kg woman and would have a target dose that is 50% of the normal adult dose).We then initiate therapy with one-half the target dose, and in 2-week increments increase to three-quarters the dose and then the full target dose. Escalation of dose depends on tolerability and on results of liver function tests (LFTs) and complete blood count studies. These laboratory studies are performed at baseline, and then monthly for 6 months. If liver function results are normal at 6 months, then subsequent studies can be performed every 6 months thereafter. GA is initiated at the full adult dose. Before initiating therapy, contraceptive counseling is provided to all sexually active adolescents, as the safety of these medications during pregnancy is unknown.

To date, we have documented elevation in serum liver transaminases in four of our patients, necessitating reduction in dose in three and discontinuation of interferon in one child. Flu-like side effects have been noted in 20% of children on interferons, but these symptoms have been easily managed with ibuprofen. Brief episodes of chest tightness and tachycardia were described by two children receiving GA. Overall, we have found disease modifying therapies to be well tolerated in children.

Efficacy of disease-modifying agents cannot be accurately assessed without a formal efficacy trial. Such a trial would require collaboration among multiple sites and poses numerous logistical considerations. It is unlikely that a placebo-controlled trial would be considered, given the proven efficacy of disease-modifying therapies in adult MS.

Mitoxantrone

Mitoxantrone is a cytotoxic anthracenedione antineoplastic agent that has potent immunomodulatory effects on both humoral and T cell–mediated immunity. Mitoxantrone is administered as a monthly intravenous dose of 8 mg/m2 or as 12 mg/m2 every 3 months. In the pivotal trial, mitoxantrone was shown to reduce the rate of disability progression. However, mitoxantrone is associated with a cumulative dose-related cardiotoxicity and a significant risk of leukopenia. Thus, the use of this agent is largely restricted to adults with aggressive MS. The use of mitoxantrone in pediatric MS has yet to be described.

Cyclophosphamide

Cyclophosphamide is an alkylating agent with potent immunosuppressive properties. The use of cyclophosphamide in MS is controversial. One trial found no benefit of cyclophosphamide, whereas another demonstrated a significant reduction in disease progression. Cyclophosphamide is used in pediatric patients with neoplastic or autoimmune disorders (ie, SLE). Familiarity with the use of cyclophosphamide in pediatrics, combined with data from the studies of cyclophosphamide in adults that suggest a role for this medication in patients with aggressive MS associated with frequent relapses, has led to the use of cyclophosphamide in a small number of pediatric MS patients worldwide. Cyclophosphamide is associated with long-term risks of infertility and bladder carcinoma or other malignancies and short-term risks of alopecia, immune suppression, hemorrhagic cystitis, and nausea. Thus, toxicity will restrict the use of cyclophosphamide to children with highly active disease who have failed all other forms of conventional MS therapy. Our experience, and that of other centers (personal communications), is that cyclophosphamide reduces acute relapse disability, reduces relapse frequency, and improves fatigue significantly in some highly selected patients.

Natalizumab (Tysabri)

Natalizumab, an α-4 integrin inhibitor, has been shown to reduce MS relapse rate by 68%, and reduced disability accrual by 42%. However, three patients developed JC virus-medicated posterior multifocal leukoenceophalopathy- an often fatal infection of the CNS white matter. Natalizumab has recently been re-released for use in MS, under strict safety monitoring guidelines. The use of this medication for children with MS is not currently endorsed.

Symptomatic Therapies

The most important aspect of symptomatic therapy is to fully evaluate the symptoms in the context of the child's daily life. Increasing fatigue may be a sign of MS or a feature of poor sleep hygiene, depression, stress, or school pressures. Bladder dysfunction may be due to spinal cord involvement or to urinary tract infection. Depression can yield numerous symptoms and may not be readily identified by a young child or their parents. Management of pediatric MS patients requires an in-depth understanding of the child and a well-established relationship of trust. It is important for patients, particularly adolescents, to have an opportunity to discuss their concerns privately with their health care team. Sexual dysfunction, alcohol and drug use, pregnancy and contraception, and mental health issues may never be mentioned unless the patient has the opportunity to confide in his or her physician.

There are several specific symptoms that will be discussed:

Fatigue is defined in our pediatric MS population as a subjective lack of physical or mental energy of sufficient severity as to interfere with the child's ability to complete requisite school work, engage in extracurricular activities, or interact socially with peers. Modafinil (Provigil®) and amantadine have been shown to be efficacious in reducing fatigue in MS and have proved beneficial for those children for whom therapy was indicated.

Management of spasticity requires physiotherapy as well as medication. Oral botulinum toxin, tizanidine, and benzodiazepines may be effective. Neuropathic pain is managed with use of gabapentin.

Bladder dysfunction may occur acutely during transverse myelitis or as a chronic condition. Treatment of acute bladder failure centers on avoidance of infection by the use of intermittent catheterization or indwelling catheters (if necessary). Chronic bladder dysfunction is a common symptom in adult MS but appears to be less frequent in children. Symptoms of urgency, hesitancy, or incontinence require careful evaluation. Infection must be excluded. Bladder spasticity, leading to difficulty with initiation of voiding, frequency, and urgency, is managed with the use of oral Ditropan®. Bladder retention, leading to overflow incontinence and risk of urinary tract infection, may require intermittent catheterization or other techniques to ensure bladder emptying. A full urodynamic evaluation is strongly advised to ensure proper bladder care.

Cognitive deficits occur in 50 to 65% of adult MS patients and may occur early in the disease. The onset of MS during early childhood occurs during the period of primary myelin maturation and during the formative academic years. Cognitive deficits have also been demonstrated in children with MS. These deficits are notable in children with no demonstrable physical disability, suggesting that cognitive deficits may be the most functionally important consequence of early-onset MS.

Cognitive rehabilitation is an area of research in adult MS and is most certainly an area that merits urgent exploration in pediatric-onset MS as well.

The onset of MS in a child or adolescent invariably leads to shock and dismay for parents and caregivers facing the diagnosis of an "adult disease" in their child. The psychological impact of MS on the child or adolescent may also be profound, although in our experience most children cope well with their diagnosis. This perception of coping may reflect the common "invincible" attitude adopted by children and adolescents. Depression is diagnosed in 30 to 50% of adult MS patients at some point during their disease. The Pediatric MS Clinic is staffed by two pediatric psychiatrists who offer assessments for all children and adolescents in our clinic. This has proved to be invaluable.

Summary

The onset of demyelination in childhood or adolescence poses a wealth of challenges to the patient, family, and medical team. Acute symptoms must be fully investigated and managed. Many children will experience a monophasic illness. However, the risk of the subsequent diagnosis of MS must be recognized and appropriate long-term care provided. Advances in MS therapeutics highlight the importance of prompt diagnosis and early initiation of MS-targeted therapies. The long-term impact of pediatric-onset MS on physical and mental functioning, as well as on ultimate vocational and social independence, is likely to be profound. It is hoped that comprehensive care of MS-affected children will serve to mitigate the long-term impact of this disease.

Suggested Readings

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Practitioner and Patient Resources

National Multiple Sclerosis Society
http://www.nmss.org/
The Society and its network of chapters nationwide promote research, educate, advocate on critical issues, and organize a wide range of programs—including support for the newly diagnosed and those living with MS over time.

Canadian Multiple Sclerosis Society
http:// www.mssociety.ca
kidswithms@mssociety.ca

Section 3

The Hospitalized Child

CHAPTER 87

NEUROLOGIC CONDITIONS ARISING FROM TROPICAL AND SUBTROPICAL REGIONS

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With the increase in travel to and from tropical and subtropical countries, child neurologists are likely to encounter tropical neurologic conditions more frequently. This chapter outlines some of the most common conditions that may be encountered, in particular neurocysticercosis, falciparum malaria, tetanus, polio, subacute sclerosing pan encephalitis, and neurobrucellosis.

With the increase in international travel, either for vacations or with migrant populations, children with neurologic conditions that are common in tropical and subtropical regions may present to neurologists anywhere in the world. The diagnosis of these conditions depends on eliciting a thorough travel history (including stopovers in airports) and awareness of the distribution of these conditions throughout the world. The latter can change, and updated information can be obtained from Web sites listed at the end of the chapter.

Neurocystercosis

Taenia solium is endemic in Latin America, India, China, and many parts of sub-Saharan Africa, although there are few studies to date that focus on this condition. It occurs in areas with poor hygiene and living conditions, particularly where pigs have access to human feces. Humans may ingest cysticerci from infected pigs or fecal matter, with the eggs hatching in the small intestine and invading striated muscle and the central nervous system (CNS). The CNS manifestations usually occur when a cyst is degenerating or as a result of a chronic, calcified lesion.

Clinical Presentation

Most cysterci invade the CNS asymptomatically, but some children complain of headaches, vomiting, fever, myalgia, and seizures. The clinical features depend on the size, number, type, location, and stage of the cysterci. The main clinical features are seizures, symptoms of raised intracranial pressure, alterations of mental status, and focal neurologic signs.

Seizures are the most common symptom, and despite the focal lesion, many are generalized tonic-clonic seizures. Ventricular cysts may cause seizures or meningeal irritation. Nausea, vomiting, headache, ataxia, and confusion occur, but focal neurologic deficits are uncommon. Intracranial hypertension may occur. Patients with cysts in the basal cisterns can present with meningeal signs, hydrocephalus, vasculitis, and stroke. Neurocysticercosis may present with altered mental state, migraine headaches, or neurocognitive deficits. Cysticercal encephalitis caused by multiple parenchymal cysts, associated with diffuse cerebral edema, occurs particularly in young girls, and these patients may develop severe neurologic sequelae. Other manifestations include radicular pain or paraesthesiae (spinal cysticercosis) or progressive cord compression. Ophthalmic manifestations include blurred vision, proptosis with restriction of ocular movements, papilledema, atypical optic neuritis, cyst, or nodules in the eye.

Electroencephalography (EEG) may show focal abnormalities, but have generalized abnormalities or are normal. The examination of the cerebrospinal fluid (CSF) may

have mild abnormalities such as elevated protein or pleocytosis often with eosinophils.

Diagnosis

The diagnosis of neurocysticercosis largely depends on neuroimaging. Computerized tomography (CT) is useful for the detection of calcified inactive lesions, but magnetic resonance imaging (MRI) is better for detecting intraventricular or subarachnoid cysts and demonstrating inflammation around cysts. The cysts may be single or multiple, scattered through out the brain, and in different stages. Active cysts are often asymptomatic and appear as rounded, hypodense areas on CT scans and with CSF-like signal on MRI. Sometimes the invaginated scolexes can bee seen as an eccentric mural nodule, which if multiple give rise to the starry night effect, which is pathognomic of neurocysticercosis. When the cyst degenerates, it produces a diffuse hypodense lesion with an irregular border on CT, which enhances with contrast. These appear as low signal areas on T2-weighted MRI images. The dead cyst may not be detectable by neuroimaging, appear as an inactive calcified nodule on CT, or appear low intensity on proton-weighted MRI. Single enhancing lesions on CT scans have increased signal intensity on MRI and may be caused by resolution or calcification. They need to be differentiated from tuberculomas, although abscess, fungal infection, vasculitis, and neoplasia may produce similar appearances.

Immunologic tests are not reliable for the diagnosis of neurocysticercosis. Standard enzyme-linked immunosorbent assay techniques are relatively insensitive and nonspecific. The enzyme-linked immunoelectrotransfer blot assays on blood or CSF have a higher sensitivity and specificity, but these findings vary with region. Other tests include an antigen detection of viable metacestodes in CSF, but this test is not widely validated.

Management

Most active cysts within the CNS are not associated with symptoms, and the cysts usually die within 2 years without any manifestations. In symptomatic neurocysticercosis, the use of cysticidal agents and steroids for epilepsy is controversial. Cysticidal therapy appears to improve the resolution of cysts but has been associated with an exacerbation of neurologic symptoms. There are case reports of severe cerebral edema and death in patients with multiple cysts. Thus, corticosteroids have been suggested to reduce the inflammatory response and prevent the neurologic deterioration, but randomized controlled trials have been inconclusive. The most commonly used cysticidal agents are praziquantel (20 mg/kg/d) and albendazole (10 mg/kg/d) for at least 8 days. Randomized clinical trials of cysticidal drugs have failed to show consistent clinical benefit, and an increase in hydrocephalus and seizure frequency has been reported. The hepatic metabolism of praziquantel is inducible by phenobarbital and phenytoin, which may limit its usefulness, since these drugs are commonly used to control the seizures. The seizures in neurocystercercosis are often controlled with one antiepileptic drug.

Malaria

Plasmodium falciparum is one of the four species that infects humans and is responsible for almost all the severe disease and death related to malaria in the world. Children living in sub-Saharan Africa are exposed to infections from birth and bear the brunt of the morbidity and mortality. The erythrocytic stages of the parasite are responsible for the symptoms. *P. falciparum* is unique in that later erythrocytic stages sequester within postcapillary venules of the deep vascular beds, particularly the brain, which is thought to cause the severe manifestations. The neurologic manifestations of falciparum malaria include seizures, agitation, or coma. The direct CNS involvement of *P. falciparum* is difficult to define since there are no pathognomonic pathologic features. CNS manifestations such as seizures, drowsiness, or flaccidity may be induced by the systemic effects of the falciparum infection (eg, fever or hyponatremia). There are differences in the pathophysiology of severe malaria in children growing up in malaria endemic areas compared with those unexposed to infections (nonimmune).

Seizures are common in falciparum malaria, but the cause is unclear. They are not simply febrile seizures since many of them occur when the child is afebrile, and they are often complicated in that many are repetitive (more than one during the acute illness), focal, or prolonged. They do not appear to be related to electrolyte abnormalities, hypoglycemia, or antimalarial drugs. Cerebral malaria is the most severe neurologic manifestation. The World Health Organization has adopted strict criteria for the diagnosis of cerebral malaria, which are as follows: (1) a patient is unable to localize a painful stimulus (such as pressure on the sternum) at least one hour after last seizure; (2) asexual parasites are present in the peripheral blood; and (3) other causes of encephalopathy (eg, meningitis, encephalitis, or hypoglycemia) are excluded. Although this definition is suitable for research purposes, any child with *P. falciparum* infection and disturbed consciousness should be treated for cerebral malaria.

Clinical Presentation

Falciparum malaria should be suspected in any child who has visited or even transiently landed at an airport in an endemic area within the last 3 months and develops CNS symptoms.

Children with malaria usually have a history of fever, headache, irritability, restlessness, or drowsiness. Vomiting

and to a lesser extent diarrhea are common and may contribute to dehydration or electrolyte depletion. Fever is usually present, although its absence does not exclude the diagnosis. In most children, the temperature is greater than 39°C, often continuous or irregular, and without any definite pattern. Meningism may be present such that cerebral malaria cannot be differentiated clinically from bacterial meningitis. Seizures are common and often precipitate the lapse into coma. Brainstem signs including dysconjugate eye movement and decerebrate posturing occur. Falciparum malaria is associated with a distinctive retinopathy, which includes retinal hemorrhages, retinal whitening, color changes in the vessels, and less frequently papilledema. These features are associated with sequestration in the brain and may help differentiate cerebral malaria from other causes of encephalopathy.

Laboratory Features

The diagnosis of malaria can be made by detecting parasites on a peripheral blood film. The lack of a detectable parasitemia does not exclude the diagnosis of cerebral malaria since the parasites may be sequestered within the deep vascular beds or chemoprophylaxis may have suppressed the parasitemia. Thus, blood films need to be examined every 6 hours for 48 hours to exclude this infection.

Rapid diagnostic tests such as the immunochromatographic test for *P. falciparum* histidine-rich protein 2 and lactate dehydrogenase may be helpful, particularly in the absence of positive blood smear. Parasite messenger RNA or DNA polymerase chain reaction testing is more sensitive than microscopy but is expensive, more laborious, and does not estimate parasite load.

Anemia, usually with evidence of hemolysis (raised unconjugated bilirubinemia, low haptoglobin concentration), is a consequence of the infection. Thrombocytopenia is common but rarely severe enough to cause bleeding. Fibrin degradation products are raised, but laboratory features of frank disseminated intravascular coagulation are uncommon. Hypoglycemia and a lactic acidosis are the major metabolic complications. Hypoxemia is associated with pulmonary edema in nonimmune individuals and chest infections. Renal impairment is common. Hyponatremia is mainly caused by salt depletion, but some cases may be caused by inappropriate antidiuretic hormone secretion. Hypophosphatemia is a feature of severe malaria and may be exacerbated by glucose therapy.

The CSF is usually acellular, and other diagnoses such as encephalitis should be considered if a pleocytosis is found, but cerebral malaria cannot be excluded. CSF lactate concentrations are raised, but total protein and glucose concentrations are usually normal. Blood cultures may detect bacteremia, particularly caused by gram-negative organisms. Concurrent urinary tract infections can occur.

Management

Antimalarial Therapy

Treatment of severe falciparum malaria is complicated by the emergence of parasites that are resistant to antimalarial drugs and the difficulty of obtaining specific antimalarial drugs locally. A combination of antimalarials with different actions should be used in order to prevent the emergence of resistant parasites. This should include a first line parenteral drug, either the cinchinoid alkaloids (quinine, and its diastereomer quinidine) or the artemisinin compounds (Table 87-1). The artemisinin compounds are more parasiticidal but are currently not licensed in North America. Since quinine for intravenous administration is unavailable in the United States, quinidine is used.

The cinchinoid alkaloids are effective against the later erythrocytic stages. Most authorities recommend a loading dose to rapidly achieve high therapeutic levels, but this should be avoided in those children who have been given cinchinoids or mefloquine within the last 24 hours. Side effects are common, particularly cinchonism (tinnitus, hearing loss, nausea, restlessness, and blurred vision). Serious cardiovascular side effects, such as hypotension and cardiac arrhythmias, may occur if the drugs are administered undiluted and too rapidly. The QT interval should be monitored during the infusion.

TABLE 87-1. Parenteral Antimalarial Treatment for Severe Falciparum Malaria

Drug	Route	Loading Dose	Maintenance Dose
Quinidine gluconate	IV	15 mg base/kg (24 mg/kg salt) in normal saline over 4 h or 6.25 mg base/kg (10 mg salt/kg) over 2 h	7.5 mg base/kg (12 mg salt/kg) infused over 4 h, every 8–12 h with electrocardiogram monitoring, then 0.0125 mg base/kg/min (0.02 mg salt/kg/min) as a continuous infusion for 24 h
Quinine dihydrochloride	IV	20 mg salt/kg over 2–4 h	10 mg salt/kg every 8–12 h, until able to take orally
Quinine dihydrochloride	IM	20 mg salt/kg (dilute IV formulation to 60 mg/mL) given in 2 injection sites (anterior thigh)	10 mg salt/kg every 8–12 h, until able to take orally
Artemether	IM	3.2 mg/kg	1.6 mg/kg/d for a minimum of 5 d
Artesunate	IV/IM	2.4 mg/kg	1.2 mg/kg after 24 h, then 1.2 mg/kg/d for 7 d

The artemisinin compounds (artesunate, artemether, and arteether) are fast-acting and act against all blood stages, reducing the time to parasite clearance and fever resolution in comparison with the cinchinoid alkaloids. Artesunate is the favored drug since it can be administered intravenously or intramuscularly, is associated with less neurotoxicity in animal models, and has reduced mortality in adults with severe malaria.

Other Antimalarial Drugs

Currently, other antimalarial drugs should be combined with parenteral antimalarials to prevent the emergence of resistant parasites. They can be used in parasites that are relatively resistant to the cinchinoids, to shorten the course of therapy, or for the treatment of nonsevere falciparum malaria. Atovaquone-proguanil (Malarone) and mefloquine can be used, although parasite resistance is increasing to the latter and it should not be used alone in the treatment of severe falciparum malaria. Likewise, the spread of resistance to the sulfonamides (sulfadoxine, sulfalene, and cotrimoxazole) has limited their usefulness. Halofantrine is an effective drug, but the likelihood of cardiovascular toxicity has limited its use. Antibiotics (clindamycin) are effective against the blood stages but should not be used as primary antimalarial drugs.

Supportive Treatment

Supportive treatment is important in children with severe malaria since most children die within 24 hours before the antimalarials have had time to work. Children with severe falciparum malaria should be monitored closely. Blood glucose and fluid balance should be measured every 6 hours and parasitemia and hematocrit every 12 hours. Electrolytes, tests of renal function, albumin, calcium, phosphate, and blood gases should be performed at least daily during the acute stages.

Hyperpyrexia should be treated with standard modalities for lowering temperature, although paracetamol (acetaminophen) is associated with decrease parasite clearance. Fluid balance is critical in severe malaria, as many children are hypovolemic, but over aggressive fluid therapy can precipitate pulmonary edema and aggravate intracranial hypertension. Renal function needs to be carefully monitored because acute renal failure is a common cause of death in nonimmune patients. Patients with pulmonary edema or adult respiratory distress syndrome require supplemental oxygen and positive pressure ventilation, with positive end expiratory pressure to maintain adequate oxygenation, and diuretics or hemofiltration to correct the fluid overload.

Blood transfusions should be considered when the hematocrit falls toward 20% or the child has evidence of cardiovascular compromise. The role of exchange transfusions in the management of cerebral malaria is controversial, but most authorities recommend exchange transfusion in patients who have a parasitemia in excess of 10% or who are deteriorating in spite of conventional treatment.

Seizures must be treated promptly, and a prophylactic anticonvulsant such as phenytoin or phenobarbital should be used if they recur. A CT or MRI scan should be performed to exclude brain swelling before a lumbar puncture is performed. If brain swelling is detected, intracranial pressure monitoring should be considered. Steroids appear to be deleterious, increasing the incidence of bleeding without any beneficial effect on outcome.

Secondary bacterial infections should always be suspected. Blood, urine, and CSF should be sent for culture, and repeated examinations of the chest should be performed since aspiration or hypostatic pneumonia is common. Broad-spectrum antimicrobial treatment should be started as soon as a complicating infection is suspected.

Outcome

The mortality of cerebral malaria in nonimmune individuals ranges from 15 to 26%, with patients usually dying within the first 4 days of the illness, often from renal failure or pulmonary edema. African children have the same mortality but die from acidosis or brain stem herniation.

Neurologic sequelae occur in about 5% of nonimmune individuals and include cranial nerve lesions, extrapyramidal tremor, polyneuropathy, epilepsy, or psychiatric manifestations. In African children, sequelae are more common and more severe. Hemiparesis, ataxia, and cortical blindness are the most common sequelae, but some children are left in a vegetative state. Impairment of a wide range of cognitive functions has been documented, particularly in memory, executive functions, and language.

Tetanus

Tetanus is caused by toxins produced by *Clostridium tetani* and is characterized by increased muscular tone and spasms. It occurs in two different clinical situations, neonates (neonatal tetanus) and older children and adults (nonneonatal tetanus). Tetanus toxoid has almost eliminated tetanus from many countries; however, this condition is still seen in many parts of the developing world.

As the *C. tetani* grows, it produces at least two exotoxins: tetanospasmin and tetanolysin. Tetanospasmin produces the clinical manifestations of tetanus by inhibiting neurotransmitter release from a presynaptic terminal of nerves. The lack of inhibitory control on the α motor neurons promotes sustained excitatory discharge causing the motor spasms. The toxin exerts its effects on the muscles,

neuromuscular junctions, peripheral nerves, spinal cord, and the brain stem. Autonomic dysfunction with labile hypertension, tachycardia, tachyarrhythmias, vasoconstriction, and sweating is common in severe cases. Profound bradycardia and hypotension may also occur and are often preterminal events.

Clinical Features

Tetanus is a clinical diagnosis that is made easily in areas where it is seen frequently. The route of entry in neonatal tetanus is the umbilical cord, while in nonneonatal tetanus, wounds on the lower limbs, compound fractures, and nonsterile intramuscular injections. It can also follow procedures such as scarification, earpiercing, circumcision, dental procedures, or infections, eg, otitis media. Often, the route of entry is not identified.

Neonatal Tetanus

Neonates with tetanus present a median 6 (range 3–10) days after birth with refusal to feed, mainly due to difficulty in opening the mouth. Thereafter, sucking stops and "risus sardonicus" may develop. The hands often become clenched, the feet dorsiflexed, with increased tone, progressing to rigidity and opisthotonus. Spasms of the limbs develop early but become generalized, occurring spontaneously or provoked by touching the body, sound, or light.

Mortality is high, with 65% neonates dying in hospitals who lack facilities for ventilation, but if ventilation and intensive care are available, the mortality decreases to 22%. The infants may require ventilation for up to 2 months. Factors associated with a poor prognosis include onset of symptoms within the first 6 days of life, low birth weight (especially < 2.5 kg), and recurrent apnea. In neonates who survive, microcephaly, mild neurologic, developmental, and behavioral problems have been reported.

Nonneonatal Tetanus

The incubation period is usually 4 days to 3 weeks after the insult. The first symptom is often inability to open the mouth fully owing to rigidity of the masseters (trismus or lockjaw). Pain, headache, stiffness, rigidity, opisthotonus, laryngeal obstruction, and spasms may follow. The spasms may be precipitated by stimuli such as noise, touch, and/or bright light but also occur spontaneously. The spasms are most prominent in the first 2 weeks and are very painful. Dysphagia can occur. Autonomic dysfunction (labile blood pressure especially hypertension, tachyarrhythmias, hyperpyrexia, and hypersalivation) usually starts some days after the spasms and reaches a peak during the second week of the disease. The condition tends to improve thereafter, but the rigidity may last beyond the duration of both spasms and autonomic disturbance, for up to 6 weeks. Tetanus can be localized at the site of injury causing local rigidity and pain. This form has the lowest mortality, although cephalic tetanus (in which the cranial nerves, especially VII nerve, are effected) is a local form with a higher mortality.

Mortality varies from 20 to 50%, with the lowest mortalities occur in hospitals that can perform tracheostomies and/or provide ventilation. The commonest cause of death is respiratory failure (secondary to uncontrolled spasms), autonomic dysfunction, and septicemia. In those who survive, most patients do not have any sequelae, but others have contractures, chest deformities, seizures, myoclonus, and the consequences of hypoxia.

Diagnosis

Tetanus is a clinical diagnosis since *C. tetani* is difficult to culture, a positive result does not indicate if the organism contains the toxin producing plasmids, and *C. tetani* may be present without disease in patients with protective immunity. The differential diagnosis includes strychnine poisoning, drug-induced dystonic reactions (phenothiazines), rabies, orofacial infection, and hysteria. Patients who present with stiff necks are often thought to have meningitis. In neonates, birth asphyxia, hypocalcaemic tetany, and seizures can sometimes cause confusion.

Management

The main aims of management are to support the patient during the time it takes for new vesicles to replace those that the toxin is bound.

Nursing Care

Good quality nursing is important to reduce stimuli that may precipitate spasms (nursing in a quiet, darkened environment, limiting physical contact with the patient).

Treat the Infection

Benzyl penicillin is most often used to kill *C. tetani*, but since it may aggravate the condition, Metronidazole is often used. Antimicrobial sensitivity patterns of clinical isolates of *C. tetani* are often unknown, but erythromycin, vancomycin, and clindamycin may kill the bacteria.

Neutralize the Toxin

Tetanus immunoglobulin shortens the course and may reduce the severity of tetanus. Human antiserum is the preferred choice and has a half-life of 25 to 32 days. The antiserum will neutralize only the circulating and unbound toxin, but it should be administered to all patients with tetanus. It should be administered intravenously, and it is unclear if there is an advantage in administering it at the site of entry or intrathecally. The side effects of immunoglobin include acute anaphylactic reactions or delayed serum sickness. Active vaccination needs to be started in patients not

previously vaccinated, with the toxoid and the human (or equine) antitetanus immunoglobulin administered at different sites on the body to prevent interaction at the injection site. If both are to be administered together no more than 1,000 IU human should be administered, higher doses can neutralize the immunogenicity of the toxoid.

Reduction of Spasms and Respiratory Complications

Sedation is useful for controlling spasms and rigidity. Benzodiazepines are the most commonly used as a sedative and muscle relaxant, as they compete with an endogenous inhibitor at the gamma-aminobutyric acid $(GABA)_A$ receptor. Midazolam is the benzodiazepine of choice. Propofol can be used. Phenobarbitone and phenothiazines are commonly used as sedatives, despite the lack of controlled trials. Chlorpromazine acts on the reticular activating system, and whereas in moderate doses, it can reduce muscle spasm, and in high doses, it may aggravate the condition. Paralysis and ventilation significantly improve the outcome of tetanus. Pancuronium and tubocurarine are often used as long acting muscular relaxants, but since pancuronium inhibits catecholamine reuptake, it could worsen autonomic instability in severely affected patients. Other muscular relaxants used include alloferin (used in neonates), alcuronium, vecuronium (less cardiovascular side effects, but short acting), or rocuronium. Ventilation is necessary when the patient is paralyzed with the above drugs. Intermittent positive pressure ventilation with positive end expiratory pressure is often required. Other modes of respiratory support, eg, continuous positive airway pressure may be useful when the sedation has been reduced, particularly in the later stages, since they will optimize respiratory pattern, minimize muscle wasting, and reduce the likelihood of acquired critical illness neuropathy or myopathy. Elective tracheostomy can prevent death from laryngeal spasm but is often not used in neonates since it is associated with hemorrhage, creation of a false passage, surgical emphysema, and hematoma leading to asphyxia and tracheal stenosis.

Cardiovascular Complications

Autonomic perturbations are difficult to control Adrenoceptor blocking drugs, such as propranolol, betanidine, or labetolol, appear not to reduce mortality. Esmolol, an ultrashort-acting β-blocker, may have advantages over other drugs. Morphine is found to be useful by some authors. Oral clonidine and epidural or spinal bupivacaine may also be useful, but these treatments have not been properly assessed. Blockade of the parasympathetic nervous system has been suggested with high doses of atropine.

Provide Fluids and Calories

Tetanus is associated with an increase in energy and fluid demands (muscular contractions, excessive sweating, and sepsis). Weight loss is almost inevitable. Enteral feeding should be started as soon as possible but can be difficult if the spasms are uncontrolled. Parenteral feeding is rarely available and associated with many complications. Percutaneous endoscopic gastrostomy may be useful.

Other Complications

The other common complications in tetanus are often attributable to prolonged periods in intensive care or the force of the spasms. They include secondary infections (particularly of the respiratory tract, urinary tract (catheterization), or wound sepsis), thromboembolism, and rhabdomyolysis. Other treatments such as magnesium sulphate, pyridoxine (enhances the production of GABA), and corticosteroids have not been adequately tested.

Poliomyelitis

Although there has been a concerted effort to eradicate poliomyelitis from the world, and it is now rare in industrialized countries, there are still outbreaks in Asia and Africa. Poliomyelitis is caused by polioviruses type 1, 2, and 3 which are ingested and multiply in the tonsils and the Peyer's patches of the gut. In most cases, the infection is asymptomatic. In a minority of children, a viremia will cause nonspecific symptoms of nausea, vomiting, abdominal pain, and sore throat. Others may develop CNS complications after an incubation period of 10 to 14 days, which are classified as nonparalytic or paralytic poliomyelitis. In nonparalytic poliomyelitis, the child develops fever, headache, 2 to 5 days later signs of meningeal irritation, and severe pain and stiffness of the neck, back, and limbs. The CSF shows a polymorphonuclear leukocytosis, but the glucose is normal and protein normal or slightly elevated. Poliovirus can be cultured from the stool and throat. In paralytic poliomyelitis, the paralysis occurs within the first 2 days of the onset of the febrile illness and can affect any muscles but particularly those of the lower limbs. The paralysis is characteristically asymmetric with the flaccid muscles and absent tendon reflexes. Sensation is intact. The paralysis is maximal within 3 to 5 days of onset and rarely extends once the temperature is settled. In the bulbar form, involvement of the cranial nerve nuclei and vital centers in the brain stem results in paralysis of the facial, pharyngeal, laryngeal, and tongue muscles, causing swallowing difficulties and aspiration. Hypertension and respiratory failure may also occur and prove fatal.

Diagnosis

The CSF initially shows a leukocyte predominance but after 5 to 7 days is mainly lymphocytic. Virus can be isolated from throat and stool for up to 3 months after the onset. The differential diagnosis includes other causes of acute flaccid paralysis.

Management

There is no specific treatment.

Supportive Care

Bed rest is mandatory, with the avoidance of injections and exercise during the acute phase. Analgesics are given for the severe pain. Paralyzed muscles should be kept in neutral position to prevent contractures. Gentle passive exercises and warm compresses help relieve the pain. Active exercises are introduced when the temperature has settled for a few days. Respiratory paralysis will require ventilatory support and bulbar paralysis, nasogastric tube feeding, and possibly tracheostomy. During the convalescent phase, the aim is to improve motor function and prevent deformities. The services of orthopedic surgeons and orthoptists may be required.

Prognosis

The prognosis depends on the extent of involvement and quality of care during the acute phase. Early identification of and intervention for respiratory and bulbar paralysis will reduce mortality to 5 to 10%. With appropriate physiotherapy, improvement in function of paralyzed muscles can occur for up to 18 months. Factors that adversely affect outcome are injections into muscles, muscle fatigue, corticosteroid therapy, and other immunocompromised states. Removal of tonsils and teeth during the incubation period increases the risk of bulbar paralysis.

Subacute Sclerosing Pan Encephalitis

Subacute sclerosing pan encephalitis (SSPE) is caused by the persistence of measles virus in the CNS. Although SSPE most commonly occurs after a measles infection, it can occur following measles vaccination. The clinical symptoms usually develop insidiously 4 to 8 years following the infection. The initial symptoms are subtle and include declining school performance, intellectual deterioration with loss of memory and language impairment, changes in behavior (particularly withdrawal and irritability), and an altered sleep pattern. Thereafter, myoclonic jerks develop, sometimes in association with seizures, and there is a marked deterioration of motor function. Extrapyramidal features and visual loss can occur. In the later stages of SSPE, the myoclonic jerks may disappear as the child looses cognitive functioning, sphincter control, and lapses into coma. The rate of progression may vary, and the symptoms may fluctuate, but most die within 1 to 3 years of the onset of symptoms. Some children have a more fulminant course, dying within months.

The diagnosis is based on finding raised measles antibody titer in the CSF. The EEG during the myoclonic phases is characterized by episodes of burst suppression in which high amplitude slow and sharp waves occur at intervals of 3 to 5 Hz on a slow background. MRI scans show focal T-2 intensity white matter signals, followed by atrophic changes. In the later stages, there is significant loss of white matter with involvement of the basal ganglia. The MRI changes do not appear to reflect the clinical stage.

The management of SSPE includes treatment of the myoclonic jerks and seizures and medication that interferes with the degenerative process. The myoclonic jerks appear to be resistant to treatment, although trihexyphenidil appears to be useful. Isoprinosine and interferon α are the drugs that have been most used to prevent progression, but the results of a multicenter trial did not show any benefit in terms of survival or neurologic impairment. However, further data suggests that isoprinosine may be useful in slowing the progression.

Neurobrucellosis

Brucellosis is still endemic in many parts of the world and is often acquired by contact with infected animals (mainly cattle, sheep, goats, dogs, or pigs) or ingestion of unpasteurized milk. It usually causes a nonspecific febrile illness, which waxes and wanes (undulant fever), often with arthralgia. It affects many organs of the body, but in children, CNS involvement is rare. Brucella can cause meningoencephalitis, brain abscess, cranial nerve palsies (particularly VIII nerve), myelitis, radiculitis, and a polyneuropathy. Most reports of children describe presentation with features of meningoencephalitis. However, brucella also causes poor concentration, depression, and chronic fatigue. The CSF often has a pleocytosis with raised protein but normal glucose. *Brucella* sp are difficult to culture, but cultures of blood or bone marrow may isolate the organism. The diagnosis is usually made on a rising titer in serologic tests, particular the brucella microagglutination test or brucella specific ELISA. Brucella antibodies may also be found in the CSF.

The treatment of brucellosis varies with age and country. In general, children younger than 10 years should be treated with trimethoprim/sulfamethoxazole (10 mg/d of trimethoprim IV or PO) and rifampicin (20 mg/kg/d divided into 2 doses) for at least 4 weeks. Tetracyclines may be used in older children instead of trimethoprim/sulfamethoxazole and streptomycin or gentamicin can be used instead of rifampicin.

Suggested Readings

Campbell C, Levin S, Humphreys P, et al. Subacute sclerosing pan encephalitis: results of the Canadian Paediatric Surveillance Program and review of the literature. BMC Pediatr 2005;5:47.

Hsu SS, Groleau G. Tetanus in the emergency department: a current review. J Emerg Med 2001;20:357–65.

Idro R, Jenkins N, Newton CRJC. Cerebral Malaria. Lancet Neurol 2005;4:827–40.

Singhi P, Singhi S. Neurocysticercosis in children. J Child Neurol 2004;19:482–92.

Practitioner and Patient Resources

Center for Disease Control

Atlanta, USA
Traveler's advice: <http://www.cdc.gov/travel>
Information about malaria: <http://www.cdc.gov/Malaria/diagnosis_treatment/tx_clinicians.htm>
World health Organization traveler's advice: <http://www.who.int/ith/en/>

Chapter 88

Neonatal Seizures

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Seizures are a common manifestation of neurological dysfunction in the newborn. Their clinical seatures may be subtle, and electroencephalography is often required to confirm the diagnosis. Management involves urgent maintenance of hemodynamic and respiratory functions, identification and treatment of the underlying cause, and pharmacologic treatment of the seizures.

Seizures are the most easily recognized manifestation of neurologic disease in the newborn. Their detection and management is important for two major reasons: a) seizures in this age group are symptoms of an underlying neurologic disease that may require specific treatment; and b) both animal and human studies suggest that, at least in certain circumstances, seizures in the newborn may cause or worsen brain injury.

Seizures occur much more commonly in the newborn than in the infant and older child. The incidence has been reported to be 2 to 3 per 1,000 live births in term newborns, 10 to 15 per 1,000 in preterm newborns, and more than 50 per 1,000 in those weighing less than 1,500 g. However, these data are based on clinical diagnosis of seizures and may underrepresent the true incidence as electroencephalographic seizures are often associated with no clinical signs, particularly in the very immature newborn.

The clinical manifestations of neonatal seizures are more subtle and less well organized than in the infant or older child. These differences relate to the relative immaturity of the brain at birth. Much of cortical organization and myelination occurs after birth. In addition, the rates of development of excitatory and inhibitory neurotransmitters differ. Excitatory activity, mediated primarily by glutamate, is observed early in development at which time inhibitory systems are relatively underdeveloped. Furthermore, the action of GABA at the $GABA_A$ receptor results in excitation rather than inhibition at early stages of brain development. Consequently, the clinical assessment and management of neonatal seizures present different challenges from those in the older child, and only limited inferences can be drawn from studies in older children.

Seizure Characteristics

Neonatal seizures can be categorized as subtle, focal or multifocal clonic, focal or generalized tonic, and myoclonic (Volpe). The motor manifestations are often more disorganized than in older children, and both generalized tonic clonic seizures and partial seizures with secondary generalization are rare. Focal clonic seizures occur more often in the term infant, whereas tonic and myoclonic seizures occur in both term and preterm infants. However, this may reflect the association of cerebral infarction with focal clonic seizures and of intraventricular hemorrhage (IVH) with tonic seizures.

Neonatal seizures are often subtle and can be difficult to recognize, particularly in preterm infants. These subtle seizures may manifest as bicycling or pedaling movements, blinking, sustained eye opening, ocular fixation, lip smacking, chewing, and autonomic phenomena, eg, tachycardia, increase in blood pressure, apnea, cutaneous vasomotor modification, pupillary change, salivation, or drooling. Stimulation of the inferior colliculus and midbrain in animals has resulted in complex motor automatisms similar to subtle seizures in human newborns, and it has been suggested that some subtle seizures may have a subcortical origin. This may be a factor in the absence of electroencephalographic abnormalities in some neonatal seizures, particularly those in the preterm newborn.

It may be difficult to distinguish normal motor activity in the newborn from a seizure, eg, roving eye movements or sucking movements can be mistakenly diagnosed as a seizure. The most easily confused movement is jitteriness that is frequently observed in newborns with hypoxic-ischemic encephalopathy, hypocalcemia, hypoglycemia, and drug withdrawal. Volpe has suggested clinical features that may help to distinguish rhythmic movements from a seizure. Jitteriness is a rhythmical, repetitive movement that is exquisitely stimulus, sensitive, and ceases with passive restraint or repositioning. In contrast, a clonic seizure has a fast and slow component and is often associated with eye fixation or deviation and autonomic changes. Benign neonatal sleep myoclonus is also relatively common, presents usually during the first week of life with paroxysmal myoclonus, and disappears spontaneously over weeks or months. The myoclonus may appear quite striking but appears only during quiet sleep and can be precipitated and increased by tactile stimuli or restraint. The neurologic examination is normal, and the electroencephalogram (EEG) demonstrates no correlate during the jerks.

Etiology

Table 88-1 lists the causes of seizures in the newborn period. In the development of an initial differential diagnosis, it is important to consider particularly the more common causes and those that may require specific treatment to prevent further brain injury. The time of onset of the seizures is often the most important clue to the etiology (see Table 88-1). Hypoxic-ischemic brain injury is the most common cause during the first 24 hours. Similarly, unilateral cerebral infarction presents in the first or second postnatal day, usually with focal clonic seizures. Bacterial meningitis and intrauterine infections usually present in the first 72 hours, although herpex simplex virus (HSV) encephalitis transmitted during delivery is usually only symptomatic after the end of the first week. Developmental brain abnormalities, intracerebral hemorrhage, and familial neonatal seizures can present either early or late. Certain inborn errors of metabolism, such as nonketotic hyperglycinemia, present in the first two days, but many other amino acidopathies or organic acidurias often do not manifest until feeding has been established.

Hypoxic-Ischemia

Hypoxia-ischemia is the etiology in 60% of newborns with seizures and may occur before, during, or following delivery. Intrapartum asphyxia is usually associated with a history of fetal distress, a low 5-minute Apgar score, metabolic acidosis, and altered neurologic state in the first day. Seizures usually occur in the setting of moderate to severe encephalopathy. Affected babies are hypotonic and may have altered deep tendon reflexes and cranial nerve abnormalities. Evidence of ischemic injury to the liver, kidneys, heart, and gut may be demonstrated biochemically. Seizures tend to be clonic or multifocal and appear in the first 12 hours in 50% of the infants.

TABLE 88-1. Causes of Neonatal Seizures

Hypoxic-ischemic encephalopathy*
Cerebral infarction
Intracranial hemorrhage
Germinal matrix-intraventricular
Subarachnoid
Subdural
Intracranial infection*
Bacterial meningitis
Viral encephalitis
Metabolic disturbance
Hypoglycemia*
Hypocalcemia
Hypo/hypernatremia
Local anesthetic toxicity*
Drug withdrawal
Developmental brain abnormality
Inborn errors of metabolism that require urgent specific treatment
Early onset pyridoxine-dependent seizures
Pyridoxine phosphate oxidase deficiency
Folinic acid responsive seizures
Glucose transporter disorder
Biotinidase deficiency
Other inborn errors of metabolism
Nonketotic hyperglycinemia*
Transient neonatal hyperglycinemia
Sulfite oxidase deficiency and molybdenum cofactor deficiency
Multiple carboxylase deficiency
Pyruvate dehydrogenase deficiency
Glutaric aciduria type 2
Cytochrome-c oxidase deficiency
Epileptic syndromes
Benign familial neonatal convulsions
Benign neonatal convulsions
Early myoclonic encephalopathy
EIEE

Causes in italics require specific treatment.

*These etiologies often manifest with seizures on day 1.

Cerebral Infarction

Focal seizures are the most common sign of arterial stroke, the second most common cause of neonatal seizures (15%). The majority of infants demonstrate a focal motor abnormality but are not encephalopathic. In cerebral vein thrombosis, lethargy may be the only feature, but seizures occur eventually in 60%.

Intracranial Hemorrhage

IVH may present with seizures, usually generalized tonic, when the hemorrhage involves the brain parenchyma or

the IVH is extensive. IVH and seizures occur earlier in full term (first 24 h) than in premature babies (24–72 h). Subarachnoid hemorrhage can present with seizures that occur usually on the second day of life in an otherwise healthy looking term baby.

Infections

Bacterial meningitis may present at any time in the newborn period, requires specific antibiotic treatment, and should always be considered in newborns presenting with seizures. The most common bacterial pathogens in this age group are group B *streptococcus*, *listeria monocytogenes*, and *Escherichia coli*. Seizures due to intrauterine infections present usually during the first 3 days of life, but seizures due to intrapartum-acquired HSV infection occur typically in the second week.

Metabolic Disturbances

Hypoglycemia, hypocalcemia, hypomagnesemia, and hyper/hyponatremia may present with neonatal seizures. Hypoglycemia is more likely to cause seizures in newborns that are small for gestational age than in infants of diabetic mothers. Animal studies have demonstrated that the seizure per se will result in a further decrease in brain glucose, which may exacerbate the brain injury in other disorders such as hypoxic-ischemic brain injury and bacterial meningitis. Consequently, blood glucose requires to be monitored in these conditions and hypoglycemia treated promptly. Hypocalcemia may present at under 72 hours, particularly in newborns with low birth weight, perinatal asphyxia, or maternal diabetes. Onset, later in the first week of life, has occurred largely due to the use of improper milk formula. Hypomagnesemia, if present, should be treated along with hypocalcemia.

Local Anesthetic Toxicity

Local anesthetic intended for mother may be injected directly into the newborn, who can present with meconium staining, flaccidity, apnea, and seizures. The diagnosis is suggested if there are cranial nerve abnormalities, cardiac arrhythmias, or a history of absence of pain relief in the mother. Diuresis and acidification of the urine facilitate recovery.

Abnormalities of Brain Development

Disorders of neuronal migration or organization may be the cause of neonatal seizures. Only the larger abnormalities may be identified on computed tomography (CT) or magnetic resonance imaging (MRI) head scan in the newborn period. When these abnormalities present with neonatal seizures, the prognosis for seizure control and neurologic development is very poor.

Inborn Errors of Metabolism That Require Early Treatment

Early onset pyridoxine dependency, pyridoxine phosphate oxidase deficiency, folinic acid reponsive seizures, and glucose transporter deficiency are disorders in which delay in treatment can result in permanent brain injury. Seizures due to pyridoxine dependency in the newborn occur usually in the first 2 days. Low Apgar scores and encephalopathy are observed in many affected children, and this disorder may mimic hypoxic-ischemic encephalopathy. The diagnosis can be confirmed by measurement of pipecolic acid and/or α-aminoadipic semialdehyde in the blood and/or cerebrospinal fluid (CSF). Pyridoxine phosphate oxidase catalyzes the conversion of pyridoxine phosphate to pyridoxal phosphate and a deficiency may present with features similar to early pyridoxine dependency. The seizures in pyridoxine phosphate oxidase deficiency respond to oral or nasogastric pyridoxal phosphate but not to pyridoxine. This disorder is extremely rare, and it is not clear whether early treatment improves the very poor prognosis. Folinic acid responsive seizures are less common than pyridoxine dependency. The diagnosis can be confirmed in patients who respond to treatment by analysis of CSF biogenic amines. Glucose transporter deficiency presents very rarely in the newborn period but should be suspected if the CSF glucose level is low and CSF:blood glucose ratio is < 0.4. Severe biotinidase deficiency may manifest with neonatal seizures usually in association with profound hypotonia and urine organic acid abnormalities.

Other Inborn Errors of Metabolism

Neonatal seizures may be a manifestation of other inborn errors of metabolism that do not respond to a specific treatment (Table 88-1). However, it is important to establish the correct diagnosis for genetic counseling.

Epileptic Syndromes

Benign neonatal convulsions occur usually between the 4th and 6th days of life in term infants, who appear otherwise neurologically normal. They are usually brief, focal clonic seizures that often recur frequently over a 24-to 48-hour period. It is a diagnosis of exclusion.

Benign familial neonatal convulsions are due to mutations in potassium channel subunit genes that are inherited in an autosomal dominant fashion. The seizures present in otherwise normal infants, usually in the first 2 weeks of life but occasionally as late as 3 months of age. The seizures are brief but may occur between 20 and 30 times per day. They start with a tonic component, followed by various autonomic and motor changes, which can be unilateral or bilateral. The seizures usually remit by 16 months of age.

Early myoclonic encephalopathy present in the first 3 months, usually in the newborn period, with myoclonic and partial seizures. Tonic spasms may occur later. The EEG is characterized by burst suppression that is more apparent in sleep and which may not be present at the onset of the epilepsy. There is a high incidence of familial cases, and inborn errors of metabolism are the most commonly recognized etiology, although the underlying cause is not demonstrated in most infants. MRI head scan is usually normal in the newborn period. This syndrome is associated with a very poor neurologic prognosis.

Early infantile epileptic encephalopathy also present in the first 3 months, usually in the newborn period. It is characterized by tonic spasms and partial seizures, but myoclonic seizures are rare. There is a pattern of burst suppression on the EEG, which is present from the onset of the epilepsy in both the waking and sleep state and which disappears by 6 months of age. Malformations of the brain are the most commonly recognized etiology. The seizures are usually intractable and often progress to spasms. The prognosis for normal neurological development is very poor.

Investigations

Investigation and management of neonatal seizures should be concurrent, and diagnostic tests should not delay treatment. The initial investigations should include a complete blood count, and blood for glucose, electrolytes, calcium, magnesium, urea, liver enzymes, lactate, and capillary blood gas. Blood, urine, and CSF should be sent for culture and sensitivity. The CSF should also be sent for cell count, glucose, protein, lactate and some saved for further metabolic studies. CSF PCR for herpes virus should also be done unless the cause of the seizure is evident. Other investigations are determined by the differential diagnosis developed from the history and clinical examination. Inborn errors of metabolism are relatively rare causes of seizures in neonates (see Table 88-1). If seizures are difficult to control and the etiology is not clear, there should be a more thorough metabolic investigation. This will involve blood lactate, pyruvate, ammonia, uric acid, biotinidase, amino acids, and very long chain fatty acids. Urine should be sent for organic acids, sulfite, and CSF for glucose, pyruvate, lactate, and amino acids.

The major roles of EEG in the newborn are as follows: to determine whether subtle clinical features are seizures; to determine whether a paralyzed infant is having seizures; to determine whether a newborn whose clinical seizures have responded to treatment is continuing to have electrical seizures; and to assist in prognosis. It is important to appreciate that absence of an EEG correlate does not preclude the event being a seizure. However, most seizures are associated with an EEG correlate, and EEG is particularly useful in the paralyzed newborn and in the newborn in whom clinical seizures are no longer apparent following treatment. Thus, video-EEG studies have demonstrated that many newborns that respond clinically to phenobarbital continue to have subclinical seizures (electroclinical dissociation). The diagnosis of subclinical seizures may be important in that preliminary studies have suggested that their treatment may be associated with a lower incidence of later epilepsy. A randomized study of the effectiveness of treatment of subclinical neonatal seizures is underway (De Vries). The ideal approach would be continuous EEG monitoring on a 24 hour basis, but the manpower and equipment requirements are formidable. Amplitude-integrated EEG (aEEG) has been used to monitor continuously a single or dual channel, usually from a pair of biparietally placed electrodes. Despite the inherent limitations of EEG measurements from a single channel, aEEG is fairly reliable in recognition of background abnormalities, which are of prognostic significance, and, in experienced hands, detects most seizures in newborns with hypoxic-ischemic encephalopathy. In neonatal units that do not have continuous video-EEG facilities, aEEG may help to increase the number of subclinical seizures that are recognized and assist in management. It is important to appreciate that aEEG does not supplant conventional EEG, and indeed, units experienced in aEEG have observed that its introduction has resulted in increased use of conventional EEG. The best results appear to be obtained in those units in which neonatologists work closely with neurologists and electroencephalographers.

Brain imaging plays an important role in determination of the etiology of newborn seizures. A head ultrasound may exclude major IVH or ventriculomegaly, but a brain CT or MRI is preferable.

Management

Rationale for Treatment

Although the immature brain appears more resistant to seizure-induced neuronal death, animal studies suggest that repeated seizures may cause brain injury, and that the risk is greater in the presence of a preexisting insult, eg, asphyxia or hypoglycemia. Energy metabolism is compromised during a neonatal seizure, and brain glucose levels fall rapidly to nearly undetectable levels by 30 minutes. Animal studies have also demonstrated that prolonged seizures in the developing brain result in synaptic reorganization, reduced cell numbers, and decreased plasticity. Studies suggest that seizures are particularly detrimental in the setting of hypoxic-ischemic brain injury. Although these changes have not been proven to occur in

humans, observations with phosphorous and proton MR spectroscopy suggest that seizures in the newborn impair brain metabolism and should be prevented because of the risk of brain injury from the seizures themselves.

Who to Treat

An EEG should be ordered when the newborn has an episode suggestive of an epileptic seizure, and if available, aEEG should be correlated with the EEG. However, EEGs and the necessary expertise in newborn EEG interpretation are not always available when seizures occur. This emphasizes the importance of recognizing the clinical features that distinguish between epileptic and nonepileptic phenomena in the newborn and the potential for aEEG. Treatment should be instituted while the EEG is awaited for all clinically definite seizures and for all clinically probable episodes that are repeated or prolonged.

How to Treat

Seizures may disturb the hemodynamic and respiratory functions of the newborn and lead to further brain injury. Ensuring adequate ventilation and cerebral perfusion is important. Seizures may also result in cerebral energy depletion and compromise further the immature brain. Consequently, blood glucose should be monitored regularly and hypoglycemia corrected.

Neonatal seizures are often a manifestation of an acute brain injury. It is particularly important to consider those conditions in which delay in instituting specific treatment may result in further brain injury (see Table 88-1). CNS infection must always be suspected in newborns with seizures. Antibiotics should be started as soon as blood cultures are obtained and maintained until blood and CSF culture results are available. Unless the cause is obviously not CNS infection, it is important to treat with acyclovir and to perform PCR for HSV because specific IgM may not be detected for up to 3 weeks. Up to 30% of newborns with pyridoxine responsive seizures present with clinical and EEG features suggestive of hypoxic-ischemic encephalopathy. Consequently, treatment should be considered in newborns when the seizures do not respond to the first two antiepileptic drugs, and the etiology is not established. Intravenous pyridoxine is administered optimally with simultaneous EEG recording, but treatment should not be delayed if an EEG cannot be performed. Intravenous or oral pyridoxine (30 mg/kg/d) should be administered on three consecutive days. Both intravenous and oral pyridoxine challenges have resulted in respiratory depression and encephalopathy in newborns with pyridoxine dependency, and treatment should only be performed in an intensive care setting. Pyridoxine should not be withdrawn in patients who respond to treatment, but the diagnosis should be established by measurement of blood and/or CSF biomarkers (see above). Pyridoxal phosphate (30 mg/kg/d) should be given enterally to those newborns who continue to have seizures after 3 days of pyridoxine and in whom the etiology is not established. Thereafter, folinic acid (3 mg/kg/d) should be added if the seizures persist after a further 3 days. Glucose transporter deficiency presents very rarely in the newborn period but is responsive to the ketogenic diet and should be considered if the CSF: blood glucose ratio is less than 0.4. Treatment with biotin (5 mg/d) is usually restricted to those in whom the diagnosis of biotinidase deficiency has been established.

Seizures in the newborn period are less responsive to conventional antiepileptic drugs than in older children. Antiepileptic drug therapy is largely empirical and based on limited data. Drug dosages that have been used in newborns are listed in Table 88-2. Although phenobarbital has traditionally been the first-line drug in treatment of neonatal seizures, Painter and colleagues demonstrated in a randomized study that phenobarbital and phenytoin were equally effective. Just under half of the infants responded to the first drug used, and only 60% responded to the combination of both drugs. Both diazepam and lorazepam have long half-lives in the newborn, which complicate their administration as continuous infusion and limit their use to single or repeated doses. Lorazepam is preferable to diazepam because a) it has a smaller volume of distribution, which results in higher brain concentrations for longer periods, b) it is less likely to produce respiratory depression and hypotension, and c) it does not involve the administration of benzoate, which uncouples the bilirubin-albumin complex and may increase the risk of kernicterus. Thus, several doses of intravenous lorazepam may be sufficient to control seizures during the first few days when the newborn is at greatest risk of seizures. Midazolam has a short half-life that makes it more suited to continuous infusion. However, there are limited data on its use in the newborn, although it was reported to be effective in controlling EEG-confirmed seizures in all 13 children who did not respond to phenobarbital in a retrospective study (Castro Conde). In addition, midazolam may result in paroxysmal movements in the newborn, which can be mistaken for seizures and lead to excessive use of antiepileptic drugs.

The limited success of the present antiepileptic drugs emphasizes the importance of considering new treatments. Lidocaine has been used in Europe for many years and the limited studies suggest that it may be effective. Seizure control was reported in over 80% of newborns in two observational studies of refractory seizures. Lidocaine has a narrow therapeutic range, and 10 of 207 newborns in one retrospective study demonstrated an altered cardiac rhythm,

TABLE 88-2. Antiepileptic Drugs used in Neonatal Seizures

Drug	Loading Dose	Maintenance Dose	Comments
Phenobarbital	20 mg/kg IV at a rate of 5 mg/min; additional doses of 5 mg/kg up to 40 mg/kg	4 mg/kg/d given bid	An EEG should be performed following treatment to detect electroclinical dissociation. EEG monitoring is optimal; phenobarbital level should be monitored
Phenytoin	20 mg/kg IV at a rate <1 mg/kg/min; additional doses of 5 mg/kg up to 30 mg/kg	5–10 mg/kg/d given bid	Hypotension and arrhythmias may occur and cardiac rate and rhythm should be monitored. Fosphenytoin is a prodrug of phenytoin and less likely to cause soft-tissue necrosis. A 1.5 mg dose of fosphenytoin is equivalent to 1 mg of Phenytoin. phenytoin level should be monitored.
Lorazepam	0.05–0.1 mg/kg IV over 2–5 min; additional doses of 0.05 mg/kg up to 0.15 mg/kg if the seizures persist		
Midazolam	0.15 mg/kg IV bolus	Continuous infusion starting at 1 μg/kg/min and increasing by 0.5–1 μg/kg/min every 2 mins until a favourable response; the maximum dose has not been established	Lower doses and slower infusion rates of midazolam should be considered in premature newborns and neonates with reduced cardiac output. Can cause myoclonic jerks and dystonic posturing, which may be mistaken as seizures.
Lidocaine	1.5–2 mg/kg IV	Continuous infusion of 4–6 mg/kg/h	Lidocaine accumulates in the body and infusions should be restricted to 48 h. Cardiac arrythmias observed in 5%, and cardiac rate and rhythm should be monitored.
Carbamazepine	10 mg/kg by NG tube	10–20 mg/kg/d by NG tube as bid or tid	

EEG = electroencephalogram.

indicating that continuous cardiac monitoring should be used in neonates who receive lidocaine for neonatal seizures. Carbamazepine given by nasogastric tube has been reported to be effective and well tolerated in both preterm and term newborns with seizures, and levels within the "therapeutic range" were reached in 2 to 4 hours. Topiramate acts on the AMPA receptor and also has neuroprotective properties in a rat model of perinatal hypoxia-induced seizures. However, the use of topiramate in neonatal seizures is limited by the absence of an intravenous formulation. Bumetamide, a diuretic, has been demonstrated to prevent seizures in premature rats by inhibition of NKCC1, a sodium and potassium co-transporter that causes accumulation of chloride in neurons and facilitates seizures in the premature brain. Clinical trials of bumetamide to treat seizures in the newborn are needed.

The usefulness of treating electrographic seizures not associated with clinical signs has not been demonstrated. However, in view of the increasing number of animal and human studies that suggest that seizures themselves may cause or exacerbate brain injury, it would seem reasonable to treat repeated or prolonged electrographic seizures.

When to Discontinue Drug Treatment

There are limited data on the optimal time to discontinue antiepileptic drug therapy, and this is usually a pragmatic decision. Widespread apoptosis of neurons has been described in immature rats exposed to traditional antiepileptic drugs that block voltage-dependent sodium channels or act on the $GABA_A$ receptor. This would suggest that antiepileptic drugs should be discontinued as soon as possible unless they confer a clear benefit. Phenytoin is usually discontinued when the intravenous line is removed, but there is less clarity on when to discontinue phenobarbital. The cause of the seizures influences the risk of recurrence and should be considered. Thus, the recurrence rate is almost 100% in those with abnormalities of brain development, approximately 30% in those with perinatal asphyxia but is negligible when the seizures are due to hypocalcemia. The risk is much less in children in whom the neurologic examination is normal and in those with minimal

abnormalities on the EEG. Volpe suggests discontinuation of all therapy if the neurologic examination is normal. If the neurologic examination is abnormal, discontinuation of phenobarbital should be considered prior to discharge if the EEG is normal or the etiology is a transient metabolic abnormality. Those other infants should be monitored monthly, and the phenobarbital discontinued if the examination becomes normal or the EEG is not overtly paroxysmal. Patients with treatable inborn errors of metabolism require lifelong treatment of the metabolic disorder.

Outcomes

The mortality associated with neonatal seizures approaches 20% and approximately one-third of the survivors will demonstrate a neurologic handicap in later childhood. Later, epilepsy is seen in approximately 15 to 30% of children with neonatal seizures but usually occurs only in those with other neurological handicap. The preterm infant is more vulnerable, and approximately two-thirds of those with birth weights less than 2,500 g have neurologic handicap in later childhood. Electroencephalographic seizures lasting more than 30 minutes, seizures that persist for more then four days, and those that do not respond to two antiepileptic drugs are all associated with a poor neurologic outcome.

The underlying cause of the seizures is a major predictor of neurologic outcome. Children with developmental brain abnormalities that present with neonatal seizures seldom, if ever, have normal neurologic development. Similarly, seizures associated with IVH have a very poor prognosis. The prognosis is somewhat better in those with neonatal seizures due to hypoxic-ischemic brain injury, hypoglycemia, and bacterial meningitis in whom approximately 50% have normal development. When neonatal seizures are due to subarachnoid hemorrhage or hypocalcemia, 90% or more will have normal development. The prognosis in treatable inborn errors of metabolism is influenced by early diagnosis and initiation of specific treatment.

The EEG background can be a helpful predictor of neurologic outcome. When the background is normal in an EEG in which seizures are recorded, the prognosis is generally good. In contrast, when full-term infants have a burst suppression pattern or marked attenuation occurring more than 12 hours after birth, the neurologic outcome is usually very poor. The EEG is of less predictive value in the preterm infant, particularly in infants less than 34 weeks.

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Practitioner and Patient Resources

International League Against Epilepsy Web site provides detailed descriptions of epilepsy syndromes that present in newborn period.
<http://www.ilae-epilepsy.org/Visitors/Centre/ctf/syn_frame.html>

CHAPTER 89

FACIAL DYSMORPHISM IN THE NEONATE AND INFANT

HARVEY B. SARNAT, MD, FRCPC, LAURA FLORES-SARNAT, MD

Facial dysmorphisms in the fetus and neonate may result from congenital myopathies, neuropathies, brainstem lesions, and mechanical factors affecting facial development, but the majority are due to defective genetic programming of neural induction of craniofacial ontogenesis, mediated by mesencephalic and prosencephalic neural crest tissue. The dysmorphisms associated with cerebral malformations and with neurocutaneous syndromes can be explained by this mechanism.

Abnormal facies in the neonate may result from acquired lesions, neuromuscular diseases, and genetic disorders of the nervous system. Craniofacial development is closely linked to ontogenesis of the neural tube because the neural tube induces most of the nonneural structures of the face and cranial vault. This induction is mediated through the neural crest. An additional neural factor in craniofacial development is the role of striated muscles in stimulating the growth of bones into which they insert. Micrognathia occurs if the muscles of mastication, innervated by the motor trigeminal nerve, are denervated during a period of rapid mandibular growth as in the last month of gestation.

The recognition of abnormal facies in the neonate should pose questions not only of a descriptive nature to label the dysmorphism but also, and of greater importance, to define the mechanisms of pathogenesis that often disclose the etiology. As with all developmental disorders, the key to understanding is knowledge of embryology, in this case, the embryology of the neural tube and neural crest as well as of the soft tissues and bony structures of the head and face.

The most immediate clinical problem with facial paralyses or facial dysmorphism is related to ability of the infant to suck and feed adequately.

Acquired Lesions Producing Congenital Facial Paralysis

Traumatic Facial Palsy at Birth

The facial (CN VII) is the most frequent cranial nerve to be involved in birth trauma and is evident in as many as 6% of live born term neonates in some series, though it usually is transitory and leaves no permanent facial weakness. The injury results from pressure of the sacral prominence of the maternal pelvis against the facial nerve distal to its emergence from the stylomastoid foramen (pes anserinus); another intrapartum injury of the facial nerve may occur from forceps application to the infant's face. A rare cause of facial nerve palsy at birth is traumatic basilar skull fracture that injures the nerve within its bony foramen. In most cases, the palsy is due to tissue edema around and within the nerve or compression or crushing of the nerve and only rarely causes partial or complete anatomic interruption of axons. In other cases, only the lower face, including the *depressor angularis oris* and *mentalis* muscles (see below), may be involved, but in most cases, the upper face also is involved, and the infant cannot completely shut his/her eye on that side. Most cases recover fully within a week. Electrical studies of

facial nerve conduction do not become abnormal until 72 hours after the injury. These studies should be performed if no recovery is seen by 3 to 4 weeks of age to determine whether there is continuity of the nerve peripherally and whether regeneration is occurring (axonal regeneration proceeds at a rate of 0.8 mm/d). Steroids or medications to reduce tissue edema are not useful. Electrical stimulation of the facial nerve does not hasten regeneration and recovery. Methylcellulose eye drops or ointment should be applied to the involved eye, particularly when sleeping, to prevent desiccation and scarring of the exposed cornea.

Mobius Syndrome and Brainstem Watershed Infarcts

The most frequent lower motor neuron lesion causing congenital facial paralysis is Mobius syndrome. The facial palsy is nearly always bilateral and is associated with bilateral abducens palsy and often involvement of other cranial nerves, such as the motor trigeminal and hypoglossal, and often involvement of the brainstem respiratory center (*fasciculus solitarius*) and deglutition center (*nucleus ambiguus*). The facial nerve loops around the abducens nucleus dorsally before coursing ventrally and emerging from the pontomedullary junction; hence, a lesion in the region of the abducens nucleus in the floor of the 4th ventricle also involves the intramedullary loop of the facial nerve. Micrognathia is another complication of Mobius syndrome because of involvement of the motor trigeminal nuclei that innervate muscles of mastication and stimulate growth of the mandible, particularly in the last month of gestation. Cerebral infarcts, particularly those of middle cerebral artery distribution, can produce supranuclear facial weakness that may resemble lower motor neuron lesions of the facial nucleus or nerve but arising on the contralateral side of the brain.

The most frequent cause of Mobius syndrome is a transient period in fetal life of vertebrobasilar insufficiency, usually due to maternal hypotension, shock, or placental abruption. A longitudinal column in the tegmentum of the brainstem, extending from the midbrain to the lower medulla oblongata, is a watershed zone of overlapping arterial territories of the parasagittal penetrating arteries and the long circumferential arteries, both sides being supplied by the basilar artery; these branches of the basilar occur in a series of 25 to 30 bilateral sets along the pons and medulla oblongata. Hence, Mobius syndrome is a bilateral watershed zone infarction of the brainstem tegmentum. Whereas there may also be genetic forms of Mobius syndrome, these represent only a tiny fraction of all Mobius cases. The prognosis depends upon the involvement of vital brainstem centers for respiration and swallowing and whether the infarcts are complete or partial, enabling some compensation after the initial local parenchymal edema resolves and compensatory neural circuitry may be established.

Neuromuscular Disorders Affecting Facial Muscles

Congenital Absence of the Depressor Angularis Oris Muscle

This uncommon congenital anomaly is usually unilateral. The infant cannot draw the corner of the mouth ventrally when crying, and the nasolabial fold is asymmetric. When smiling, the facial asymmetry is not evident because the corner of the mouth curls upward rather than down. When the child has a neutral face, the asymmetry is subtle or not evident. Clinically, the most important differential diagnosis is facial nerve palsy, from which it is easily distinguished because the defect is limited to one small muscle that pulls the corner of the mouth down. The same branch of the facial nerve that innervates the *depressor angularis oris* muscle also innervates the mentalis muscle. This detail is important clinically because if the mentalis is spared and the muscle of the chin is functional, facial nerve injury at birth can be excluded. Agenesis of the *depressor angularis oris* is not accompanied by agenesis of the mentalis.

This anomaly has also been termed the "asymmetric crying facies syndrome" or "Cayler cardiofacial syndrome" because of its association in many, but not all, cases with congenital cardiac anomalies, sometimes other visceral anomalies, cleft palate, and, rarely, hypocalcemia seizures, and autism. Other minor facial dysmorphisms include epicanthal folds, prominent nasal root, and bulbous nasal tip with hypoplastic nasal alae. It is associated with 22q11.2 deletions, the same locus as in most patients with DiGeorge syndrome. A mutation in the *EYA1* gene is demonstrated in some cases. For this reason, patients with congenital absence of the depressor angularis oris muscle should have a cardiac evaluation and chromosomal karyotype analysis.

Myotonic Muscular Dystrophy, Severe Neonatal Form

Bilateral facial wasting and weakness are cardinal signs in myotonic dystrophy and enable the diagnosis at times simply by casual observation. In the severe neonatal form of myotonic dystrophy, facial weakness and thinness of the facial musculature are already markedly evident at birth. The upper lip has a characteristic inverted V-shape. Involved infants often additionally have congenital contractures of the ankles and other joints, respiratory insufficiency including at times hemidiaphragmatic paralysis, generalized weakness and hypotonia with a reduced muscle bulk, and poor peristalsis from smooth muscle involvement that leads to gaseous distension of the abdomen, fecal impactions, and obstipation. Myotonia is not expressed in infancy. Since the mother is the affected parent in 94% of cases of this autosomal dominant disease, the mother

should always be examined for myotonic dystrophy; some mothers are unaware of their disease until their newborn is diagnosed.

Other Muscular Dystrophies

Facial dysmorphism and facial muscle weakness are not features of Duchenne muscular dystrophy or of most congenital muscular dystrophies. In severe neonatal cases of facioscapulohumeral muscular dystrophy, however, facial weakness may be present at birth. The abnormal shape of the mouth differs from myotonic dystrophy because weakness of the orbicularis oris muscle in its entire perimeter causes the lips to protrude and invert, exposing some of the mucosa of the inner lip, both upper and lower. The mouth thus has a round contour rather than the inverted V-shape of myotonic dystrophy.

Spinal Muscular Atrophies

Though infants with the severe Werdnig-Hoffmann disease or spinal muscular atrophy (SMA) type I, and also the recently described severe fetal form called SMA type 0, have generalized muscle wasting at birth and this may involve facial muscles, the face is usually relatively spared until late in the course as with the selective sparing of the diaphragm, extraocular muscles, and urethral and anal sphincters.

Bony Alterations of the Cranium

Abnormal cranial growth may distort the face and give the impression of a facial dysmorphism. Bossing, frontal prominence or forward protrusion of the forehead, is associated with congenital hydrocephalus and an excessively large head circumference. Macrocephaly without intracranial hypertension usually does not produce this frontal bossing but at times may also do so. Posterior sloping of the forehead, by contrast, is frequent in microcephaly (small head) secondary to micrencephaly (small brain). Craniosynostosis may distort the face as well as the head or produce asymmetries. In many genetic syndromes, craniosynostosis is a component, and there are characteristic alterations in the shape of the head and face, as with the short anterioposterior axis and widening in the horizontal plane (brachiocephaly) seen in Apert and Crouzon syndromes, often also causing abnormally shallow orbits with protrusion of the eyes and sometimes optic nerve damage from stretching. In Apert, Crouzon, Pfeiffer, and Saethre-Chotzen syndromes, the molecular genetic bases have been identified. In scaphocephaly, by contrast, the face is normal. In plagiocephaly, a normal face is preserved, but prominence on one side may give an illusion of facial dysmorphism. Hemimegalencephaly also may be associated with facial asymmetry, usually because of lipoma formation on one side only but in isolated cases also due to unilateral facial paralysis. There are several surgical treatments of craniosynostosis that enable cranial growth to accommodate the growing brain and for cosmetic normalization of head shape.

Positional plagiocephaly is flattening of the occiput with prominence of one frontal and of the contralateral occipital regions; it is now seen with greater frequency than in earlier generations because of the American Academy of Pediatrics recommendation that young infants be laid on their backs to sleep to minimize the risk of sudden infant death syndrome, which this sleeping position indeed accomplishes. Infants with weakness who move little or who lie on one side more than the other also may develop an asymmetric head shape. Muscular torticollis also can cause asymmetry in postnatal head growth, especially if the head is continuously rotated and tilted to one side. Premature infants usually have dolichocephaly (a long, narrow head), not due to scaphocephaly (premature closure of the sagittal suture), but because they lie on the side of their head, the soft calvarial bones assume this shape due to gravity. The proper way to examine an infant's head for plagiocephaly is to view it from above the vertex so that the frontal and occipital regions are seen together and asymmetries or a parallelogram shape become more easily evident. Positional plagiocephaly is a cosmetic disfigurement but is not a neurologic problem because the intracranial volume of the two sides of the head remains equal, and hydrocephalus is not a complication. It can be treated by special helmets that reshape the head during the period of rapid growth in early infancy. In mild cases, simply repositioning the infant during sleep in particular may be adequate to reshape the head without a constant helmet. Many hospitals now have special "Head Shape Clinics" to treat this previously infrequent, but now common, problem. Surgery is required only rarely in positional plagiocephaly with open sutures, unlike the need for surgery if craniosynostosis is present.

Chromosomal and Genetic Disorders, Including Neurocutaneous Syndromes Associated With Facial Dysmorphism

Numerous genetic syndromes are associated with facial dysmorphism and, indeed, provide a basis for clinical diagnosis. Examples fill entire genetics textbooks. In Goldenhar syndrome, hypoplasia of facial musculature is associated with anomalies of the ear and vertebrae. The velocardiofacial syndrome is due to a microdeletion of chromosome 22q11.2 (see above). Most, but not all, genetic syndromes involving facial muscles or facial

dysmorphism are bilateral, helping distinguish them from traumatic facial palsy as a birth injury.

Genetic and Metabolic Diseases Affecting Facial Soft Tissues

Unique, coarse, characteristic facies occur in many mucopolysaccharidoses, sometimes called "gargoylism." Examples are Hurler, Hunter, and Morquio syndromes. In part, these facial dysmorphisms are due to the accumulation of metabolic storage products in the subcutaneous soft tissues. Bony overgrowth also may contribute to the coarse facies. In mucopolysaccharidoses, these facial features usually are not observed at birth and become evident and progressive after 2 years of age. Newborn infants of diabetic mothers have excessive subcutaneous fat in the face, giving an appearance of facial dysmorphism but more similar to cushingoid facies. In Goldenhar syndrome, hypoplasia of facial musculature is associated with anomalies of the ear and vertebrae. The velocardiofacial syndrome is due to a microdeletion of chromosome 22q11.2 (see above).

Most, but not all, genetic syndromes involving facial muscles or facial dysmorphism are bilateral, helping distinguish them from traumatic facial palsy as a birth injury. In several conditions, there may be asymmetric overgrowth so that half of the face may be enlarged, for example, in Beckwith-Wiedeman syndrome and in hemimegalencephaly.

Neurocutaneous Syndromes

Numerous genetic syndromes are associated with facial dysmorphism and, indeed, provide a basis for clinical diagnosis. Examples fill entire genetics textbooks.

In most neurocutaneous syndromes, characteristic cutaneous or subcutaneous marker lesions involve the face. Examples include the naevus flammeus in Sturge-Weber syndrome, white, depigmented spots in tuberous sclerosis, palpebral fibromas and, less often, café-au-lait spots in neurofibromatosis 1 (more frequent on the trunk and extremities than on the face), and the nevi in epidermal nevus syndrome, of which the most typical is the midline nevus of Jadasshon. A hemifacial lipoma is an anomaly present at birth in several neurocutaneous syndromes; they are terminal overgrowths due to dysregulation of pluripotential neural crest cells. Some examples of neurocutaneous syndromes coexisting with lipomas (they also can be corporal or intracranial) are epidermal nevus syndrome, proteus syndrome, Klippel-Trenaunay syndrome, and encephalocraniocutaneous lipomatosis. Some patients develop a more severe condition of a unilateral facial fatty mass called congenital infiltrating lipomatosis of the face. This is a nonencapsulated lesion of mature lipocytes, typically located in the cheek, which infiltrates into adjacent tissues such as dermis, tongue, masticatory muscles, lower lip, and the parotid gland, with a tendency to recur after resection. When fatty facial lesions are associated with neurocutaneous syndromes, hemimegalencephaly often coexists.

Cerebral Dysgeneses Associated with Facial Dysmorphism

Many major malformations of the brain are associated with characteristic facial dysmorphisms. Only recently, however, we have been able to understand the mechanisms of these dysmorphic facies in terms of neural induction mediated through the neural crest tissues. Neural crest forms nearly all of the facial bones, cartilages, and soft tissues, most of the ocular globe (except the retina, choroid, lens, and cornea), nerve sheaths, blood vessels, and connective tissue. It also forms the membranous bones of the cranial vault. Neural crest arises from three sites in the dorsal midline of the neural tube: rhombencephalon, mesencephalon and prosencephalon.

Mesencephalic neural crest forms most of the face, including the orbits and nose. The reason that midfacial hypoplasia occurs in holoprosencephaly, and also other malformations including anencephaly and some cases of septo-optic dysplasia, is that the gradient of the defective gene extends caudally in the longitudinal axis from the forebrain (prosencephalon) to reach the midbrain, where it causes dorsal midline hypoplasia with noncleavage of the colliculi on the two sides, absence of the dorsal median septum from the cerebral aqueduct dorsally in the midline and aqueductal stenosis or atresia. The mesencephalic neural crest forms in the dorsal midline of the midbrain and is deficient, defective, or prevented from migrating forward, away from the neural tube, hence does not form the midline structures of the face. The mesencephalic neural crest migrates rostrally as parallel streams of cells from medial to lateral (Figure 89-1). If the first stream A0 does not migrate, the premaxilla (PM) and vomer do not form, and the fetus has a midline "cleft" in the lip and palate, which is really not a cleft at all but absence of structure, but both nares and both eyes are formed. The orbits are cl oser together than normal, termed hypotelorism. If the second stream A1 is defective but the A0 managed to survive, cebocephaly results: the PM is present, hence no midline cleft of the lip, but the nose has a single nare because the medial side of each nare failed to form and the two lateral sides (from A2) did form and came together in the midline. In a more extreme form, fusion of the eyes as cyclopia follows the same principle. The globes of the eyes form from a medial half from A1 and a lateral half from the A2 stream of mesencephalic neural crest; if A1 is absent, the A2

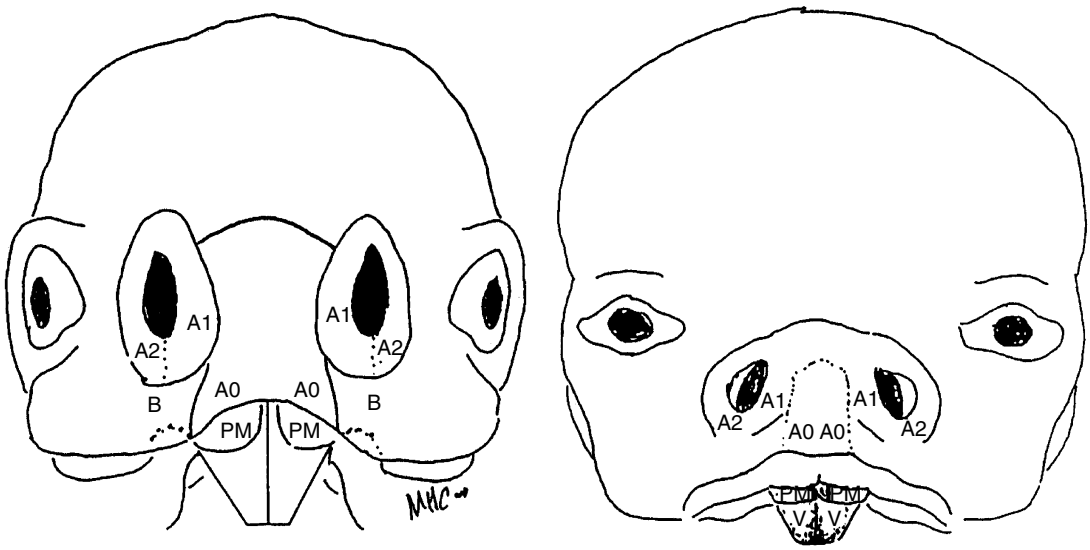

FIGURE 89-1. Drawing of facial targets of three principal streams of mesencephalic neural crest migration (A0, A1, A2), respectively, in more lateral zones in the late human embryo at 5 to 6 weeks gestation. If the A0 stream is defective, the premaxilla (PM) and vomer fail to form, producing a midline "cleft" lip and palate, and hypotelorism results from midfacial hypoplasia; two nares develop, even if the bridge of the nose is hypoplastic. If A0 is preserved but A1 is defective, the PM is formed, but the medial sides of the nares fail to form and the two lateral sides fuse in the midline to produce a single nare, the pathogenesis of cebocephaly. Failure of the medial sides of each eye to develop results in a similar fusion of the lateral halves of each eyeball to form the single median eye, the pathogenesis of cyclopia. Mesencephalic neural crest induction of craniofacial structures is most frequent in holoprosencephaly when the rostrocaudal genetic gradient of the longitudinal axis of the neural tube extends as far caudally as the midbrain, though defective genetic expression in the dorsoventral gradient of the vertical axis also is involved. Reproduced with permission from Carstens MH.[2]

contribution to each eye comes together in the midline to form a single median eye. The orbits also form a midline single (though deformed) orbit from the two lateral sides. In holoprosencephaly, the clinical observation of DeMyer et al. in 1964 "The face predicts the brain" was modified in 2001 by Sarnat to a mechanistic statement "The face predicts the mesencephalic neural crest migration" and in 2004 by Carstens to an etiologic statement "The brain predicts the face."

Prosencephalic neural crest migrates not in streams but as a vertical sheet in the midline. The vertical pigmented or, less frequently, depigmented midline in the skin of the forehead and nose in epidermal nevus syndrome demonstrates well the migration of the prosencephalic neural crest. This neural crest does not contribute to the orbits themselves but does form the intercanthal ligament, a structure that holds the orbits together during fetal development so that the eyes face forward rather than being on the lateral surface of the head. The development of the intercanthal ligament is species-specific. Those animals that have it (primates, cats, dogs, bears, owls) have eyes directed forward. Those animals that lack the genetic program (horses, cows, whales, elephants, all birds except owls) have eyes on the side of the head. A defective prosencephalic neural crest does not keep the orbits close enough together during fetal development so that affected infants have hypertelorism. Such children also frequently have agenesis of the corpus callosum and sometimes of the anterior commissure as well though the latter structure forms 3 weeks earlier than the corpus callosum. This association is not coincidental. Both the callosal plate (or bridge) and the prosencephalic neural crest form from the dorsal part of the lamina terminalis, and a defect in this embryonic structure may cause both anomalies.

In sum, both hypotelorism and hypertelorism are neural crest disorders, but hypotelorism is a disturbance of mesencephalic neural crest, and hypertelorism is a disturbance of prosencephalic neural crest. Gradients of genetic expression in the axes of the neural tube underlie both.

Miller-Dieker syndrome is a familial lissencephaly characterized clinically by microcephaly and a peculiar facies that includes micrognathia, high forehead, thin upper lip, short nose with anteverted nares, and low-set ears. Neurologically, these infants and children have severe developmental delay and epilepsy. Neuropathologically, a characteristic 4-layered cortex is found (lissencephaly type 1) that differs from the cortical dysplasias of other lissencephalies, such as those of Walker-Warburg and Fukuyama (lissencephaly type 2).

Unexplained facial dysmorphism in the neonate is justification to perform imaging of the brain to determine whether there is an associated cerebral malformation.

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CHAPTER 90

STATUS EPILEPTICUS

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This chapter reviews common presentations of pediatric status epilepticus (SE) and discusses its management, evaluation, treatment, and prognosis. SE is a common neurologic emergency in children that signifies severe central nervous system (CNS) dysfunction. Initial management is directed at stabilization of vital functions and a quick but thorough investigation for an etiology. An organized treatment paradigm is essential and reduces associated morbidity and mortality.

Status epilepticus (SE) is a common pediatric emergency that is potentially life threatening. Of the 100,000 to 150,000 cases that occur each year in the United States, most take place in children. Additionally, close to 400,000 patients per year visit emergency departments for treatment of acute seizures.

Between the extremes of isolated seizure and SE lies the phenomenon of acute repetitive seizures (ARSs). ARSs are a severe form of epilepsy that differs from the patient's normal pattern in seizure type, frequency, duration, or severity. ARSs may occur in any patient with epilepsy, despite chronic antiepileptic drug (AED) therapy, and require additional treatment. The cluster of seizures may be related to specific situations (eg, concurrent illnesses or sleep deprivation) or have no apparent precipitant.

The child who presents in generalized convulsive SE (GCSE) creates a frightening scenario for both the parents and the pediatrician or neurologist who is called to the emergency department. There is a perceived fear of permanent brain damage if the seizures are not quickly terminated. Most of these children have no prior history of epilepsy. In some children, SE is a response to an acute cerebral insult. In others, SE is the first manifestation of an ongoing seizure disorder. In 1981, the International League Against Epilepsy (ILAE) defined SE as "a seizure that persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur." The core facet is that of a continuous seizure or of repeating seizures that occur so rapidly that the patient does not recover consciousness.

The ILAE definition did not include a specific duration. Recent literature has incorporated a 30-minute duration in the definition of SE, on the basis of research showing that deleterious effects in neurons occur after 30 minutes of continuous seizure activity in experimental animals. However, this specified duration is misleading as a guide to treatment decisions. The vast majority of self-limiting generalized convulsive seizures stop within 2 to 3 minutes of onset, with almost all ceasing within 5 minutes. As such, a more practical definition of SE has emerged as any seizure that lasts more than 5 to 10 minutes.

This rationale for earlier treatment is supported by evidence that the longer the seizures persist, the more difficult they are to stop and the higher the mortality. Less than 10% of the total cases are subsumed under the rubric of nonconvulsive SE (NCSE). Some forms of NCSE also may lead to neuronal injury, but others may not. Complex partial SE is more likely to result in neuronal injury similar to GCSE. Absence SE is much less likely to result in neuronal injury and complications, probably because it is mediated primarily through excess inhibition (not excess excitation). The comments below refer to GCSE, except where noted. Compared with adults with SE, children have unique differences (ie, etiology, intravenous [IV] access, drug side effects, treatment response, and mortality) that influence therapeutic decisions.

Background

Children younger than 3 years of age are most likely to develop SE. Febrile seizures are the most common seizure type. The initial febrile seizure is longer than 15 minutes in 9% of patients (9,000 children per year in the United States)

and longer than 30 minutes in 5% (5,000 children per year in the United States). This is the most common cause of SE in children; however, it also has the most favorable prognosis. A subpopulation of children with epilepsy are prone to SE, and they can be identified early in the course of their epilepsy. Children without SE in the first 2 years after onset of epilepsy have very little risk of experiencing SE later. Twelve percent of patients with newly diagnosed epilepsy present with SE. Although seizure duration does not predict recurrence risk, if a second seizure does occur it is likely to be prolonged. This same trend is observed in afebrile and febrile seizures.

The common pediatric causes of SE are directly related to the child's age. The child who develops seizures at < 1 year of age has a 70% chance of developing SE at some time. This age group also has the highest pediatric mortality due to SE. SE in a child younger than 3 years of age is more likely to occur in a neurologically normal child and be the result of an acute illness. Systemic infections and febrile illness are common precipitators. Other acute disorders include head trauma, meningitis, encephalitis, dehydration, and electrolyte disorders.

In children 3 to 16 years of age with symptomatic or cryptogenic partial seizures, 20% will develop SE within 5 years of their original epilepsy diagnosis. The 3- to 16-year-old child with SE is more likely to have a chronic encephalopathy and be neurologically abnormal. The chronic encephalopathy may be related to perinatal problems, a brain malformation, neurocutaneous syndrome, or a prior history of head trauma, meningitis, or stroke. In these patients, SE may be acutely precipitated by a febrile illness or subtherapeutic AED levels (often due to a medication change) in a child with a known seizure disorder. The outcome of SE is strongly influenced by the etiology. The worst prognosis occurs in children whose SE is precipitated by serious intracranial insults, such as encephalitis, cerebral hemorrhage, anoxia, stroke, or CNS toxins. Although children are at higher risk of SE than are adults, morbidity and mortality rates are lower in children (typically 3–15%) than in adults.

Key factors that influence the patient's prognosis include (1) the patient's age, (2) the etiology, and (3) the duration of SE (this is the only factor influenced by AED treatment). Long-term complications include epilepsy, encephalopathy, and focal neurologic deficits. Death after SE is usually secondary to the underlying cause, not to the prolonged seizure activity per se. Rapid intervention with safe, effective treatments will minimize the sequelae of SE.

Treatment

The child in SE requires prompt intervention. This is a medical emergency. It is extremely important to have a treatment protocol in place and to work through it quickly. The goals of treating SE include stopping the seizure safely and in a timely manner and minimizing treatment-related morbidity. The systemic effects of SE must be understood and the side effects of the prescribed treatment (sedation and cardiovascular or respiratory compromise) anticipated.

Management of SE begins with the ABCs of life support (establishing an *a*irway and supporting respiration, maintaining *b*lood pressure, access to *c*irculation) and, when possible, identifying and treating the cause (Tables 90-1 and 90-2). Vital signs, pulse oximetry, and the electrocardiogram (ECG) should be monitored closely. Skilled nursing care is crucial to the management of SE. Rapid determination of blood glucose level should be undertaken in all patients. If hypoglycemia is found or suspected, intravenous (IV) glucose is administered (in adolescents, IV thiamine 100 mg should be given first). Additional blood should be drawn for a complete blood count, serum chemistries, toxicology screening, and AED levels.

All patients in SE show an acidosis that usually resolves once seizure control is achieved. Treatment with sodium bicarbonate is indicated only in severe acidosis. Hyperthermia, which occurs in 28 to 79% of patients, is important to recognize. Prevention of significant hyperthermia is a top priority, as it may contribute to brain damage. Further evaluation, which should not delay the administration of AED

TABLE 90-1. Guidelines for Treatment of Pediatric Generalized Convulsive Status Epilepticus (GCSE)

I. Stabilization
- Note time, diagnose status epilepticus
- Check ABCs (airway, breathing, circulation), vital signs
- ECG monitoring, frequent suctioning
- Nasal oxygen, give antipyretics as needed
- Obtain IV access*, pulse oximetry
- Blood for laboratory tests (if hypoglycemic, 25% glucose 2 mL/kg), AEDs, toxicology

II. Treatment
- Lorazepam 0.1 mg/kg at 2 mg/min (or diazepam 0.3 to 0.5 mg/kg at 5 mg/min). If seizures stop, no other therapy may be required if cause is corrected.
- Fosphenytoin 20 mg PE/kg at 3 mg/kg/min (maximum rate, 150 mg PE/min). If seizures continue, fosphenytoin 5–10 mg PE/kg; anticipate intubation.
- If seizures continue, anesthesia. Midazolam 0.2 mg/kg, then 1–10 μg/kg/min (or pentobarbital 5 to15 mg/kg, then 1–5 mg/kg/h) to produce a burst-suppression EEG pattern.

Age (yr)	Rectal Diazepam Gel Dose**
2–5	0.5 mg/kg
6–11	0.3 mg/kg
> 12	0.2 mg/kg

AED = antiepileptic drug; ECG = electrocardiogram; EEG = electroencephalogram; IV = intravenous; PE = phenytoin equivalent.

*If unable to obtain immediate IV access, administer rectal diazepam gel, on the basis of the child's age and weight, and continue to establish IV access.

**Supplied as 2.5, 5, 10, 15, or 20 mg syringes, to maximum 20 mg.

TABLE 90-2. Guidelines for Treatment of Pediatric Nonconvulsive Status Epilepticus (NCSE)

I. Stabilization
   Same as generalized convulsive status epilepticus

II. Treatment
   Lorazepam 0.1 mg/kg at 2 mg/min (or diazepam 0.3 to 0.5 mg/kg at 5 mg/min). If seizures stop, slowly load with fosphenytoin or valproate.
   Fosphenytoin 20 mg PE/kg at 3 mg/kg/min (maximum rate, 150 mg PE/min). If seizures continue, fosphenytoin 5–10 PE/kg.
   Valproate 25 mg/kg at 3 to 6 mg/kg/min. (Use this first or second in absence or atonic or myoclonic SE). (If partial SE, may use or go directly to next step.)
   If seizures continue, anesthesia. Midazolam 0.2 mg/kg, then 1–10 μg/kg/min (or pentobarbital 15 mg/kg, then 1–5 mg/kg/h) to produce a burst-suppression EEG pattern.

EEG = electroencephalogram; PE = phenytoin equivalent.

therapy, includes a directed history and examination, with specific references to trauma, substance abuse, preexisting epilepsy, neurologic or medical disorders, and the presence of any focal neurologic signs. This initial stabilization phase should be accomplished within the first 5 to 10 minutes of the child's arrival in the emergency department.

Treatment is then begun, with a clear plan, prompt administration of adequate doses of an effective drug, and attention to the possibility of hypoventilation or apnea. As far as possible, drugs should be given only intravenously. When an IV line cannot be established, diazepam may be administered rectally. If this is successful, and an IV line has still not been established, the loading dose of fosphenytoin can be given intramuscularly. This provides seizure protection while the evaluation is completed. The average time from onset of seizures to ambulance arrival can be 30 minutes. The development of a rectal diazepam gel may broaden treatment horizons as this allows treatment of the SE before the patient reaches the hospital (and IV access is established).

The ideal drug to treat SE does not exist (Table 90-3). Several effective drugs have led to numerous treatment protocols. More than one drug is often used to achieve all the goals of the ideal drug. The strategy is to combine the drugs necessary for each patient for appropriate treatment. The treatment protocol for GCSE (see Table 90-1) is designed to follow a logical sequence, assessing the patient for response at each interval between the steps and moving to the next step if the patient continues to be in SE. If the seizures stop, no further therapy may be needed, or decisions can be made about the choice of an AED for long-term therapy.

A benzodiazepine is administered as initial treatment. The onset of action is rapid, often within 1 to 2 minutes. Most patient's seizures will stop. Too rapid IV administration of a benzodiazepine may produce cardiac or respiratory arrest. If diazepam is used, it may be necessary to administer a long-acting drug, preferably fosphenytoin, to prevent recurrent convulsions. If the seizures have not stopped, a loading dose of fosphenytoin should be administered. ECG and blood pressure monitoring are imperative. If hypotension develops, the infusion should be slowed or stopped. If the seizure ceases, the infusion rate should be slowed. Within 10 minutes of the end of the infusion, if not before, the seizures should stop. If the SE persists, an additional fosphenytoin dose can be given.

Historically, in the event of persistent seizures, phenobarbital was given next as a loading dose. However, although effective, this is slow in onset and places the patient at risk of cardiovascular collapse. Midazolam can be infused rapidly, is effective, and has fewer cardiovascular side effects. Monitoring the treatment of SE with simultaneous electroencephalogram (EEG), although ideal, is not possible in many emergency departments. Treatment should never be delayed while awaiting an EEG, unless there is diagnostic uncertainty (eg, an adolescent with suspected nonepileptic events). If the seizures stop but the coma persists, an EEG must be obtained to exclude NCSE.

In the 15 to 25% of patients who do not respond to treatment, the question of etiology must be revisited. One must consider whether the cause is toxic or metabolic, especially in young children who are not responding. Continuous EEG monitoring is necessary at this point if it has not been obtained previously.

TABLE 90-3. Status Epilepticus: Ideal Drug Characteristics

	DZP	LZP	PHT	FosPHT	PB	VPA	LEV
Easy to administer	X	X	—	X	X	X	X
Rapid onset	X	X	X	X	—	X*	?
Long duration	—	X	X	X	X	X	X
Broad spectrum	X	X	—	—	X	X	X
Minimal morbidity	—	—	—	X	—	X	X
Useful as a chronic AED	—	—	X	X	X	X	X
IV solution compatibility	—	—	—	X	—	X	X

AED = antiepileptic drug; DZP = diazepam; FOS = fosphenytoin; LEV = levetiracetam; LZP = lorazepam; PB = phenobarbital; PHT = phenytoin; VPA = valproate.

*Based on animal studies and limited clinical observations.

The management of refractory SE has primarily used one of these three drugs: (1) midazolam 0.2 mg/kg, followed by 1 to 10 μg/kg/min, (2) pentobarbital 5 to 15 mg/kg, followed by 0.5 to 5 mg/kg/h, and (3) propofol 1 to 2 mg/kg, followed by 2 to 10 mg/kg/h. However, rare reports indicate that propofol may be associated with rhabdomyolysis, metabolic acidosis, and fatal myocardial failure in children. The U.S. Food and Drug Administration (FDA) has reviewed this, and, to date, no causal relation has been found. However, the author rarely uses this agent. If the child is treated with pentobarbital, then the author would administer a loading dose of phenobarbital prior to pentobarbital withdrawal. This should prevent potential barbiturate withdrawal seizures.

Prehospital Treatment

There is a long time period before the patient with SE arrives at the hospital. Treatments are needed for prolonged seizures that can be initiated by emergency medical technicians (EMTs) prior to the patient's arrival in the emergency department. Currently, treatment decisions are often being made during this time.

The EMTs may administer diazepam intravenously. In young children (or other patients for whom IV administration is difficult), the options are increasing; diazepam rectal gel or an intramuscular loading dose of fosphenytoin can be administered. Prehospital treatment studies indicate that if treatment is given prior to hospital arrival, seizure duration should be shortened, recurrence prevented, and the risk of intubation and admittance to the intensive care unit minimized. Paramedic out-of-hospital acute seizure treatment improves outcome in SE, but is still short of the 5- to 10-minute response advocated by the Epilepsy Foundation of America. Acute treatment of seizures at home is a way to reach this treatment goal. The only acute seizure treatment FDA-approved for at-home use is diazepam rectal gel.

Children experiencing ARS also benefit from prehospital treatment. The physician and the parents should discuss in advance and carefully decide which episodes of ARS are appropriate to recommend home therapy. Many children have episodes of ARS that are predictable, and preplanning may alter the need for emergency department visits. The advantages of effective home treatment for ARS include reducing emergency department visits and lost school and work time, resulting in an improved quality of life for both the patients and their families. In addition, effective home treatment is cost effective and allows caregivers to have a sense of empowerment. They feel they have control over the situation and that there is something they can do to prevent a true medical emergency.

Preparations of rectal diazepam have been available in Europe for 30 years. Recently, diazepam rectal gel was approved in the United States. One reason for the effectiveness of rectal administration of diazepam is the rich venous plexus just inside the second anal sphincter. The medication comes in a predosed syringe that makes it easy to deliver medication to this area. Absorption is rapid, giving quick therapeutic blood levels that are often successful in interrupting seizure clusters. The benefits of this form of medication include its premeasurement, rapid absorption, and safety (without respiratory compromise). Sedation is the only common adverse effect, as might be expected from a benzodiazepine. This is effective in terminating ARS in more than 75% of episodes, and no drug tolerance develops with uses at intervals of 5 days or more. Even if the seizures are not stopped, the administration of rectal diazepam gel does not complicate subsequent medical management.

In addition to ARS, some patients are at high risk of recurrence of SE (Table 90-4).Ten to 20% of children experience recurrent SE. This is especially true in the neurologically abnormal child, and the risk of recurrence increases with the degree of neurologic impairment. Parents of these children should be instructed in the use of rectal diazepam gel and be given a prescription for an appropriate dose (see Table 90-1). Administration of the medicine at the onset of the next seizure that is over 5 minutes in duration may eliminate the need for hospitalization or reduce the length of stay. However, this does not replace the need for evaluation by the pediatrician or child neurologist (at a minimum, this may be a telephone consultation in an established patient).

Evaluation

SE is a medical emergency that requires therapy with IV medication as soon as an IV line is established. If a treatable cause is known or found (eg, hypoglycemia), then initial therapy is directed at treatment of this cause. However, in most cases, there is no obvious cause, and treatment is directed at stopping the seizures and then initiating appropriate laboratory studies (Table 90-5). This will usually include a magnetic resonance imaging (MRI) study of the brain. If acute trauma is causally related, an emergent computed tomography (CT) scan should be obtained.

TABLE 90-4. Risk Factors for Recurrent Status Epilepticus in Children

Prior prolonged febrile seizure (> 15 minutes)
Remote symptomatic* etiology as the cause of initial SE
Progressive neurologic disease

*Remote symptomatic—a seizure occurring without acute cause in a child with a history of a prior brain insult known to be associated with an elevated risk of convulsions (eg, meningitis, cerebral palsy, head trauma, or mental retardation).

TABLE 90-5. Second-Phase Studies*

(Follow initial stabilization; see Table 90-1)
Liver function tests
Toxicology screen
EEG
Lumbar puncture
CT or MRI brain scan (epilepsy protocol)
Video-EEG monitoring

CT = computed tomography; EEG = electroencephalogram; MRI = magnetic resonance imaging.

*Studies vary depending on the clinic situation.

Other studies (eg, toxicology, urine drug screen, and lumbar puncture) may be necessary as clinically indicated. If the child is not beginning to awaken and show an improved mental status in the first 30 to 60 minutes after the seizure is stopped, an EEG should be obtained. If the child's mental status is improving, an EEG may still be necessary but not urgent. The child may be maintained on AED therapy during the initial evaluation. Depending on the results of this evaluation, a decision will have to be made regarding the need for long-term AED therapy.

Conclusion

SE is a common neurologic emergency in children. It signifies severe CNS dysfunction. Initial management is directed at stabilization of vital functions and a quick but thorough investigation for an etiology. An organized treatment paradigm is essential and reduces the morbidity and mortality associated with SE. Inadequate treatment regimens and failure to recognize cardiorespiratory collapse are the common treatment errors. The treatment strategy for SE should accomplish four goals: (1) ensure adequate cardiorespiratory function, (2) stop seizure activity, (3) prevent recurrent of seizures, and (4) identify and, if possible, treat the etiology. Achieving these four goals will improve the outcome of SE in all children.

Suggested Readings

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http://www.cene.com/Presentations/IVAEDSlideKit.ppt

Practitioner and Patient Resources

Epilepsy Foundation
4351 Garden City Drive, Suite 406
Landover, MD 20785-2267
Phone: (301) 459-3700 or 800-332-1000
E-mail: postmaster@efa.org
http://www.epilepsyfoundation.org
The Epilepsy Foundation will ensure that people with seizures are able to participate in all life experiences and will prevent, control and cure epilepsy through research, education, advocacy and services.

The Epilepsy Research Foundation
PO Box 3004
London, England W4 1XT
Phone: 020 8995 4781
E-mail: info@erf.org.uk
http://www.erf.org.uk
Devoted solely to sponsoring effective research for all who now suffer from epilepsy.

H.O.P.E. Mentoring Program
(a part of the Epilepsy Foundation)
Phone: 877-467-3496
http://www.epilepsyfoundation.org/programs/hope.cfm
H.O.P.E. was created to allow people who live with epilepsy to educate others and to share their experiences. H.O.P.E. trains people with epilepsy to be "patient educators" throughout the epilepsy and neurologic communities.

Epilepsy Information Service (EIS)
Department of Neurology
Wake Forest University School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157
Phone: 800-642-0500
http://www.bgsm.edu/neuro/disease/epilinfo.shtml
The EIS is a nonprofit resource center that offers a nationwide toll-free information line for people with epilepsy and their families, professionals, and the public. Free educational packets are available to all callers.

Epilepsy.com
11911 Freedom Drive #730
Reston, VA 20190
Phone: (703) 437-9720
http://www.epilepsy.com
Epilepsy.com is an online resource with information for children, parents, and professionals, provided by The Epilepsy Project, a nonprofit center that supports research.

CHAPTER 91

MENINGITIS AND ENCEPHALITIS

JAMES F. BALE JR. MD

Despite the availability of effective vaccines and well-tolerated antimicrobial agents, meningitis and encephalitis remain important causes of death and neurodevelopmental complications among infants and young children. This chapter discusses the epidemiology, clinical manifestations, diagnosis, treatment, and prognosis of these disorders.

Meningitis refers to inflammation of the leptomeninges, the connective tissue layers in closest proximity to the surface of the brain. Meningitis can be caused by bacteria, viruses, parasites, and fungi, as well as by noninfectious conditions, including inflammatory disorders (eg, systemic lupus erythematosus or Kawasaki disease) and neoplasia (eg, leukemic meningitis). This chapter focuses on bacterial and viral meningitis.

Bacterial Meningitis

Pathophysiology and Epidemiology

Bacterial meningitis usually occurs as the consequence of hematogenous seeding of the choroid plexus, a highly vascular structure that produces cerebrospinal fluid (CSF). Less commonly, bacteria enter the CSF directly, as might occur with implantation of a bacterially contaminated ventriculoperitoneal shunt device. Because the CSF generally lacks organism-specific antibodies and complement, bacteria can grow unchecked, leading to the signs and symptoms discussed later in this chapter. Inflammatory cytokines, especially tumor necrosis factor, participate in the host responses to bacterial infection, but they also contribute to certain complications of meningitis, such as sensorineural hearing loss.

The agents causing bacterial meningitis differ substantially according to the age of the child. In the neonatal period, a relatively large group of organisms, including *Streptococcus agalactiae* (group B streptococcus), *Escherichia coli*, *Staphylococcus* species, *Listeria monocytogenes*, and *Pseudomonas aeruginosa* cause sepsis and bacterial meningitis. *Citrobacter* species cause less than 5% of cases of neonatal meningitis but produce brain abscesses in approximately 75% of the infected infants.

In contrast, only two organisms, *Streptococcus pneumoniae*, a gram-positive diplococcus, and *Neisseria meningitidis*, a gram-negative diplococcus, currently account for most cases of bacterial meningitis among children and adolescents living in regions with compulsory immunization for *Haemophilus influenzae* type b (Hib). Prior to the development and marketing of an effective Hib vaccine, however, as many as 1 in every 400 children between the ages of 1 and 4 years experienced bacterial meningitis due to this organism.

Among unimmunized children, *H. influenzae* meningitis occurs more commonly in people with sickle cell anemia, asplenia, or human immunodeficiency virus (HIV) infection, as well as in certain populations, including African-Americans and native Americans. Risk factors for *S. pneumoniae* meningitis include many of the above variables, as well as nephrotic syndrome, cochlear implantation, and CSF leaks. College students and people with inherited complement deficiencies have an increased risk of meningitis with *N. meningitidis*. Common to many of the risk variables are immunodeficiency states that sustain bacteremia, increased exposure to the carriers of bacteria, or defects in the barriers that prevent entry of bacteria into the CSF.

Clinical Manifestations and Diagnosis

The early signs of bacterial meningitis in the neonate can be subtle and consist only of low-grade fever, poor feeding, somnolence, "fussy" behavior, or irritability. Later, vomiting, lethargy, and seizures ensue. The physical examination can be equally nonspecific in the young infant, demonstrating somnolence, irritability, hyperreflexia, and a full or bulging fontanelle. Meningeal signs

are present infrequently. Systemic signs can include hypotension and features of disseminated intravascular coagulopathy (DIC).

The older child typically experiences signs that localize to the central nervous system (CNS), including headache, somnolence, and manifestations of meningeal irritation, the Kernig sign (involuntary spasm of the hamstring muscle provoked by knee extension with the patient supine), and the Brudzinski sign (flexion of the legs provoked by flexion of the neck). Systemic signs can include pneumonia in children with pneumococcal or *H. influenzae* meningitis and petechiae, purpura, or signs of DIC in children with meningococcal meningitis. Septic arthritis, rash, and DIC can be observed in children with *H. influenzae* meningitis.

The diagnosis of bacterial meningitis is established by lumbar puncture. The CSF in bacterial meningitis shows a neutrophilic pleocytosis, elevated protein content, and reduced glucose content. Gram stain reveals leukocytosis and the presence of bacteria, either gram-positive or-negative. The etiologic diagnosis of bacterial meningitis is confirmed by detecting specific bacterial pathogens using culture methods. Cultures can be negative when children receive oral antibiotics prior to CSF sampling, reflecting partially treated meningitis. Partial treatment can sterilize the CSF and modify the white blood cell count, but protein and glucose contact usually remain abnormal. Low CSF glucose in the setting of antibiotic pretreatment should be considered prima facie evidence of bacterial infection. In children with radiographic or clinical signs of increased intracranial pressure (ICP), antibiotics must be initiated empirically, and lumbar puncture should be deferred until treatment of the increased ICP.

Treatment and Prognosis

Because of the life-threatening nature of bacterial meningitis and the potential for permanent neurodevelopmental sequelae, antibiotic therapy should be instituted as soon as the diagnosis is suspected. Empiric antibiotic therapy for meningitis in infants less than 1 month of age consists of ampicillin (150–300 mg/kg/d in divided doses every 6–8 h) with gentamicin (2.5–7.5 mg/kg/d in 1–3 divided doses) or ampicillin (150–300 mg/kg/d divided every 6–8 h, depending upon the gestational and postnatal age of the infant) with cefotaxime (150–300 mg/kg/d divided every 6–8 h).

Antibiotic therapy should be modified once the identity and sensitivity profile of the pathogen have been determined. Therapy for group B streptococcal meningitis can consist of ampicillin, as above, or penicillin G 250,000 to 450,000 U/kg/d intravenously in three divided doses for infants less than 1 week old, and 450,000 U/kg/d in four divided doses for infants older than 1 week. Some infectious disease experts add gentamicin, 2.5 to 7.5 mg/kg/d in one to three divided doses. *E. coli* meningitis can be treated with ampicillin or an expanded-spectrum cephalosporin and gentamicin, as above. *Listeria spp.* are not sensitive to cephalosporins, including the expanded-spectrum formulations, so therapy should consist of 14 to 21 days of intravenous ampicillin, 150 to 300 mg/kg/d in three to four divided doses and gentamicin, 2.5 to 7.5 mg/kg/d in one to three divided doses, depending upon the infant's gestational and postnatal age. Infants with uncomplicated cases of meningitis require 14 to 21 days of intravenous antibiotic therapy, and infants with complicated cases may require longer courses.

Empiric antibiotic therapy for suspected bacterial meningitis in children older than 1 month of age consists of vancomycin 60 mg/kg/d in four divided doses along with either cefotaxime (300 mg/kg/d in 3 or 4 divided doses) or ceftriaxone (100 mg/kg/d intravenously divided q12 h). Vancomycin, used because of potential resistance of *S. pneumoniae* to penicillin and cephalosporins, should be discontinued as soon as the causative organism is shown to be susceptible to penicillin, cefotaxime, or ceftriaxone. Resistance of *S. pneumoniae* to penicillin and cephalosporins remains a problem worldwide. Penicillin G 250,000 U/kg/d (maximum dose 12 million U/d) can be used in children or adolescents with meningococcal meningitis.

Children or adolescents with suspected meningitis require droplet and standard precautions for the first 24 hours of appropriate antibiotic therapy. Repeat lumbar puncture should be considered after 24 to 48 hours of therapy to confirm sterilization of the CSF in neonates and in children with pneumococcal meningitis who received dexamethasone or have infections with strains that are not susceptible to penicillin or cephalosporins. Infants older than 1 month of age, children, and adolescents with bacterial meningitis should receive 7 to 14 days of therapy, depending upon the organism and the response to therapy.

Despite appropriate therapy, mortality rates for infants with bacterial meningitis range from less than 10% for term infants to more than 30% for infants weighing under 1,000 g. Approximately 40% of the infants who survive neonatal meningitis have neurologic sequelae, consisting of cerebral palsy, behavioral disorders, developmental delay, hydrocephalus, and epilepsy. Stroke or cystic encephalomalacia can be detected in survivors by computed tomography (CT) or magnetic resonance imaging (MRI). Among infants older than 1 month of age, children, and adolescents the prognosis depends upon the pathogen and the presence of any underlying medical condition. Mortality rates as high as 30% can occur with pneumococcal meningitis. Sensorineural hearing loss, the most common sequela, affects 5 to 20% of the survivors; additional complications include hydrocephalus (Figure 91-1), stroke, motor disability, cognitive dysfunction, and behavioral disorders. Dexamethasone therapy, shown to reduce the

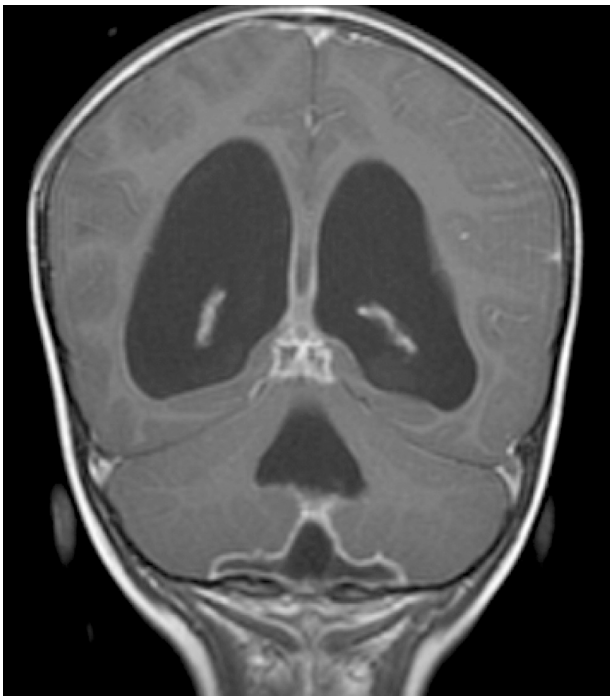

FIGURE 91-1. Gadolinium–enhanced T_1–weighted coronal MRI in a child with *Haemophilus influenzae* meningitis shows marked basilar enhancement and enlargement of the 4th and lateral ventricles due to obstruction of the basal foramina. Similar abnormalities can be observed during neonatal bacterial meningitis.

risk of sequelae in infants and children with *H. influenzae* meningitis and also in adults with meningitis, remains controversial in children with *S. pneumoniae* or *N. meningitides* meningitis.

Viral Meningitis

In contrast to bacterial meningitis, viral or aseptic meningitis usually represents a benign disorder with very low rates of morbidity and mortality. However, death can occur in neonates with aseptic meningitis as a consequence of hepatitis or viral myocarditis. Although many viral (Table 91-1) and some nonviral pathogens can produce aseptic meningitis, most cases result from infections with the nonpolio enteroviruses. These ribonucleic acid (RNA) viruses, comprising approximately 70 distinct serotypes, circulate among humans, and frequently cause outbreaks of disease during the summer months.

Infants with viral meningitis have fever, anorexia, vomiting, and irritability. Older children and adolescents commonly experience fever, vomiting, headache, photophobia, and signs of meningeal irritation, including the Kernig and Brudzinski signs. Systemic features at any age can include rash, myalgias, diarrhea, or signs of an upper respiratory tract illness. Hepatomegaly, congestive heart failure, or DIC can accompany meningitis in severe neonatal viral infections, especially those due to the nonpolio enteroviruses.

The CSF in viral meningitis usually shows a mixed or lymphocytic pleocytosis, normal glucose concentration, and normal or mildly elevated protein concentration. Gram stain may show leukocytes without bacteria. Analysis of CSF using the polymerase chain reaction (PCR) has become the gold standard for diagnosing enteroviral aseptic meningitis. PCR can also be used to detect other viral and nonviral causes of meningitis, including herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus (HHV)-6, HHV-7, *Mycoplasma pneumoniae*, and *Mycobacterium tuberculosis*. An etiologic diagnosis can be established in certain infections by serologic studies or by cell culture of CSF and swabbings of the oropharynx, rectum, and skin lesions.

The management of infants and children with viral meningitis consists predominantly of supportive care, including the provision of intravenous fluids and analgesia.

TABLE 91-1. Microbiologic Evaluation for Viruses Causing Meningitis or Encephalitis

Pathogen	Diagnostic Method(S)
Herpes simplex virus type 1 (HSV–1)	CSF PCR[1]
Herpes simplex virus type 2 (HSV-2)	CSF PCR
Epstein-Barr virus (EBV)	CSF PCR; Serum titers[2]
Varicella-zoster virus (VZV)	CSF PCR
Cytomegalovirus (CMV)	CSF PCR; culture of urine or saliva
Human herpes virus 6 (HHV-6)	CSF PCR
Human herpes virus 7 (HHV-7)	CSF PCR
Human herpes virus 8 (HHV-8)	CSF PCR
Non-polio enteroviruses, including EV-71	CSF RT-PCR; Culture of stool or oropharyngeal secretions
Western and Eastern equine viruses	Serology[3]; CSF IgM
St. Louis encephalitis virus	Serology
Japanese encephalitis virus	Serology; CSF RT-PCR; CSF IgM
West Nile virus	Serology[4]; CSF RT-PCR; CSF IgM
LaCrosse virus	Serology; CSF IgM
Tick-borne encephalitis virus group	Serology
Colorado tick fever	Serology
Rabies virus	Serum titers; IFA[5]

[1]Polymerase chain reaction.

[2]Acute EBV infection can be confirmed by the presence of anti-EBV viral capsid antigen (VCA) IgG and/or IgM and the absence of anti-EBV nuclear antigen (EBNA) IgG.

[3]Agent specific IgM and IgG in acute and convalescent serum samples.

[4]WN virus-specific IgM can persist for extended periods (> 12 months). WN virus-specific IgG has limited or no diagnostic value.

[5]Immunofluorescence antibody staining of skin from the nape of the neck. Rabies-specific antibodies can be detected after 10 days of symptoms in human rabies.

Pleconaril, a novel antiviral agent with activity against several RNA viruses, may be of benefit in severe, life threatening enteroviral infections, especially in infants or immunocompromised patients. Disease-specific therapy is required for conditions, such as tuberculous, carcinomatous, fungal, or parasitic diseases, that mimic viral or aseptic meningitis.

Encephalitis

Epidemiology

When encephalitis was a notifiable disease in the United States, the Centers for Disease Control and Prevention (CDC) received reports of 2,000 or more cases of viral encephalitis annually, corresponding to approximately 0.5 cases per 100,000 inhabitants of the United States. Approximately 2,500 cases of HSV-1 encephalitis, a nonreportable disorder, also occur annually in the United States. During epidemics, the number of encephalitis cases can be substantially greater. More than 4,000 human cases of West Nile virus infection, an Old World flavivirus first observed in the United States in 1999, were confirmed in both 2002 and 2003. Although human rabies remains rare in most developed countries, including the United States, several thousand deaths result from rabies worldwide each year.

Information regarding residence, travel, occupational or recreational activities, and exposure to vectors provides useful clues regarding the etiology of encephalitis. Pathogens transmitted by mosquitoes or ticks, for example, typically cause encephalitis during the summer months. La Crosse virus, a mosquito-borne bunyavirus, causes summertime encephalitis in children living in the Midwestern United States, whereas Japanese encephalitis, the most common arboviral encephalitis worldwide, affects people residing throughout Asia and India. *Rickettsia rickettsii*, the bacterial cause of Rocky Mountain spotted fever, a disorder that mimics viral encephalitis, causes disease from April through September in endemic regions of the U.S.

Clinical Features and Diagnosis

The clinical manifestations of viral encephalitis include fever, headache, vomiting, altered mental status, and seizures, either partial or generalized. Partial seizures or focal neurologic deficits may indicate HSV-1 encephalitis, but focal features can also be observed in other types of viral encephalitis, including relatively benign childhood cases caused by the La Crosse virus. The neurologic examination may show hyperreflexia, ataxia, cognitive disturbances, and focal deficits, including aphasia and hemiparesis. Young infants with encephalitis often have nonspecific signs, such as inactivity, poor feeding, irritability, "fussy" behavior, and "high-pitched" cries.

The CSF in viral encephalitis usually shows an elevated protein content, normal glucose content, and a lymphocytic pleocytosis. However, the CSF findings can vary, and in some patients, the CSF can be entirely normal. Between 5 and 15% of individuals with HSV-1 encephalitis initially lack pleocytosis (CSF cell count < 5/μL), a feature that complicates the diagnosis of HSV encephalitis, especially in young children. Children with CNS viral infections can have a mixed or neutrophilic pleocytosis that can resemble bacterial meningitis, especially during the early stages of viral infection. Some viruses produce mild hypoglycorrhachia, but very low CSF glucose values suggest bacterial disease rather than viral infection. Erythrocytes can be observed, particularly in HSV encephalitis, but a hemorrhagic CSF profile has little diagnostic specificity.

MRI may show unique patterns that suggest a specific pathogen. For example, children and adolescents with HSV-1 encephalitis characteristically have T_2 prolongation or gadolinium enhancement of the insular cortex, mesial temporal lobe, inferior frontal lobe, and cingulate gyrus. Japanese encephalitis produces abnormalities of the thalamus, basal ganglia, and brain stem. West Nile virus encephalitis can be associated with lesions in the basal ganglia, thalamus, brain stem and cerebellum, although MRIs are often normal in such patients. Children with acute disseminated encephalomyelitis (ADEM), an immunemediated disorder that accounts for 15% of encephalitis cases, have multifocal areas of T_2 prolongation that can involve the cerebrum, cerebellum, brainstem, and spinal cord.

The electroencephalogram (EEG) should be obtained when clinicians suspect viral encephalitis; particularly when seizures complicate the illness. In patients older than 5 months with HSV-1 encephalitis, approximately 80% have focal slowing or repetitive epileptiform discharges localized to the temporal lobes. Nearly one-half of children with La Crosse virus encephalitis also have focal EEG abnormalities, indicating that the diagnosis of HSV-1 encephalitis cannot rely upon the EEG findings alone. Diffuse slowing of background rhythms or multifocal epileptiform discharges are commonly seen in children with many forms of viral or nonviral encephalitis and in ADEM.

Children with suspected viral encephalitis require a comprehensive microbiologic evaluation that reflects the season, the geographic location, and the presence of immunocompromising conditions, such as HIV infection. Numerous neurotropic viruses cause encephalitis in children (see Table 91-1). In addition, certain nonviral pathogens, such as *M. pneumoniae, R. rickettsii,* and *Bartonella henselae* (the cause of cat-scratch disease), as well as postinfectious conditions, including acute disseminated encephalomyelitis, mimic viral infection of the CNS.

Specimens for conventional virus isolation consist of cultures of urine, blood, CSF, feces, throat washings, and fluid from skin lesions, depending upon the suspected pathogen. Serologic studies may be the only means to confirm infections with certain pathogens, including EBV, many arboviruses, and organisms such as *M. pneumoniae* and *B. henselae*. Detecting virus-specific immunoglobulin M in CSF or serum can confirm infection with certain arboviruses, including La Crosse, West Nile, and St. Louis encephalitis viruses.

PCR can be used to detect several viruses, including HSV-1, CMV, EBV, varicella-zoster virus (VZV), HHV-6, HHV-7, and the nonpolio enteroviruses. The sensitivity of CSF PCR in children with HSV-1 encephalitis averages 90% to 95%, but it can be as low as 70% in neonates with proven HSV disease. By combining the results of CSF PCR and MRI, the ability to detect HSV encephalitis reliably can approach 100%. Reverse transcription (RT) PCR has high sensitivity for the nonpolio enteroviruses. In contrast, the sensitivity and predictive values of PCR or RT-PCR for many other viruses are unknown, indicating that sound clinical judgment must guide the therapy of children with suspected viral encephalitis.

Treatment

The treatment of children with viral CNS infections consists of supportive care, anticipation of potential complications, and initiation of the available specific antiviral chemotherapy. Often, acyclovir is provided empirically until HSV encephalitis can be excluded Children with encephalitis should be hospitalized and monitored closely for the development of increased ICP and seizures. Seizures affect 15 to 50% of the infants, children, or adolescents with encephalitis.

Brief or infrequent seizures can be treated with benzodiazepines (lorazepam or diazepam) using standard weight-appropriate doses (eg, 0.05 to 0.1 mg/kg of lorazepam administered intravenously; maximum single dose of 4 mg). Prolonged or repetitive seizures require loading doses of fosphenytoin, 15 to 20 mg/kg of phenytoin equivalents intravenously, or phenobarbital, 10 to 15 mg/kg intravenously in infants or toddler-aged children. Increased ICP, manifested by clinical or radiographic features, may require mannitol, hyperventilation, or placement of an extraventricular drainage catheter.

Children with suspected HSV-1 encephalitis require treatment with acyclovir, using 60 mg/kg/d divided every 8 hours. Doses of 1,500 mg/m2/d can be used in adolescents. Neonates with suspected HSV encephalitis, usually due to HSV-2, should receive 60 mg/kg/d divided every 8 hours. Dose reductions are necessary in children with impaired renal function because of the drug's potential nephrotoxicity.

Patients with confirmed HSV encephalitis require therapy for 14 to 21 days (neonates with HSV encephalitis require 21 days of therapy). Complete blood cell counts should be measured twice weekly during prolonged therapy, given the potential for acyclovir-induced neutropenia. When doubt exists regarding the possibility of HSV encephalitis, full courses of acyclovir may be necessary. Patients with encephalitis due to VZV should receive acyclovir, 30 mg/kg/d in children under 1 year of age and 1,500 mg/m2/d in older children for 10 to 14 days. Ganciclovir, using doses of 10 to 12 mg/kg/d, can be considered in patients with EBV or CMV encephalitis, but the potential side effects, nephrotoxicity, and myelotoxicity should be balanced cautiously against anticipated benefits. Children or adults with severe nonpolio enteroviral CNS infections, including disease caused by EV 71, an especially neurovirulent enterovirus, may receive benefit from pleconaril, a novel antiviral agent with activity against several RNA viruses. Anecdotal information suggests that ribavirin may have utility in West Nile or La Crosse virus encephalitis, but no controlled trials have been conducted. Patients with ADEM may respond to corticosteroid therapy.

Viral encephalitis has a variable prognosis that reflects several factors, including the etiologic agent, the patient's age, and any underlying medical conditions. Encephalitis

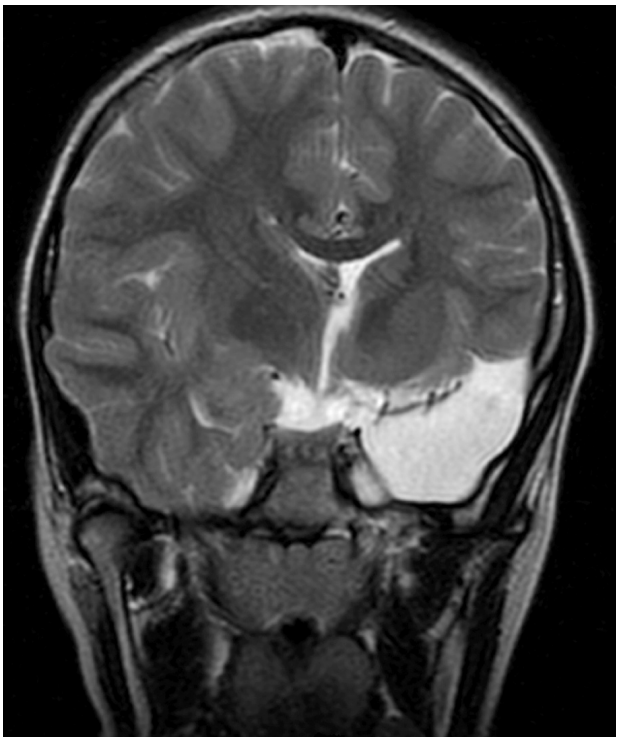

FIGURE 91-2. Coronal T_2-weighted MRI in a child who survived HSV-1 encephalitis shows complete cystic encephalomalacia of the left temporal lobe and volume loss of the left hemisphere.

due to the nonpolio enteroviruses and the La Crosse virus produce low rates of mortality or morbidity. Mortality in acyclovir-treated patients with HSV encephalitis currently averages less than 20%, but as many as 50% of the survivors have seizures, cognitive dysfunction, or behavioral abnormalities despite appropriate medical management (Figure 91-2). Survivors of West Nile CNS infections may also have sequelae, given the propensity of this virus to damage the brainstem and spinal cord. Human rabies encephalitis virtually always causes death.

Practitioner and Patient Resources

Centers for Disease Control and Prevention. West Nile virus. Available at: http://www.cdc.gov/ncidod/dvbid/ westnile (accessed October 8, 2004).

National Institute of Neurologic Disorders and Stroke. NINDS encephalitis and meningitis information page. Available at: http://www.ninds.nih.gov/health_and_medical/disorders/encmenin_doc.htm (accessed date October 8, 2004).

Saez-Llorens X, McCracken GH Jr. Bacterial meningitis in children. Lancet 2003:361(9375):2139–48.

Whitley RJ, Gnann JW. Viral encephalitis: familiar infections and emerging pathogens. Lancet 2002;359(9305): 507–13.

Meningitis Foundation of America (MFA)
6610 Shadeland Station, Suite 200
Indianapolis, IN 46220-4393
E-mail: support@musa org
http://www.musa.org
Phone: 800-668-1129 or (317) 595-6383
Fax: (317) 595-6370
MFA's goals are to help support sufferers of spinal meningitis and their families, provide information to educate the public and medical professionals about meningitis so that its early diagnosis and treatment will save lives, and help support the development of vaccines and other means of treating and/or preventing meningitis. This site provides information on symptoms, treatment, prevention, and recovery.

National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health
31 Center Drive, Room 7A50 MSC 2520
Bethesda, MD 20892-2520
Phone: (301) 496-5717
http://www.niaid.nih.gov
NIAID conducts and supports research that strives to understand, treat, and ultimately prevent the myriad infectious, immunologic, and allergic diseases that threaten hundreds of millions of people worldwide. Information on allergic and infectious diseases can be found on this site.

The Encephalitis Society
Information for families and professionals can be found at this site. The aim of the Society is to improve the quality of life of all people affected directly and indirectly by encephalitis. It fulfills this aim by supporting individuals and families of people with encephalitis and promoting better services; raising awareness among relevant professionals, statutory agencies, and the wider public about the condition and its subsequent problems; and promoting research into encephalitis.

Chapter 92

Traumatic Brain and Spinal Cord Injuries in Children

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Trauma is one of the most common causes of admission of children to hospitals. This chapter reviews the neurologic complications from trauma and their management.

In the Western world, accidents constitute the major cause of death for children 5 to 19 years of age. Between 1951 and 1971, the number of children with head injury admitted to hospitals in Newcastle-upon-Tyne, United Kingdom, increased six-fold, reaching 13.9% of all admissions to pediatric wards. (This increase probably was due, in part, to a change in policy that resulted in a greater number of patients whose injuries appeared minor being admitted for observation.) In the United States, the situation is similar. Cranial and major facial injuries are responsible for 3.6% of hospital admissions and 3.3% of days spent in the hospital, and they are the most common neurologic conditions associated with hospital admission for patients younger than 19 years of age. Each year, about 7,000 children die from head injuries, currently the most common cause of death and disability of children in the United States. They are also the cause of substantial cognitive and motor or sensory dysfunction in the pediatric population, with an estimated economic burden of nearly $10 billion a year in the United States alone.

A large number of patients who suffer head injuries die at the scene of the accident or on the way to the hospital, so admission figures reflect only part of the incidence. In the San Diego Prospective Survey, as many as 85% of fatalities occurred at these times. In addition, since the 1980s, child abuse has been increasingly recognized as a cause of head injury. Between 1976 and 1990, the incidence of reported cases rose from 10.1 in 100,000 children to 39 in 100,000 children. In one series, 36% of all head injuries and 95% of injuries resulting in intracranial hemorrhage or other major cerebral complications in infants younger than 1 year old were due to child abuse. A survey conducted in North Carolina during 2000 and 2001 found that 53% of children aged 2 years or younger who were admitted to the hospital or who died with traumatic brain injuries were found to have an inflicted injury. In older children, the proportion of injury from abuse is lower but still significant.

Cranial trauma also commonly occurs in childhood sports. Brain concussion occurs in an estimated 19 in 100 American football players per year. Bicycling is probably the second most common sport leading to head injury. In an Australian series, bicycling was responsible for more than 20% of all head injuries in children.

Traumatic Brain Injuries

General Considerations

Injuries expected from various accidents are depicted in Table 92-1. The damages that can result from head injuries have been grouped into primary and secondary injuries. Primary injuries are those that occur immediately at the moment of impact, whereas secondary injuries evolve later. The various traumatic intracranial lesions are listed in Table 92-2. The most common cause of secondary brain injury is cerebral edema. The effects of traumatic brain injury on cerebral blood flow are crucial to the development of cerebral edema. Early after severe

TABLE 92-1. Expected Injury Types Associated With Accidental Mechanisms in Very Young Children*

Mechanism	Injury Types
Fall < 4 ft	Concussion/soft tissue injury
	Linear fracture
	Epidural hematoma
	Ping-pong fracture
	? Depressed fracture
Fall > 4 ft	Injuries listed above plus the following:
	Depressed fracture
	Basilar fracture
	Multiple fractures
	Subarachnoid hemorrhage
	Contusion
	? Subdural hematoma*
	? Stellate fracture*
Motor vehicle accident	Injuries listed above plus the following:
	Subdural hematoma
	Diffuse axonal injury

From Dumaine AC. Head injury in very young children. Pediatrics 1992;90:184. With permission of the author, and from Menkes JH, Ellenbogen RG. Postnatal trauma and injuries by physical agents. In: Menkes JH, Sarnat HB, Maria, BL, editors. *Child Neurology.* 7th ed. Philadelphia (PA):Lippincott, Williams & Wilkins; 2006; pp. 659–702.

*Injury types preceded by question marks are uncommonly associated with the given mechanism.

traumatic brain injury, marked hypoperfusion develops, with reduction in oxygen delivery and cerebral ischemia. Some 24 hours later, cerebral blood flow increases. Posttraumatic hyperemia is more common in infants and children than in adults and is probably the consequence of a loss of cerebral autoregulation. Hyperemia, in turn, contributes to massive brain swelling, which is not uncommon in infants and young children, and has been termed "malignant brain edema." The role of the aquaporin water transporting proteins in the evolution of brain edema has yet to be fully delineated.

When the additive effects of injury and brain swelling are severe, a self-perpetuating sequence develops, which can lead to further increase of intracranial pressure, with collapse of cerebral venules. This collapse, in turn, reduces cerebral perfusion and causes tissue hypoxia, leading to further cerebral edema. A loss of selective permeability of cell membranes results, with increased loss of fluid from the vascular compartment into the parenchyma, thereby increasing cerebral swelling. Recovery has not been seen when intracranial pressure equals or exceeds mean systemic arterial pressure, at which point cerebral perfusion ceases.

More than 90% of major pediatric head injuries are nonpenetrating and closed; that is, the dura is not perforated. The clinical picture is highlighted by alterations in consciousness. When the injury is mild, initial unconsciousness is brief and is followed by confusion, somnolence, and listlessness. Vomiting, pallor, and irritability are common and, particularly in infants, can occur in the apparent absence of an initial loss of consciousness. Concussion is defined as an injury to the head sufficient to cause a transient loss of consciousness or amnesia for the event. It is unclear, and often debated, whether alteration in mental status from a concussion is a result of diffuse cortical dysfunction or injury to the reticular activating system in the brainstem. The etiology may vary depending on the mechanism that causes the concussion. However, by definition a concussion with a transient loss of consciousness is followed by return of normal mentation and neurological function. When persistent sensory, motor or neurological findings are noted an alternative diagnosis should be sought for by further examinations and radiological imaging.

As a rule, a computed tomography (CT) scan clarifies the differential diagnosis of cerebral contusion, subarachnoid or intraventricular hemorrhage, extra-axial hematoma, midline shift, or other manifestations of a more serious closed head injury. A lumbar puncture is not warranted for diagnosis of intracranial hemorrhage, including subarachnoid hemorrhage in a child, unless there is a question of a CNS infection, notably meningitis. This procedure should only be performed after a CT scan has

TABLE 92-2. Classification of Traumatic Intracranial Lesions

Primary lesions
Intra-axial
Diffuse axonal injury
Cortical contusion
Subcortical matter injury
Primary brainstem injury
Extra-axial hematomas
Extradural
Subdural
Diffuse hemorrhage
Subarachnoid
Intraventricular
Primary vascular injuries
Secondary lesions
Pressure necrosis (secondary to brain displacement and herniations)
Tentorial arterial infarction
Diffuse hypoxic injury
Diffuse brain swelling
Boundary and terminal zone infarction
Others
Fatty embolism
Secondary hemorrhage
Infection

From Gentry LR, Godersky JC, Thompson B. MR imaging of head trauma: review of the distribution and radiopathologic features of traumatic lesions. AJR Am J Roentgenol 1988;15:663–72, and from Menkes JH, Ellenbogen RG. Postnatal trauma and injuries by physical agents. In: Menkes JH, Sarnat HB, Maria, BL, editors. *Child Neurology.* 7th ed. Philadelphia (PA): Lippincott, Williams & Wilkins; 2006; pp. 659–702.

ruled out a mass effect. Cerebral contusions consist mainly of petechial hemorrhages in the superficial cortical layers. They occur at the site of impact (coup injuries) or opposite to the site of impact (contrecoup injuries). Cerebral lacerations usually result from penetrating wounds or depressed skull fractures. Seven to 40% of children with mild head injuries have associated linear fractures of the skull. These fractures are most common in the parietal region. With major closed head injuries, consciousness is interrupted more profoundly and for longer periods than with minor head injuries, and focal neurologic signs point to localized brain contusion. The clinical picture in such cases is outlined in Table 92-3. Generally, the greatest neurologic deficit is found at the time of injury. New neurologic signs appearing subsequent to the initial injury indicate progressive brain swelling. If localized, they indicate secondary intracranial hemorrhage, vasospasm, or thrombosis. The duration of coma depends on the site and severity of injury. The ability of magnetic resonance imaging (MRI) to detect subtle cortical and white matter changes has expanded the role of this procedure in the management and prognosis of head injuries after their initial acute treatment.

The clinical picture can follow one of several courses. Many children die without recovering consciousness. In a smaller number of patients, coma can persist. Prognosis for survival is relatively good in children who are alive 48 hours after injury. In half the surviving children, consciousness is regained in less than 24 hours. Recovery is often complete or nearly complete, although transient sequelae are not unusual.

TABLE 92-3. Clinical Findings in 4,465 Children with Major Closed Head Injuries*

Finding	Percent
Initial level of consciousness	
Normal	56.0
Drowsy, confused	30.2
Major impairment	13.8
Vomiting	30.3
Skull fractures	26.6
Linear	72.8
Depressed	27.2
Compound	19.7
Seizures	7.4
Paralyses	3.8
Retinal hemorrhages	2.3
Pupillary abnormalities	3.6
Papilledema	1.5
Extradural hematoma	0.9
Subdural hematoma	5.2
Mortality	5.4
Major neurologic residua	5.9

From Hendrick EB, Harwood-Nash DC, Hudson AR. Head injuries in children: a survey of 4465 consecutive cases at the Hospital for Sick Children, Toronto, Canada. *Clin Neurosurg* 1963:11:46–65, and from Menkes JH, Ellenbogen RG. Postnatal trauma and injuries by physical agents. In: Menkes JH, Sarnat HB, Maria BL, editors. *Clin Neurosurg* 7th ed. Philadelphia (PA): Lippincott, Williams & Wilkins; 2006; pp. 659–702.

*This series includes 243 infants with major birth injuries. This group had 50% mortality and a higher incidence of paralyses, retinal hemorrhages, and major residua.

Nonsurgical Treatment

The Glasgow Coma Scale (GCS) is widely used to initially assess patients with traumatic injury. Several pediatric modifications of the GCS have been proposed. One example is presented in Table 92-4.

The scale measures three neurologic responses: (1) eye opening, (2) verbal response, and (3) limb movement. Each response is given a score; the higher the score, the better the patient's condition. It should be noted that 3 is the lowest possible GCS.

Minor Head Injury

Minor head injuries have been defined as injuries with an initial and subsequent GCS of 13 to 15. The American Academy of Pediatrics has published guidelines for the management of minor head injuries in children younger than and older than 2 years of age. These have been incorporated into Table 92-5. Considerable judgment is required to avoid unnecessary hospitalization and expensive diagnostic studies, at the same time keeping in mind the possibility of post-traumatic complications that

TABLE 92-4. Pediatric Coma Scale

Eyes open	
Spontaneously	4
To speech	3
To pain	2
Not at all	1
Best verbal response	
Orientated	5
Words	4
Vocal sounds	3
Cries	2
None	1
Best motor response	
Obeys commands	5
Localizes pain	4
Flexion to pain	3
Extension to pain	2
None	1
	Normal Aggregate Score
Birth to 6 months	9
6–12 months	11
1–2 years	12
2–5 years	13
Over 5 years	14

Modified from Simpson D, Reilly P. Pediatric coma scales. Lancet 1982;2:450.

TABLE 92-5. Management Strategy for Radiographic Imaging in Pediatric Patients with Head Trauma

Low-risk Group	Moderate-risk Group	High-risk Group
Possible findings		
Asymptomatic	Brief loss of consciousness at time of injury or subsequently (< 1 min)	Depressed or decreasing level of consciousness
Dizziness	Unreliable history	Focal neurologic signs
Scalp laceration	Younger than 2 years of age	Penetrating skull injury
Scalp hematoma	Posttraumatic seizure	Depressed fracture
		Bulging fontanel
		Irritability (< 2 years)
	Vomiting	
	Signs of basilar skull fracture	
	Fracture into an air sinus	
	Possible depressed fracture	
	Suspected child abuse	
Recommendations	Recommendations	Recommendations
Observation	Hospitalization	Emergency CT scan
Discharge with head injury information sheet; have family observe child. (fewer than 1/5,000 require neurosurgical intervention)	Close observation CT scan and neurosurgical consultation (2 to 5%required neurosurgical intervention)	Neurosurgical consultation

Adapted from Masters SJ, McClean PM, Arcarese JS, et al. Skull X-ray examinations after head trauma. Recommendations by a multidisciplinary panel and validation study. N Engl J Med 1987; 316:84–91; from American Academy of Pediatrics. The management of minor closed head injuries in children. Pediatrics 1999;104:1407–15; from Schutzman SA, Barnes P, Duhaime AC, et al. Evaluation and management of children younger than two years old with apparently minor head trauma: proposed guidelines. Pediatrics 2001; 107:983-93. , and from Menkes JH, Ellenbogen RG. Postnatal trauma and injuries by physical agents. In: Menkes JH, Sarnat HB, Maria, BL, editors. *Child Neurology*. 7th ed. Philadelphia (PA): Lippincott, Williams & Wilkins; 2006; pp. 659–702.

require emergency surgery. In general, children who have suffered only a momentary loss of consciousness or amnesia to their injury (ie, concussion) are adequately managed at home, if a responsible parent or guardian can provide at least 24 hours of careful monitoring and oversight for sequelae and follow-up. This management paradigm is based on a growing body of literature showing that a normal neurological exam and normal CT scan in a child who has suffered a concussion, carries an extremely low risk of subsequent neurological deterioration. Parents are instructed to note at regular intervals the child's state of alertness and ability to follow commands appropriately especially over the subsequent 24 hours post injury. Although an evolving intracranial injury is rare, the most vulnerable and critical time to diagnose such a complication is within the first 4–8 hours after the injury. Although mild headaches and vomiting may persist post injury, a progression or intractability of symptoms requires parental judgment and timely return to a physician for re-evaluation. In addition, the guardian should be told to contact the physician if a deterioration in mental status, or the presence of a new neurological deficit is noted. This often requires a re-examination and follow-up imaging.

The role of routine CT in the management of the child with minor head injuries continues to be controversial. As indicated in Table 92-5, infants under 2 years of age or children who suffer a loss of consciousness should undergo CT or be transferred to an institution where this procedure can be performed. The use of skull radiography as a screening device for children who have minor head injuries has serious limitations and should no longer be used, as a CT with bone windows to show the presence of fractures is superior diagnostically. According to some authorities, the presence of a linear skull fracture should not influence the decision to send the child home or not; others suggest that such a child is at increased risk for an extradural hematoma and should, therefore, be observed in the hospital. We believe that whenever the fracture line crosses the groove of the middle meningeal artery or crosses the path of the sagittal or other major venous sinus, the possibility of an extradural hemorrhage is increased and the child should be hospitalized for the initial 24 hours. If the fracture involves an air sinus, checking for the next 10 days for signs of intracranial infection is recommended, even if the child is not hospitalized.

Major Head Injury

Recommended management consists of these four steps: (1) rapid initial evaluation; (2) resuscitation; (3) a more extensive secondary evaluation, including radiologic assessment; and (4) definitive treatment. In many instances of major closed head injury, diagnosis of the injury is performed as emergency treatment is administered.

Health care practitioners should remain highly alert and be prepared to treat sudden, frequent changes in a child's clinical condition.

Neurologic Examination

The neurologic examination should be conducted carefully and recorded, with particular emphasis on state of consciousness; pupillary size, equality, and response to light; extent and symmetry of spontaneous movements; and reflex responses. The *sine qua non* of the neurological exam in head injury is the mental status. An altered mental status is indicative of an underlying brain injury Recording of blood pressure, pulse, and respiration is likewise essential. Caloric and optokinetic responses are useful for evaluating brainstem function. Some or all of these observations, especially level of consciousness and motor activity, are principally of value when made serially at intervals that can be as frequent as every 5 minutes. The importance of repeated observations of vital signs and neurologic status cannot be overemphasized.

In addition, the extent of retrograde and posttraumatic amnesia should be recorded when possible. The length of pre- and post-traumatic amnesia is a useful indicator of the severity of the head injury.

Maintenance of Airway and Circulation

Hypoxemia and hypotension can occur before the child reaches the hospital and significantly increase the likelihood of a poor outcome. After immediately evaluating the child's general condition, an adequate airway should be established and maintained. Airway obstruction is the most frequent cause of respiratory failure. Maintenance of patency requires suction of mouth or pharyngeal contents, or endotracheal intubation followed, when necessary, by artificial respiration. Tracheostomy may be indicated to bypass mechanical obstruction of the airway caused by facial or mandibular injuries. Because an injury to the cervical spine must be presumed until proved absent, the neck must be stabilized while an airway is established. Arterial pressure is monitored by cannulation of a peripheral artery and maintained by administration of crystalloid, colloid, or blood products. Gas exchange also must be monitored.

Shock in closed head injuries is usually caused by blood loss elsewhere in the body. Rarely, it indicates damage to the medullary cardiovascular centers. The exception to that is seen in infants, in whom subgaleal, subdural, or extradural hemorrhages can be sufficiently extensive to induce shock. Whenever head injury is accompanied by systemic hypotension, the outcome is significantly worse.

Neuroimaging Studies

CT of the head is the most appropriate study for the assessment of intracranial complications and takes precedence over MRI, which usually contributes little to the initial management of major closed head injury. A suggested strategy for determining the need and timing of such imaging studies is outlined in Table 92-5.

MRI is more sensitive than CT in detecting an extra-axial hematoma and thin collections of fluid. In addition, MRI provides better visualization of subacute and chronic contusions and of injuries to the white matter, such as those resulting from shearing injuries associated with shaken baby syndrome or high-speed motor vehicle accidents. MR spectroscopy has been used to indicate the severity of the head injury, and predict the outcome. Altered brain metabolites are sensitive indicators of injury, and lowered N-Acetylaspartate levels correlate with ultimate cognitive function.

One must guard against excessive complacency on the basis of a single normal CT obtained in the early hours after an injury, because hemorrhagic complications can evolve subacutely after an interval of several hours or days. A repeat CT is indicated under the following circumstances: (1) when there is doubt about the presence of a mass lesion, (2) when intracranial pressure monitoring demonstrates a rise in pressure, (3) when a patient is unconscious despite an initial benign-appearing CT, and (4) when a contusion is accompanied by a neurologic deficit. A normal CT also does not exclude the presence of cerebral edema.

Fluid and Electrolytes

The appropriate fluid management of the hypovolemic head-injury patient is still controversial, although both clinical and experimental studies indicate that the most important goals are to correct any hypovolemia and prevent reduction of osmolality. A period of hyponatremia with natriuresis is a common response to severe brain injury.

The relationship between fluid load, sodium balance, and intracranial pressure is still unclear. The traditional view is that during the early post-traumatic period, there is danger of overloading the patient with fluids, which can increase intracranial pressure and thus diminish the level of consciousness. Fluid restriction, however, increases the likelihood of cerebral infarction, and to avoid cerebral ischemia most centers currently recommend that hypertonic or isotonic crystalloid solutions be given intravenously to maintain a normal intravascular volume and adequate cerebral perfusion pressure.

Coagulation Defects

A substantial number of patients with head injuries severe enough to result in destruction of brain tissue show clinical and laboratory evidence of impaired coagulation. These patients have low fibrinogen levels, diminished amounts of factors V and VIII, and thrombocytopenia. Treatment can require emergency replacement of hemostatic factors. Disseminated intravascular coagulation can be seen in a small number of children with severe head injury or extensive hemorrhage.

Seizures

Seizures can occur shortly after the injury or can appear following an interval of days to years. Seizures appearing during the acute stage can increase intracranial pressure and aggravate any pre-existing hypoxia. Status epilepticus resulting from head trauma must be treated early and aggressively. Seizures generally are managed with intravenous (IV) fosphenytoin (10–15 mg/kg loading dose, followed by a maintenance dose of 4–8 mg/kg/d, administered in one to two divided doses). Compared with phenytoin, fosphenytoin, a phenytoin pro-drug, is easier to administer intravenously, has fewer side effects, and is less caustic to the veins. Diazepam (0.1–0.3 mg/kg) or lorazepam (0.05–0.1 mg/kg) are suitable alternatives. Electroencephalogram (EEG) monitoring is desirable to detect electrical seizures, even when paralysis of the patient prevents overt seizures.

Increased Intracranial Pressure

Children tend to have a lower incidence of surgically treatable mass lesions than have adults, but a higher incidence of increased intracranial pressure. Increased intracranial pressure reduces cerebral perfusion and is an important factor in the production of secondary brain injury. Therefore, in the infant or child who has sustained a severe head injury, control of increased intracranial pressure becomes the most important problem of medical management. For this purpose, continuous pressure monitoring is necessary for the more seriously injured patients and for infants who are more likely to experience increased intracranial pressure.

Various monitoring techniques are currently in use, each with its advantages and disadvantages. Ventriculostomy remains the most effective way to monitor intracranial pressure and treat elevated pressure via continuous or intermittent cerebrospinal fluid (CSF) drainage. In the USA, fiberoptic ICP monitors are commonly used when ventricular drainage is not required. The normal range for intracranial pressure is 0 to 10 mm Hg. Intracranial pressure is usually maintained below 15 mm Hg, although temporary rises to 20 mm Hg are often unavoidable and can occur in the course of nursing procedures. Monitoring intracranial pressure also permits calculation of cerebral perfusion pressure (CPP). CPP is defined as the difference between mean arterial blood pressure (MAP) and intracranial pressure (ICP): CCP = MAP – ICP.

The initial step in lowering intracranial pressure is to induce hypocarbia by hyperventilation and reduce carbon dioxide partial pressure (pCO_2) to between 25 and 30 mm Hg. This maneuver causes cerebral vasoconstriction, thereby decreasing cerebral blood flow and volume. The response to hyperventilation is rapid but short-lived, and hyperventilation must be continued or increased to remain effective. Prolonged and routine use of hyperventilation may be deleterious in some patients by exacerbating ischemic brain injuries. Infants and children are at particular risk for this complication. Therefore, in the absence of elevated intracranial pressure, we no longer recommend the prophylactic use of hyperventilation.

Raising the head to between 0 and 30° in the neutral, midline position is commonly performed after severe head injury. This facilitates blood return from the brain to the heart and, thus, decreases intracranial pressure.

Diuretics have been used in a number of centers, mainly as a temporary measure while the patient and operating room are readied for surgery and while diagnostic studies are performed or for acute control of elevated intracranial pressure. Mannitol given in amounts of 0.25 to 1.0 g/kg body weight in the form of a 20% solution is the most commonly used osmotic diuretic. Furosemide is used in some institutions. One appropriate dosage for furosemide is 0.5 to 1.0 mg/kg, administered every 4 to 6 hours. Numerous well-controlled clinical studies have failed to demonstrate any significant effectiveness of corticosteroids in counteracting brain swelling in children with head injuries, and their use may be deleterious under some circumstances in that they increase the risk of deep vein thromboses and secondary infections in adult neurosurgical patients. High doses of barbiturates, generally pentobarbital, have been advocated whenever intracranial pressure does not respond to other forms of therapy. This therapy must be used cautiously, as it can cause cardiovascular collapse.

Sedation with pharmacologically induced paralysis is often used in the treatment of the child with severe head injury. IV narcotics in small doses by continuous or bolus infusion, short-acting benzodiazepines, and nondepolarizing muscle relaxants are used effectively for this purpose. Induced mild hypothermia (cooling to 32° to 33°) within 4 hours of injury in conjunction with hyperventilation (pCO_2 25–30 mm Hg) and barbiturates (4–6 mg/kg IV thiopental, followed by 6–8 mg/kg/h of continuous thiopental) has

reemerged as another measure to lower increased intracranial pressure and increase cerebral perfusion by lowering metabolic demands in severe head injury. A multicenter randomized study is currently being conducted on the efficacy and safety of hypothermia in the treatment of severe head injuries in children.

Prognosis

Children who have suffered minor head injuries—that is, head injuries without associated neurologic manifestations—generally are likely to retain full intellectual function. The prognosis for major head injuries, though less certain, is far better in children than in infants or adults. As a rule, prediction of outcome with respect to the severity of ultimate disability is accurate in only 70% by the end of the first week after injury. A low postresuscitation GCS score and the presence of cerebral swelling, particularly when it is accompanied by a shift of midline structures, are indices for a poor outcome. Early post-traumatic seizures in children with nonaccidental injuries are also of poor prognostic sign. The poor outcome in infants in all series probably reflects the higher incidence of child abuse and multiple injuries during the first year of life.

Generally, children with only behavioral abnormalities during the early post-traumatic period later return to baseline. No significant improvement in cognitive function can be expected after the first 6 to 12 months following injury. Improvement in speech and motor function can, however, continue for several years. A substantial number of survivors of major head injuries, however, suffer subsequent emotional and psychiatric disorders. These are covered in another section of this chapter.

Skull Fractures

Linear Fractures

The immature and more flexible skull of the child can sustain a greater degree of deformation than can that of an adult. Most skull fractures are linear and asymptomatic and, in the older child, are readily diagnosed by CT using bone windows. Often a subperiosteal or subgaleal hematoma, termed *cephalohematoma* in the newborn infant, accompanies a linear skull fracture. However, almost one third of linear fractures have no external sign of the underlying trauma. Palpation of the hematoma may falsely lead the examiner to think there is a depressed skull fracture. Imaging studies will disclose the underlying linear fracture. Aspiration of a traumatic hematoma is rarely indicated, and insertion of a needle or drain only increases the risk of introducing an infection into the hematoma cavity.

Closed linear fractures generally heal in 6 weeks to 3 months and, except for breaks crossing the path of major vessels or entering the paranasal sinuses, do not require special therapy or observations.

Growing Skull Fractures

Growing skull fractures complicate a benign course in less than 1% of all skull fractures. A growing skull fracture occurs when brain or CSF herniates between the edges of a skull fracture under the scalp. This occurs for two reasons: (1) the forces that cause the fracture are severe enough to tear the underlying dura, and (2) the outward vector of the growing brain drives it through the breech in the dura and skull as both the brain and skull grow rapidly in the first 3 years of life. These fractures usually occur in the very young in whom a forceful injury induces a dural laceration. Growing skull fractures can usually be diagnosed by the primary-care provider when a pulsatile scalp mass is noted in a child several months post-injury on follow-up exam. CT or MRI scans will show the fracture separation and the brain hernia or CSF out pouching. Surgical repair is almost always indicated. These fractures require repair of the dural laceration, often with a dural patch, and reconstruction of the resulting cranial defect with an autologous piece of bone or cranioplasty.

Basilar Skull Fractures

Basilar skull fractures are uncommon in children. Because imaging studies often fail to reveal basal fractures, diagnosis often depends on the clinical findings. The presence of a basal fracture can be suspected when the child has signs of bleeding from the nasopharynx or the middle ear or if the child has postauricular ecchymoses. Epistaxis is frequent in childhood head injuries, however, because of the high incidence of nasal fractures.

CSF rhinorrhea can accompany a fracture of the floor of the anterior fossa that has involved the cribriform plate. It represents a rare complication of head trauma in children, but the high risk of intracranial infections makes recognizing it imperative. The infecting agents are a variety of grampositive cocci and gram-negative bacilli. Conservative management of CSF fistulas is successful in most instances. This entails bed rest, with the head raised or with placement of a lumbar drain. If conservative treatment fails, surgical repair (intradural, extradural, or both) will be required.

Whether chemoprophylaxis should be used on all patients with basal skull fractures has been the subject of considerable debate. Prospective studies have shown that prophylactic ampicillin does not reduce the risk of meningitis but can change the flora so that gram-negative organisms become the infecting agents. We, therefore, prefer to withhold antibiotics until careful observation has

revealed evidence of infection. In penetrating injuries, such as are seen with gunshot wounds, antibiotic therapy is generally recommended.

Injury to the cranial nerves, particularly the olfactory, facial, and acoustic nerves, can accompany basilar fractures. Cranial nerve injury is the consequence of multiple mechanisms, notably injury to the nerve by bony fragments. Injuries to the olfactory nerves are the most common and are generally bilateral. In most instances, dysfunction is permanent when the palsy is immediate. The likelihood for recovery is substantially greater when the palsy is delayed. Rarely, transient total blindness can follow an apparently mild blunt head injury.

Labyrinthine disorders, notably vertigo and spontaneous or positional nystagmus, are common. The condition is usually transient. In about half the cases, an electronystagmogram provides objective evidence of the presence of an injury to the labyrinth.

Depressed Fractures

Approximately 50% of depressed skull fractures occur in children. These are usually the result of focal injuries such as when a child strikes an object like a corner of furniture or is struck by a moving object such as a ball or bat. Depressed fractures, called "ping-pong" fractures can be a consequence of perinatal injury, often the result of a difficult forceps delivery. Depressed fractures can also occur with any localized skull trauma in later childhood, and are rarely associated with dural lacerations. Often conservative therapy is warranted for simple depressed fractures without neurological deficits. However, should there be a break in the skin (compound fracture) and localized cerebral injury, the management issues are quite different. The extent of the brain and bony injury is best diagnosed by CT. The outcome appears to be the same with or without surgery in patients whose skull is depressed less than the thickness of the cortical bone. We believe that a case can be made on cosmetic grounds for elevating a deep or unsightly depression, particularly when it is located in the frontal region. Depressed skull fractures that cause dural tears, CSF leaks, or cortical injuries or that broach the paranasal sinuses may be electively repaired early postinjury to prevent sequelae such as infection.

Compound Fractures

Compound fractures of the skull are seen in about 20% of children with major head trauma. In this kind of injury, medical treatment is limited to an initial cleansing of the scalp, institution of antibiotics, and tetanus prophylaxis. There are no clear guidelines in children for seizure prophylaxis. However, extrapolating from the adult literature, there is evidence that prophylaxis for early seizures (those occurring within 1 week after the injury) is effective, it does not prevent late seizures (those occurring more than 1 week after the injury). Therefore, for a child who has not had a seizure, one week of anticonvulsant prophylaxis may be sufficient. Anticonvulsant therapy is used routinely when the bony fragments have penetrated beyond the dura. We prefer to use carbamazepine as a maintenance anticonvulsant.

Scalp Lacerations

Scalp lacerations can cause considerable blood loss. If any doubt exists about the presence of a scalp injury, the child's hair should be clipped, and the area around the wound widely shaved. If examination and radiography do not show an underlying fracture, the wound should be closed in anatomic layers after careful débridement, with strict adherence to aseptic techniques. Closure of the galeal layer to stem hemorrhage and protect from infection is optimal. Tetanus vaccination should be administered.

Complications of Traumatic Brain Injuries

Extradural Hematoma

An extradural or epidural hematoma is a localized accumulation of blood between the skull and the dura. Nearly one-half of childhood cases occur during the first 2 years of life. In this age group, the injury is usually the result of a fall less than 4 to 5 feet, and there are no other significant injuries.

In adults, an extradural hematoma manifests itself characteristically by a temporary loss of consciousness, followed by partial or full recovery, with subsequent deterioration of sensorium and appearance of focal neurologic signs. This sequence is rare in children. More commonly, the child appears little affected by the initial injury or, at worst, has a brief period of unconsciousness. After an interval of minutes to several days, a progressive impairment of consciousness develops, and neurologic signs appear. The clinical picture of extradural hematoma is summarized in Table 92-6.

The diagnosis of an extradural hematoma rests principally on the clinical picture, and in some cases, surgical treatment is so urgent there is no time for imaging studies. Extradural hematoma must be differentiated from an acute subdural hematoma, an intracerebral hematoma, and severe brain swelling with or without contusion. Because both an acute extradural hematoma and an acute subdural hematoma require immediate surgical evacuation, the distinction between these two entities is academic. CT almost always detects the hematoma, except when the collection of blood is very thin or isodense with the brain such as seen in subacute subdural hematomas from a previous injury. Some epidural hematomas in children are so

TABLE 92-6. Common Clinical Features of Extradural Hematoma

Symptom*	Percentage of Patients
Vomiting	62.5
Unequal pupils	55.0
Delayed loss of consciousness	48.7
Skull fracture, all types	40.0
Hemiparesis	25.0
Papilledema	22.5
Depressed skull fracture	20.0
Third nerve paresis, other than pupillary dilation	17.5
Retinal hemorrhages	12.5

Modified from Hendrick EB, Harwood-Nash DC, Hudson AR. Head injuries in children: a survey of 4465 consecutive cases at the Hospital for Sick Children, Toronto, Canada. Clin Neurosurg 1963;11:46–65, and from Menkes JH, Ellenbogen RG. Postnatal trauma and injuries by physical agents. In: Menkes JH, Sarnat HB, Maria BL., editors. *Child Neurology*. 7th ed. Philadelphia (PA): Lippincott, Williams & Wilkins; 2006; pp. 659–702.

*Symptoms listed occur with a significantly greater frequency in children with extradural hematomas than in the general head trauma series.

small or are discovered several days after the incident that they do not need surgical intervention. When a fracture is accompanied by a small accumulation of blood, no brain shift, and no neurological signs or symptoms, surgery may not be indicated. In such patients, follow-up exams and CT scans often are indicated.

Operative removal of the clot can occasionally be performed through burr holes but usually requires a craniotomy for complete removal and arrest of bleeding. A child's general prognosis is often quite good when the extradural hematoma is removed within the first several hours after injury. This lifesaving craniotomy can take a comatose child and return him or her to normal neurologic function if the condition is diagnosed and treated in a timely, effective fashion. As a rule, the likelihood for sequelae increases if the child continues to deteriorate or has a depressed level of consciousness for a prolonged period.

Subdural Hematoma

A subdural hematoma is a collection of bloody fluid between the dura and the arachnoid membrane over the cerebral mantle. It is a relatively common complication of recognized and unrecognized head trauma in childhood and represents one of the two major neurosurgical problems of infancy.

Subdural bleeding usually arises from veins that pass from the cerebral cortex to the dural sinuses, bridging the potential subdural space. Skull distortion at the moment of injury, particularly in infants, and possibly the relative movement of the brain within the skull can so stretch these veins that they rupture and bleed beneath the dura, separating the dura from the underlying arachnoid membrane. Venous bleeding also can arise from a laceration of the dura or from a direct injury to a dural sinus, as can happen with depressed fractures. Less often, the bleeding originates from cortical arteries and is associated with cerebral contusion. In a large percentage of infants whose hematomas result from postnatal trauma, parental abuse can be suspected from evidence of soft tissue bruising and from radiographic evidence of multiple episodes of skeletal trauma.

To a great extent, clinical manifestations depend on the patient's age. In older children, as in adults, the disorder can be acute or chronic. In both groups, symptoms of increased intracranial pressure predominate. When a subdural hematoma after a serious head injury takes an acute course, symptoms develop within the first day or two. Venous bleeding usually does not produce symptoms unless it is accompanied by a major cerebral contusion or laceration. In these conditions, the hematoma is only one of several components of the injury, and its evacuation is not usually followed by rapid recovery.

Chronic subdural hematomas are rare in children older than 2 years of age; they are more frequent during adolescence. In this age group, the clinical picture is one of a gradual change in personality and alertness, headaches, and, ultimately, seizures or rapid deterioration of consciousness. Often there is no history of antecedent head trauma, and the diagnosis is usually made by imaging studies. MRI permits better delineation of small subdural hematomas, hematomas that are adjacent to the falx or the tentorium, and isodense accumulations.

The chronic subdural hematoma of infancy is far more common and usually is encountered between the ages of 2 and 6 months. In 60% of infants, the environmental history or other evidence of recent unreported physical trauma suggests child abuse. The more serious the head injury, the greater the likelihood of abuse.

CT and MRI can be of considerable assistance in confirming that a child has been battered. An interhemispheric subdural hematoma in the subtemporal or the parieto-occipital region accompanied by a skull fracture can be documented in more than one-half of abused children, whereas in trauma unrelated to abuse, bleeding in this region accompanied by a skull fracture is seen in only 13%. Additionally, the presence of both acute and chronic hematomas supports the diagnosis of child abuse.

Several regimens have been proposed for the treatment of post-traumatic infantile subdural hematoma. Initially, subdural fluid is removed at regular intervals by subdural tapping. We have found that with serial subdural taps, the collection of fluid dries up completely in selected patients, thus eliminating the need for a surgical procedure. When fluid forms again between tapping or when imaging studies reveal the presence of a subdural clot, surgical intervention must be considered. The operative removal of subdural

membranes can never be complete and is no longer practiced. Instead, a subdural-peritoneal shunt allows the drainage of fluid and reduces the volume of dead space, allowing it to be obliterated by the growing brain. Chronic subdural hematomas occurring in older children and adolescents are drained through burr holes.

The prognosis for an infant with a subdural hematoma correlates with the extent of damage sustained by the brain rather than with the volume of subdural fluid itself. If brain injury has been extensive, the brain will not expand, and the hematoma can calcify or ossify. Removal of a calcified subdural hematoma is of no advantage.

The prognosis for children whose subdural hematomas resulted from nonaccidental trauma has been shown to be relatively poor. Even when no gross neurologic deficits are present, abused children have a higher incidence of neurologic residua, substantially lower intelligence quotient (IQ) scores, growth failure, and a substantially higher incidence of emotional handicaps than children with accidental subdural hematoma.

Post-traumatic Epilepsy

Seizures associated with trauma have been classified, according to their time of onset, into immediate, early, and late types. A few patients suffer seizures 1 or 2 seconds after head trauma. Such immediate seizures are most probably the result of direct mechanical stimulation of cerebral tissue that has a low seizure threshold.

Seizures can appear during the first week after major cerebral trauma (early post-traumatic seizures). These arise from cerebral edema or from intracranial hemorrhage, contusion, laceration, or necrosis. The convulsions are usually generalized, but unilateral seizures and focal twitching can occur.

Late post-traumatic seizures tend to develop within the first 2 years after injury. About 75% of children with late post-traumatic seizures have no significant deficits at the time of the injury. In approximately one-half of cases, seizures appear during the first 12 months after trauma. Anatomic and EEG studies indicate the seizures originate from a cerebromeningeal scar, with the epileptic focus localized to grossly normal tissue. The likelihood of late post-traumatic seizures is increased by the presence of an acute hematoma, a depressed skull fracture, or early post-traumatic seizures.

Treatment of post-traumatic epilepsy is similar to that employed for focal or generalized seizures of unknown cause. There is no evidence that prophylactic anticonvulsants such as carbamazepine or phenytoin prevent or reduce the incidence of late post-traumatic seizures. However, 1 week of anticonvulsive therapy reduces the incidence of early post-traumatic seizures. Generally, the prognosis of post-traumatic seizures is good, although once a patient has developed late post-traumatic epilepsy, he or she will always remain prone to a seizure disorder.

Delayed Deterioration after Mild Head Injury

A relatively common, potentially fatal complication of head injury in the pediatric age group is one of rapid secondary deterioration occurring within minutes or hours after relatively minor trauma and following a lucid interval or a period of improved consciousness. A substantial number of children with this symptom complex have early post-traumatic seizures, sometimes with focal or generalized status epilepticus. The syndrome also has been seen in youngsters who have experienced repeated concussive injuries in sports ("second impact syndrome").

The mechanism underlying this phenomenon is not fully understood but is probably secondary to brain swelling, which can occur after a relatively minor head injury. Most likely, the swelling results from vasodilation and hyperemia, which are probably the consequences of a loss of cerebral vascular autoregulation, with a subsequent increase in brain bulk. Treatment, directed at constricting brain vascular volume, is accomplished by prolonged (24–48 hours) hyperventilation of the intubated youngster, coupled with the treatment scheme for cerebral edema described elsewhere in this chapter.

Post-traumatic Mental Disturbances

During recovery from a major head injury, almost every child shows some abnormality of behavior or intellect that often is more disturbing to the child and family than any physical handicap. Although it is said that because of its greater plasticity a child's brain recovers more fully after injury than an adult's, this is true only in terms of gross neurologic function. When higher cognitive skills are examined, the converse appears to be the case, and various substantial deficits are uncovered that affect the way the child functions in society. In the experience of Koskiniemi and colleagues, who studied the long-term outcome of severe head injury incurred by preschool children, 30% had a below-normal IQ when tested in adulthood. Only 21% of those with normal IQ were able to work full time outside the home. None of the children who suffered head injury before 4 years of age were able to work independently.

As a rule, the child's capacity to learn is more affected than retention of previously learned information. One must conclude that a child is better able to compensate for focal brain injury than an adult, but tolerates diffuse injury less well. This difference results in subtle long-term learning difficulties that often are not apparent to family, teacher, or physician, but are detected by a neuropsychologic evaluation. However, even an apparently normal neuropsychological profile does not preclude permanent changes in behavior and personality.

Deficits in verbal and visual recognition memory are particularly evident in younger children and are proportional to the duration of impaired consciousness. These observations point to the relatively low threshold for neuropsychological dysfunction in younger children. In many instances, however, the appearance of major psychiatric disorders after head injury, including lability of mood, outbursts of anger, increased aggressiveness, sleep disturbances, nightmares, and enuresis, is unrelated to the injury itself but reflects the child's family and social environments. In this respect, it is undoubtedly significant that a large number of children showing these post-traumatic behavior disturbances had a history of previous accidents requiring medical treatment and that about 25% either were mentally retarded or had required psychiatric therapy before their head injuries.

Psychiatric symptoms of head injuries frequently can be avoided by reassuring parents, particularly mothers, or providing extensive supportive therapy at an early stage, preferably as soon as the child is admitted to the hospital. We have most of our patients return to school as soon as feasible but recommend limiting academic demands, increasing them gradually as warranted by the child's adjustment and school performance. Because there is considerable evidence that the effects of repeated concussion are additive, children who have had two or more episodes of head injury associated with loss of consciousness or amnesia should not be allowed to participate in contact sports.

Persistent Vegetative State

Persistent vegetative state (PVS) is a relatively rare sequela to major head trauma in the pediatric population. In this state, the patient exhibits periods of apparent wakefulness, during which the eyes open and move and responsiveness is limited to primitive postural and reflex movements of the limbs.

In most instances, patients blink in response to painful stimuli, exhibit spontaneous eye movements, and show a sleep-wake periodicity. Less often, yawning, chewing, and eye-following movements occur. Meaningless laughter or weeping is not unusual. Decerebrate rigidity is seen in about one-half of cases and reflects damage to the midbrain and pons.

Spinal Cord Injuries

Traumatic injury to the spinal cord in children has significant impact because it leaves survivors with lifelong needs for rehabilitative therapy. Pediatric spinal cord injury (PSCI) is different than adult spinal cord injury in causes, presentation and outcome. In children, therefore, injuries to the spinal cord are relatively uncommon. About 3.4% of all pediatric trauma patients suffer some form of spinal cord or column injury. PSCI accounts for less than 10% of all spinal cord injuries reported in the USA each year. The risk of experiencing a PSCI increases with age. Age correlates with etiology, level and neurological deficit. Males appear to be more commonly affected than females, especially in age groups that display increased risk-taking behavior. Most frequently, PSCI is the result of indirect trauma. This is seen in accidents marked by sudden hyperflexion or hyperextension of the neck or by vertical compression of the spine resulting from falls on the head or buttocks, as can occur from surfing, diving into shallow water, falling from a horse, or various other athletic accidents. In infants, spinal cord injuries can be induced by violent shaking of the head or birth trauma can induce spinal cord injuries. Birth trauma has been estimated to affect about 1 in 60, 000 births. Motor vehicle accidents remain the most common cause of PSCI in most series.

Common sites for childhood spinal cord injuries are the second cervical vertebra (27%), followed by the tenth thoracic vertebra (13%), the seventh thoracic vertebra (6%), and the first lumbar segment (6%).

With the increased use of lap belts, children can incur a horizontal splitting of the spine, also known as a Chance fracture, in the course of a motor vehicle accident. The typical fracture involves L1 with a transverse fracture through the vertebra, with compression of the anterior portion of the body and vertical distraction posteriorly. Intra-abdominal injuries are common, but the spinal canal can be compromised with resultant spinal cord injury and paraplegia.

Because of the mobility of the child's neck and the inherent anatomic characteristics of children with relatively large heads on smaller bodies, the cervical region is particularly prone to fracture and dislocation injuries. Direct violence along the axis of the vertebral column can produce fractures of the vertebral bodies, and the spinal cord can be injured by fragments of bone that enter the vertebral canal.

Spinal cord injury without radiologic abnormality (SCIWORA) is an unusual and difficult problem for the patient and physician. SCIWORA is defined as spinal cord injury in the absence of bony fracture or mal-alignment in plain films or CT scan. The incidence of SCIWORA in children with spinal cord injuries varies widely from 5 to 60%. Most (2/3) of these injuries occur in children younger than 10 years of age. SCIWORA occurs mostly in the cervical and thoracic spine. Most children will present with a complete injury, although the presentation varies from severe to partial injury. The pattern of injury is related to the mechanism of injury as well as age. The inherent hypermobility of the pediatric spine sets it up for subluxation injuries with elastic recoil that return the spine to relatively normal alignment. Young patients have the worst injuries and thus the worst outcomes. Approximately 50% of children can have a delayed presentation of their injuries, thought to be

the result of vascular compromise. The goal of management remains the same: resuscitation of the child followed by spinal immobilization, imaging, and spinal alignment by conservative or, occasionally, surgical means. Long-term outcome is related to the severity of the initial injury. Prognosis is better in children with partial injuries because they may experience some level of motor or sensory improvement. Children with complete injuries rarely show significant neurologic recovery.

Clinical Manifestations

The clinical picture depends on the severity of the injury and its location. Concussion can result from apparently minor falls on the back and is characterized by a temporary but completely reversible loss of function below the injured segment. With more extensive injuries, recovery is only partial and permanent residua can be expected.

Evaluation of the patient who has sustained injury to the spinal cord has been facilitated by a grading system devised by Frankel and coworkers. This scheme describes four levels: A—no sensory or motor function; B—incomplete sensory function, no motor function; C—incomplete sensory function, no useful motor function; and D—normal function, with some spasticity.

When the cord is seriously compromised, the clinical picture is highlighted by spinal shock. The condition is marked by the loss of all reflex function distal to the injury, with the segments closest to the injury being the most severely affected. Spinal shock represents a transient decrease of synaptic excitability of neurons distal to the injury. It is caused by a loss of supraspinal impulses, which normally produce a background of partial depolarization of the spinal neurons. Clinically, spinal shock can persist for days or weeks and can be prolonged by sepsis, particularly urinary tract infection.

Immediately after the injury, the child experiences complete loss of motor and sensory function in the segments caudal to the injury. There is complete areflexia of variable duration, usually for at least 2 to 6 weeks. Should reflex activity not return, the distal spinal cord likely has been destroyed as the result of vascular insufficiency.

During the first stage of spinal shock—the stage of flaccidity—complete bladder paralysis and urinary retention occur. Gradually, a muscular response of the lower extremities can be elicited in response to stimulation of the skin or the deeper structures. The earliest movements occur in the legs and are flexor. The deep-tendon reflexes reappear and soon become hyperactive. Abdominal reflexes also can return. A typical extensor plantar response can be induced and often is accompanied by flexor withdrawal movements of the foot, ankle, and, subsequently, the knee and hips. Contraction of the extensor muscles of the crossed limb frequently accompanies the mass flexion reflex. During this stage, the bladder empties automatically, although never completely.

In most patients, extensor reflexes involving the quadriceps and other extensor muscles ultimately appear, becoming the dominant reflex activity. Stimuli eliciting the extensor reflex are more complicated than those inducing the flexion response. They include extension of the thigh, as is seen when the patient shifts from a sitting to a supine position, and squeezing of the thigh.

Depending on the severity of the spinal cord injury, the ultimate result can be purely reflex activity of the isolated cord. With less extensive injuries, muscular function or subjective sensation can return over the course of the next few months up to 1 year.

The neurologic picture of the most common spinal cord injuries is summarized in Table 92-7.

TABLE 92-7. Clinical Features of Spinal Cord Injuries

Injury	Neurologic Features
Transverse injuries	
T12–L1	Flaccid paralysis of lower extremities
	Loss of sphincter control
	Loss of sensation below inguinal ligament
C5–C6	Flaccid quadriparesis
	Sparing of diaphragmatic movements
	Sensory level at second rib, with preservation of sensation over upper lateral aspect of arm
	Bilateral Horner's syndrome
	Loss of sphincter control
C1–C4	Respiratory paralysis, complete quadriplegia
	Rapid death
Conus medullaris	
Cauda equina syndrome	Urinary retention
	Disturbance of rectal sphincter
	Loss of sensation over lumbosacral dermatomes
	Flaccid paralysis of lower extremities
Brown-Séquard syndrome	Unilateral muscular paresis
	Contralateral disturbances of superficial sensitivity, especially pain and temperature
	Incomplete forms far more common than classic syndrome
Central cord lesion	Disproportionately more motor impairment of upper extremities (due to involvement of the more medial segments of the lateral corticospinal tracts)
	Lower motor neuron lesion of upper extremities; upper motoneuron lesion of lower extremities
	Bladder dysfunction (usually urinary retention)
	Varying degrees of sensory loss, usually pain and temperature below level of lesion
	Relatively good prognosis
	Motor power returns first to lower extremities

From Menkes JH, Ellenbogen RG. Postnatal trauma and injuries by physical agents. In: Menkes JH, Sarnat HB, Maria BL editors. *Child Neurology*. 7th ed. Philadelphia (PA): Lippincott, Williams & Wilkins; 2006; pp. 659–702.

Diagnosis

The history of trauma is usually readily elicitable, and the most common diagnostic problem is to establish the site and extent of injury. In small children, the physician can best perform a sensory examination by demonstrating impairment of autonomic response. Shortly after the injury, the dermatomes below the lesion are dry and often have a defective vasomotor response. Evaluation of reflexes and motor function should not be particularly difficult because reflex withdrawal is not seen during the acute phase of spinal shock.

The patient with a suspected cervical spinal cord injury must be moved to the radiography unit with utmost care. After plain films of the spine (including lateral films of the cervical spine) are evaluated, it is usually necessary to establish the presence or absence of a subarachnoid block, which can be caused by bone fragments, disk material, hematoma, or swelling of neural tissues. Computed tomography or MRI of the involved and adjacent spinal levels provides the most complete information on the status of the spinal column, and on the extent to which the spinal cord and canal have been compromised by the injury.

Generally, MRI centers are not equipped to image patients who have multisystem injuries and need complex life support systems, so this procedure is usually deferred until the patient is stable. Each imaging study has its advantages. CT provides a better picture of fractures and of trauma to the osseous elements, whereas MRI is better suited to view disk protrusions and the spinal cord itself, and any associated bleeding or edema. Magnetic resonance angiography can be used to screen the status of the vasculature, in particular the vertebral arteries, although angiography remains the definitive diagnostic procedure.

Three types of abnormalities of the cord can be distinguished. The most common is hyperintensity on T2-weighted images, represented by edema of the cord. Less often, one sees a central hypointensity on T1-weighted images, which evolves to a hypointensity on T2-weighted images, surrounded by a ring of hyperintensity. This finding is consistent with an intramedullary hemorrhage and is a poor prognostic sign. In some 16 to 21% of children, all imaging studies are completely normal.

The radiologic diagnosis of a dislocated cervical spine has many pitfalls. A marked anterior displacement of C2 on C3 can be seen in 20% of all children younger than 7 years of age. This variant is particularly common during the first 3 years of life. Displacement of C3 on C4 is also common, as is an apparent hypermobility of the atlas on the axis.

The severity of the injury often cannot be determined Immediately. An early return of reflex activity, particularly of extensor movements, is encouraging. In general, sensory changes give a clearer indication of the level of the lesions than do motor changes. In cervical cord injuries, bilateral meiosis is a bad prognostic sign because it indicates extensive cord damage. Prognosis is better when the cord lesion is incomplete .For example, Hamilton and Myles reported that 74% of children with a physiologically incomplete spinal cord deficit improved by one or two Frankel levels, with 59% experiencing complete recovery. When the spinal cord injury was physiologically complete, only 10% improved by one or two Frankel levels. In this study, the absence of radiologic abnormalities did not influence the outcome.

Treatment

Treatment of the child with a spinal cord injury involves a multidisciplinary approach. IV fluids, colloids, and vasopressors are administered to maintain arterial blood pressure. Sir Ludwig Guttman advanced the conservative, postural treatment of the patient with spinal cord injury and believed that operative procedures for decompression and stabilization should be used only in select cases. Because excessive movement is likely to aggravate spinal cord injury, special care is required when handling the patient, and only absolutely essential diagnostic studies should be done. In injuries of the cervical spine, the head should be maintained in the neutral position. Skeletal traction, usually by means of tongs inserted into the skull, is required for hyperflexion injuries of the cervical spine, whereas mild traction using a canvas sling is used in hyperextension injuries. The management of cervical spine injuries is reviewed by Sypert. Injuries of the lumbar spine and thoracolumbar junction are best stabilized in slight hyperextension.

A number of treatments have been proposed to reverse secondary pathophysiologic processes, such as ischemia, excitotoxicity, and lipid peroxidation. High doses of methylprednisolone, a synthetic glucocorticoid drug (given within 8 hours of the injury as a 30 mg/kg bolus, followed by 5.4 mg/kg/h for 23 hours), induce greater improvement in motor and sensory functions than does placebo in patients with complete and incomplete spinal cord deficits. At these doses, methylprednisolone may act as an antioxidant or as a free radical scavenger. The monosialoganglioside GM_1, which experimentally has been observed to increase neurite outgrowth and to prevent cell death by inhibiting glutamate-induced neuronal excitotoxicity, has been found to improve lower limb function after spinal cord injury. The drug is started within 19 to 72 hours after the injury and administered at 100 mg/d for 18 to 32 days. Optimal dosages of these drugs, their optimal initiation time, and duration of therapy are still not known. Many other drugs, notably calpain, other free radical inhibitors, and tirilazad mesylate, a 21-amino steroid that acts as a potent antioxidant with no glucocorticoid receptor activity, await preclinical and clinical investigations. In the pediatric population none of these therapies have been rigorously

tested and a disclaimer must be added when using all of these therapies including steroids.

All patients with open wounds of the spine, with injuries in which imaging studies reveal bony fragments within the spinal canal, and with an apparent total block in the presence of an incomplete transection of the cord, should undergo surgery, including débridement, removal of bone fragments, laminectomy, and dural repair, if necessary. Any patient whose neurologic deficit increases after initial assessment, either by rostral extension or by becoming more complete, also should have the benefit of an exploratory laminectomy. Surgical intervention is needed for dislocations of the spine that cannot be reduced adequately by traction and immobilization and for injuries of the spine known by past experience to be unstable. Surgery often need not be immediate. Reduction of dislocations and internal stabilization are then carried out as indicated. The long-term care of the paraplegic child is beyond the scope of this chapter.

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Sypert GW. Stabilization and management of cervical injuries. In: Pitts LH, Wagner FC, eds. *Craniospinal Trauma.* New York: Thieme, 1990; 171–185.

Practitioner and Patient Resources

Child Trauma Academy
5161 San Felipe, Suite 320
Houston, TX 77056
Phone: (281) 932-1375
Fax: (713) 481-9821
E-mail: JLRcta@aol.com
http://www.childtrauma.org/
The ChildTrauma Academy is a not-for-profit organization based in Houston, Texas. The mission of the academy is to help improve the lives of traumatized and maltreated children and their families.

Shriners Hospitals for Children
2900 Rocky Point Drive
Tampa, FL 33607-1435
Phone: (800) 237-5055
http://www.shrinershq.org
The Shrine of North America established three special rehabilitation units where young people with spinal cord injuries can find hope, strength, inspiration, and the specialized medical care needed for rehabilitation.

CHAPTER 93

NEONATAL HYPOTONIA

MONIQUE M. RYAN, MBBS, MMED, FRACP

Hypotonia in the newborn child presents as a clinical syndrome referred to as "the floppy infant," and may reflect pathology at any level of the neuraxis from cerebral cortex to muscle. Lesions referable to the brain and/or spinal cord are labeled "central." In these conditions, the infant is hypotonic but has normal muscle strength and is, therefore, floppy, but strong. Peripheral lesions are those arising from anterior horn cell, peripheral nerve, neuromuscular junction, or muscle disease. In these disorders, the infant is both floppy and weak. Distinction between these two clinical syndromes is essential in guiding investigation and management. This chapter focuses upon the clinical evaluation and differential diagnosis of hypotonia presenting in the first 4 weeks of life.

Assessment of Hypotonia

Muscle tone derives from its resistance to stretch forces. Evaluation of tone involves both assessment of resting posture (passive tone) and limb resistance to passive movement or changes in posture (active tone). The infant's gestational age, postnatal age, and level of alertness have a major influence on tone and should be factored in to the clinical evaluation. The caudal-rostral progression in normal nervous system myelination is reflected in the evolution of tone (particularly flexor tone), which is apparent on serial examination of premature and term infants (Table 93-1).

Resting Posture

The resting posture of newborn babies is best assessed with the infant quiet and drowsy. Midline head positioning minimizes the influence of neonatal reflexes on tone, although most normal neonates have an interesting, but poorly understood, preference for head positioning to the right side.

The hypotonic infant has a characteristic "frog-leg" appearance when lying supine, with decreased spontaneous movements, abduction of the hips, and either extension of the arms or flexion at the elbows, with the hands resting on the bed (Figure 93-1). There is no increase in tone with stimulation. Joint contractures, significant loss of muscle bulk, plagiocephaly, and alopecia over the occiput suggest long-standing immobility.

Passive Manipulation

Development of flexor tone in the extremities causes increasing recoil after passive limb extension. Evolving axial tone is seen as head control during traction-maneuvers, horizontal and vertical suspensions. The traction response, which is generally present by 33 weeks

TABLE 93-1. Maturation of Normal Muscle Tone

Gestational Age (wk)	Resting Posture	Response to Passive Manipulation
28	Minimal limb flexion	Minimal resistance
32	Distinct flexion of hips and knees	Distinct flexor tone lower extremities
36	Marked flexion of lower limbs, intermittent flexion at elbows	Strong flexor tone lower extremities, less tone upper extremities
40	Consistent flexion and adduction all limbs	Strong flexor tone all extremities

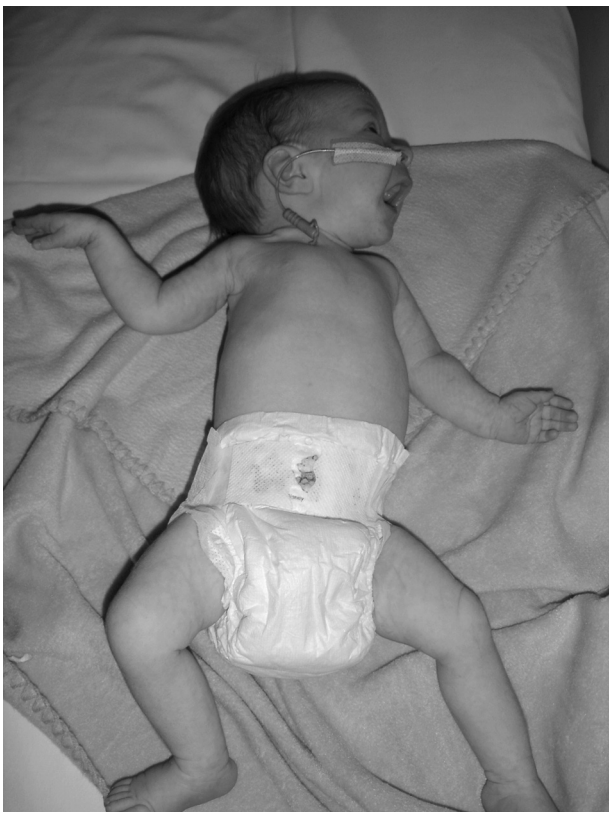

FIGURE 93-1. Hypotonic 6-week-old infant. Note extended posture with hip abduction and absence of antigravity movement of the extremities. A feeding tube is in situ, suggesting concomitant bulbar dysfunction.

gestational age, consists of active neck flexion when the baby is pulled to a sitting position, such that the head remains in the same plane as the body for several seconds. This is accompanied by flexion at the elbows, knees, and ankles. Neck extension sufficient to raise the head to a neutral position on horizontal suspension (the infant being supported prone in the examiner's hand) should be present by 40 weeks of gestation. Absence of active neck and elbow flexion on traction is indicative of hypotonia (Figure 93-2). With vertical suspension, the infant being held upright with the examiner's hands in the axillae, there should be sufficient shoulder adduction to maintain an upright posture with neck extension and flexion of the extremities. In contrast, the hypotonic infant will slip through the hands of the examiner, with the head falling forward and little flexion of the extremities.

Upper motor neuron lesions (affecting the brain and/or spinal cord) are suggested by spasticity or rigidity in newborn infants. Early or evolving spasticity (a velocity-dependent increase in resistance to passive limb movement) is also reflected in sustained limb clonus and persistent adduction of the thumbs and hips.

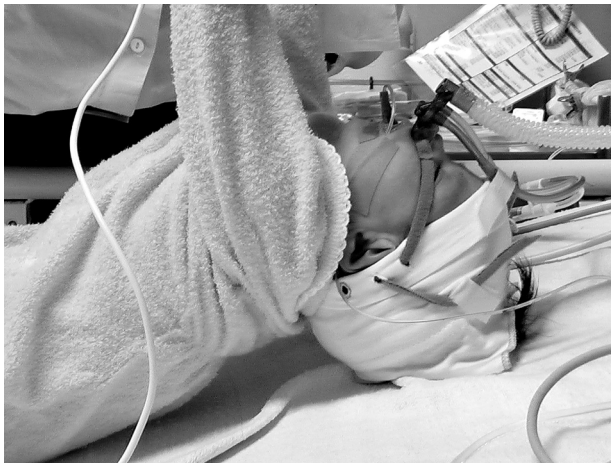

FIGURE 93-2. Abnormal traction response. This 4-week-old infant shows no antigravity neck or elbow flexion on a traction maneuvers.

Muscle Strength

Strength is the power generated in activation of volitional or reflex movement. In normal infants, strength is antigravity and antiresistance. Facial expression, extraocular movements, and adequacy of the swallow are readily assessed in neonates. Strength of the axial muscles is assessed by observation of antigravity neck and extension and respiratory (intercostal and diaphragmatic) muscle function.

Weak infants are generally hypotonic, but the reverse is not true: hypotonia can be present in the face of normal strength, usually in children with central pathology. Strength can be difficult to evaluate in infants with markedly increased joint laxity, a common finding in hypotonic children.

Movement

The quantity, quality, and symmetry of spontaneous and reactive movements should be assessed. Movements are often bilaterally symmetric in premature babies. Normal trunk and limb movements in infants of a gestational age up to 44 weeks have a writhing quality with predominantly flexor motion. Smooth alternating limb movements are seen in term babies, with subsequent evolution of more fidgety movements and higher-amplitude distal limb movements ("swipes" and "swats").

Hypotonia is often associated with a decrease in spontaneous and elicited movements. Increased or very stereotyped movements may suggest cerebral irritability or seizures. Jitteriness, with stimulus-sensitive tremulousness of the limbs that can be inhibited by changing limb position, may also reflect neurologic dysfunction (eg, hypoxic-ischemic encephalopathy [HIE] or drug withdrawal).

The Myotactic Reflexes and Plantar Responses

The amplitude of the myotactic (tendon) reflexes in newborn infants varies markedly with state of arousal. Reflexes are less active in premature infants but easily elicited in term infants (with the possible except of the triceps jerk). The lower extremity reflexes are often more brisk than those in the arms. Spread of lower extremity reflexes, especially the patellar reflexes, may be associated with crossed adductor responses and up to 10 beats of ankle clonus. These findings are more common in agitated or hungry babies and are not always abnormal in the first 6 to 8 months of life, but should be interpreted in the light of other clinical findings.

The neonatal plantar response in the newborn is generally extensor, but there is considerable variability related to methods of examination. A mild stimulus (eg, dragging the thumbnail along the lateral aspect of the sole) results in flexion of the toes in more than 90% of infants while more noxious stimuli may induce extension by activating other reflexes including withdrawal and triple flexion at the hip, knee, and ankle. The plantar responses should always be symmetrical.

The Primary Neonatal Reflexes

These complex stereotyped responses of the developing nervous system are classified as postural (eg, Moro reflex, asymmetric tonic neck reflex), or tactile (eg, sucking-swallowing and rooting reflexes, grasp reflex, placing and stepping). The maturation of some of these reflexes is outlined in Table 93-2. Abnormalities of these responses include loss of expected responses, persistent asymmetry, or retention beyond the normal age of disappearance.

The Sensory Examination

The normal neonate can discriminate touch and pain sensation from 28 weeks of gestation, responding to the former by alerting and the latter by withdrawal and cry. Examination of the response to pain includes assessment of latency, limb and facial movements, vocalization, and habituation. The sensory examination is particularly important in determining the level of spinal lesions.

Assessment of the Hypotonic Infant

In virtually all hypotonic infants, the history and physical examination are the most useful guides to etiology. The first priority in the clinical evaluation is discrimination between central causes of hypotonia, in which the baby is floppy but strong, and peripheral lesions (in which the baby is floppy and weak). Further assessment gives a good guide to the anatomic level of the underlying pathology. The differential diagnosis can then be narrowed sufficiently to enable diagnosis with minimal investigations. The major clinical features differentiating central and peripheral hypotonia are listed in Table 93-3.

The History

The obstetric history may suggest the etiology of neonatal hypotonia. Maternal febrile illness or substance abuse suggests central lesions. Polyhydramnios, which reflects decreased fetal swallowing, may relate to upper or lower motor neuron disorders, as can abnormal presentation and complicated deliveries. Prolonged or difficult deliveries may contribute to neonatal HIE and to intrapartum injuries to the cervical spine or brachial plexus. Decreased fetal movement and congenital joint contractures suggest long-standing hypotonia, which may be central or peripheral in origin.

The temporal course of neonatal hypotonia can be diagnostically useful. Hypotonia may be apparent at birth, with poor movements, respiratory insufficiency, and low Apgar scores. Apparently, normal initial tone with subsequent deterioration in tone, movement, or alertness suggests neonatal sepsis or an inborn error of metabolism. Central hypotonia is generally static, or there may be evolution of spasticity, while peripheral causes of hypotonia may progress with time, causing increased weakness. Fatigability (manifesting in the neonate as inability to maintain sucking feeds, fluctuating ptosis, and respiratory difficulties) may suggest a neuromuscular junction disorder, such as congenital myasthenia or infantile botulism.

The Family History

The family history is vitally important. The clinician should ascertain any history, in the parents or siblings, of

TABLE 93-2. Temporal Evolution of Normal Primary Neonatal Reflexes

Primary Neonatal Reflex	Age at Emergence (wk)	Age at Disappearance (mo)
Grasp	27	2
Moro reflex	28–32	6
Asymmetric tonic neck reflex	35	6
Placing and stepping	34–37	2

TABLE 93-3. Clinical Features of Central and Peripheral Hypotonia

	Central	Peripheral
Mental state	Encephalopathy	Normal alertness, responsiveness
Dysmorphism/other congenital anomalies	Common	Uncommon
Extraocular movements	Normal or strabismus	Possible ophthalmoplegia
Facies	Possible dysmorphism	Ptosis, facial weakness, high-arched palate in muscle and neuromuscular junction disorders
Bulbar function	May be impaired	May be impaired
Tongue	Normal	Fasciculations in SMA/severe neuropathies
Muscle bulk	Normal	Decreased
Myotactic reflexes	Increased/normal	Decreased/absent
Strength	Normal/mild weakness	Marked weakness
Sensation	Impaired in spinal lesions	Impaired in some neuropathies

SMA = spinal muscular atrophy.

delayed motor milestones, fatigability, muscle weakness, or myotonia. The ethnic origin of the parents, and any family history of consanguinity, should also be noted.

The Physical Examination

Dysmorphism, abnormalities of head size or shape, and malformations of other organ systems are generally suggestive of central causes for neonatal hypotonia. Apnea, seizures, altered responsiveness, and abnormal eye movements suggest cerebral dysfunction, which most often relates to hypoxic-ischemic injury.

Muscle weakness is generally more severe in children with peripheral causes of hypotonia. Significant loss of muscle bulk (atrophy) can be difficult to appreciate in chubby babies but is suggested by abnormal anterior axillary creases or excess skin over the buttocks. Facial weakness is present in the congenital myopathies and muscular dystrophies but not in spinal muscular atrophy (SMA). The deep tendon reflexes are particularly informative. Floppy infants with increased reflexes almost invariably have central hypotonia. Muscle diseases cause depression of reflexes to an extent consistent with the degree of weakness while neuropathies cause loss of reflexes, often before significant weakness is apparent. Neonatal reflexes are absent or diminished in children with lower motor neuron pathology, but increased, persistent or obligate in children with central hypotonia. Tongue fasciculations are seen in SMA and rarely in other severe neuropathies. Care should be taken to examine the tongue at rest in the floor of the mouth, as the actively protruding normal tongue may have vermiform movements resembling fasciculations.

The general physical examination may demonstrate dysfunction in other organ systems (hepatic, renal, cardiac, or respiratory), which if severe enough may cause central hypotonia.

The physical examination should include a brief assessment of the parents, focusing on facial and limb strengths and myotactic reflexes. Grip and percussion myotonia are generally not elicited in children with congenital myotonic dystrophy but invariably present in their affected parents. Fatigability of upgaze with mild proximal weakness suggests myasthenia gravis, which can cause arthrogryposis or weakness in the children of affected mothers.

Central Hypotonia

Central hypotonia results from "upper motor neuron" lesions—pathologic processes involving the cerebral cortex, basal ganglia, cerebellum, corticospinal and/or corticobulbar tracts. Clues to central lesions in hypotonic infants include altered responsiveness, seizures, and spasticity. Weakness is absent or mild. Sensation is preserved with cortical lesions but may be lost with spinal cord injuries, which are also associated with retention or overflow incontinence and with constipation. Extraocular movements are generally normal. Tongue fasciculations are absent. The neonatal reflexes are preserved and may be exaggerated or obligate (the posture is maintained while the head remains turned). Conditions most commonly causing central hypotonia in neonates are listed in Table 93-4.

TABLE 93-4. Common Causes of Neonatal Central Hypotonia

	Examples
Hypoxic-ischemic brain injury	Birth asphyxia
Chromosomal disorders	Down syndrome
Genetic conditions	Prader-Willi syndrome
Sepsis	Congenital infections
	Neonatal meningitis, encephalitis, other infections
Inborn errors of metabolism	Zellweger syndrome, Leigh syndrome, urea cycle disorders
Cerebral dysgenesis	Lissencephaly, other migrational anomalies
Endocrine disorders	Hypothyroidism, hypercalcemia
Drug intoxication	Maternal narcotic abuse
Benign congenital hypotonia	

HIE is usually suspected on the basis of the obstetric history and clinical findings (decreased responsiveness, altered consciousness, and/or seizures). Intraventricular hemorrhage is common in premature infants and may cause apnea, seizures, and anemia. Dysmorphic features are usually obvious in Down syndrome but are more subtle in Prader-Willi syndrome, a genetic condition associated with severe hypotonia and feeding difficulties in the neonate. Peroxisomal disorders, such as Zellweger syndrome, are also associated with profound hypotonia and dysmorphism.

The term "benign congenital hypotonia" describes infants who are hypotonic at birth with delayed gross motor development, in whom no specific diagnosis is made, and whose tone normalizes in early childhood. This group likely includes children with variable pathology, whose neurologic outcome is not always normal. Care should be taken to exclude treatable and other causes of hypotonia before making this diagnosis.

Peripheral Hypotonia

Peripheral hypotonia may result from disorders at any level of the lower motor neuron: anterior horn, peripheral nerve, neuromuscular junction, or muscle (Table 93-5). Muscle weakness is marked in peripheral hypotonia, and more likely to be accompanied by muscle atrophy. In many hypotonic infants, clinical findings suggestive of pathology unique to specific components of the lower motor neuron act as clues to localization. These findings are summarized in Table 93-6.

SMA type 1 (Werdnig-Hoffman disease) generally presents after the neonatal period with marked hypotonia and weakness. SMA results from recessive mutations in the survival of motor neuron gene, which causes a progressive motor neuronopathy. The diagnosis is generally confirmed on genetic testing. Neurophysiologic examination and muscle biopsy are rarely required for diagnosis of SMA. Congenital neuropathies are very uncommon, presenting in infancy with weakness, areflexia, and marked elevation of the cerebrospinal fluid (CSF) protein. Diagnosis is confirmed by nerve conduction studies and, where possible, molecular genetic testing.

Myasthenic disorders seen in neonates include transient neonatal myasthenia (caused by transplacental passage of maternal antiacetylcholine receptor antibodies) and the congenital myasthenic syndromes, genetic disorders of presynaptic or postsynaptic neuromuscular transmissions. Clues to these disorders include ptosis and fatigability. Repetitive nerve stimulation shows a decrement in the motor responses, which is reversed by administration of cholinesterase inhibitors, such as edrophonium or neostigmine. Infantile botulism results from presynaptic neuromuscular blockade by botulinum toxin released by the ingested organism *Clostridium botulinum*, which often originates from soil, agricultural products, and honey. Clues to diagnosis include constipation, dilated unresponsive pupils, hypotonia, and weakness in previously healthy children. Rapid repetitive nerve stimulation shows an incremental response, diagnosis being confirmed by isolation of toxin from stool. Management is supportive, with antitoxin showing some benefit in recent trials.

The congenital muscular dystrophies are associated with marked weakness, often with relative facial sparing, and elevation of the serum creatine kinase (CK). Muscle histology shows typical dystrophic changes. Some congenital

TABLE 93-5. The Differential Diagnosis of Neonatal Peripheral Hypotonia

		Examples
Anterior horn cell	Spinal muscular atrophy	
	Infantile poliomyelitis	
	Glycogen storage disorders	Pompe disease
Peripheral nerve	Inflammatory neuropathies	Guillain-Barré syndrome
	Demyelinating neuropathies	Déjerine-Sottas syndrome
		Congenital hypomyelinating neuropathy
	Axonal neuropathies	Spinal muscular atrophy with respiratory distress
		Infantile neuroaxonal dystrophy
	Metabolic neuropathies	Leigh syndrome
		Congenital disorders of glycosylation
Neuromuscular junction	Myasthenic conditions	Transient neonatal myasthenia gravis
		Congenital myasthenic syndromes
	Infantile botulism	
	Transient neuromuscular junction dysfunction	Hypermagnesemia
Muscle	Congenital myopathy	Nemaline, central core, myotubular, etc
	Congenital muscular dystrophy	Merosin-deficient
		Walker-Warburg syndrome
	Congenital myotonic dystrophy	
	Metabolic myopathies	Mitochondrial, glycogen storage and lipid disorders

TABLE 93-6. Clues to Localization of Peripheral Hypotonia

	Anterior Horn Cell	Peripheral Nerve	Neuromuscular Junction	Muscle
Tone			Normal or	
Fasciculations	Present	Possibly present	Absent	Absent
Muscle bulk			Normal or	
Facial weakness	Absent	Mild if present	Present	Present
Power				
Reflexes	Absent	Absent	Normal or	or absent
Sensation	Normal	Normal or	Normal	Normal

muscle dystrophies are associated with neuronal migration disorders, leukodystrophy, and ocular abnormalities (see Chapter 94, "Congenital Muscular Dystrophies"). Congenital myotonic dystrophy is a common cause of peripheral hypotonia, which is almost invariably inherited from the mother. Affected neonates have marked facial and limb weakness, respiratory and feeding difficulties. The serum CK, electromyography (EMG), and muscle biopsy are often normal or show nonspecific abnormalities. Diagnosis is based on typical findings in the mother and confirmed by genetic testing showing an expanded trinucleotide repeat sequence on chromosome 19q13.3.

Classification of the congenital myopathies is based on specific structural abnormalities on muscle histology. These conditions present with hypotonia, facial and limb weakness. Respiratory insufficiency is common in nemaline and myotubular myopathies. Diagnosis is contingent upon muscle biopsy findings. Metabolic myopathies rarely present in the neonatal period.

Investigation

The history and examination enable targeted investigation of most hypotonic infants, a process which has been greatly simplified by the availability of genetic tests for many common neuromuscular disorders of children.

Central hypotonia should be investigated by neuroimaging for structural, vascular or hypoxic-ischemic abnormalities. Magnetic resonance imaging is the imaging modality of choice. CSF should be examined for evidence of sepsis or inborn errors of metabolism. Marked increases in the CSF protein are seen in peroxisomal and lysosomal disorders but may also be present in congenital neuropathies. Chromosomal analysis excludes Down syndrome. Testing for the Prader-Willi syndrome should be considered in very hypotonic infants with feeding difficulties, with or without overt dysmorphism and cryptorchidism. Electroencephalography may be useful to exclude subtle or subclinical seizures.

The serum CK is markedly elevated in congenital muscular dystrophies but normal or only slightly elevated in myopathies and neuropathies. The CK may be elevated for a week after vaginal delivery (particularly in acidotic or asphyxiated infants), or after EMG. The serum electrolytes should be checked, particularly for hypocalcemia. Hypothyroidism can cause hypotonia and motor delay, and should be excluded, keeping in mind that most newborn screening tests do not detect secondary hypothyroidism. A urine organic and amino acid screen will exclude most inborn errors of metabolism causing neonatal hypotonia. Advanced tests for inborn errors of metabolism include measurement of blood lactate, pyruvate and ammonia, pH and anion gap calculation, and serum carnitine and acylcarnitine levels. A chest x-ray excludes cardiomegaly, from inborn errors of lipid or glycogen metabolism (ie, Pompe disease, Figure 93-3), and may show thinning or hypomineralization of the ribs suggesting long-standing weakness of the intercostal muscles. Testing of leukocyte lysosomal enzyme activity and the long-chain fatty acids excludes lysosomal and peroxisomal disorders.

Neurophysiologic studies (nerve conduction studies and EMG) should be undertaken for suspected peripheral hypotonia, with performance of repetitive nerve stimulation where a neuromuscular junction disorder is suspected. Nerve conduction studies measure the size and speed of propagation of nerve responses after electrical stimulation. Peripheral nerve function is not fully mature until 3 years of age, but age-related normal values for motor and sensory

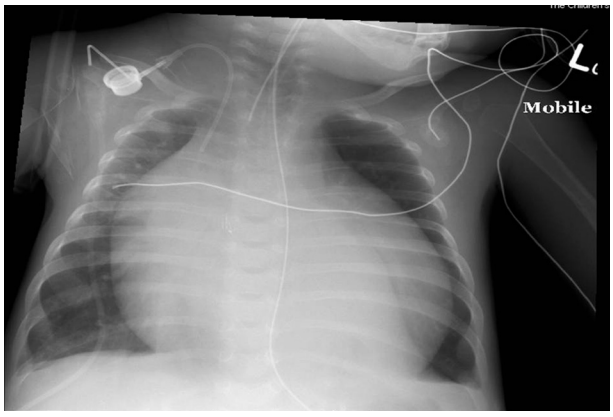

FIGURE 93-3. Chest x-ray showing gross cardiomegaly due to a hypertrophic and dilated cardiomyopathy in a 4-week-old infant with Pompe disease (infantile glycogen storage disease type II).

peripheral nerves are available from 32 weeks of gestational age. Slowing of nerve conduction is seen in disorders of peripheral nerve myelination, including some forms of Charcot-Marie-Tooth disease, Krabbe disease, and metachromatic leukodystrophy. Low-amplitude motor responses are seen in motor neuronopathies and axonal disorders, such as SMA. EMG records amplified motor unit action potentials from a needle inserted into skeletal muscles and can show patterns of abnormality suggestive of disorders of the motor nerve or muscle fiber. EMGs demonstrate active and chronic denervation in motor neuropathies and "myopathic" abnormalities in structural and metabolic myopathies or muscular dystrophies. Myotonia is present in adults with congenital myotonic dystrophy but rarely recorded in small infants. Consideration should be given to testing of parents. Neurophysiologic testing of small children is technically challenging and should generally only be undertaken by clinicians familiar with performance and interpretation of these studies.

Muscle and/or nerve biopsy are often required to establish a firm diagnosis, which may prompt genetic testing for specific conditions. Muscle biopsy is often deferred in the first few months of life but can be invaluable for establishing an exact diagnosis and guiding further management in ventilator-dependent or critically ill children. Timing of all investigations should be based on known sensitivity and specificity in early infancy, parental preferences, and the extent to which they are likely to alter clinical management. Muscle and nerve biopsies should be evaluated in a center with appropriate expertise in pediatric neuropathology.

In some cases, it will be appropriate to proceed directly to targeted genetic testing, based on the clinical history and examination. This may include testing for SMA, congenital myotonic dystrophy, or Prader-Willi syndrome.

Suggested Readings

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Jones HR. EMG evaluation of the floppy infant: differential diagnosis and technical aspects. Muscle Nerve 1990;13:338–47.

Practitioner and Patient Resources

Muscular Dystrophy Association (MDA), USA
<http://www.mdausa.org>
Provides information on neuromuscular diseases, MDA services, and publications.

Families of Spinal Muscular Atrophy
<http://www.fsma.org>
Provides information on spinal muscular atrophy, research, and fund-raising resources.

Useful Web sites:
<http://www.neuro.wustl.edu/neuromuscular>
The best neuromuscular Web site on the Internet. This site contains up-to-date information on all neuromuscular disorders.
<www.geneclinics.org>
A publicly funded medical genetics information resource developed for physicians, other health care providers, and researchers.

CHAPTER 94

CONGENITAL MUSCULAR DYSTROPHIES

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The congenital muscular dystrophies (CMDs) are inherited muscle disorders presenting at birth or in the first few months of life with hypotonia and weakness, with elevation of the serum creatine kinase (CK) and dystrophic changes on muscle biopsy. As opposed to the congenital myopathies, which are caused by genetic defects in the contractile apparatus of muscle, the CMDs are usually caused by abnormalities of the sarcolemmal membrane or supporting structures, such as cell surface receptors and extracellular matrix proteins. Most CMDs cause static or only very slowly progressive muscle weakness. The CMDs are variably associated with joint contractures, spinal rigidity or curvature, and involvement of the bulbar, respiratory, and cardiac musculatures.

The congenital muscular dystrophies (CMDs) are uncommon disorders, almost all of which are inherited in an autosomal recessive fashion. Incidence data are not available from most populations, but a single Italian study estimated their incidence at 1/21,500 live births (prevalence 1/125,000). Approximately, 60% of affected individuals have "classic" CMD (with normal cognition, although there may be central nervous system [CNS] white matter changes), most of these patients having merosin-deficient CMD. Approximately, 40% of all patients with CMD have "occidental" CMD, with structural CNS anomalies and mental retardation. Our understanding of many of these disorders has been greatly increased by recent advances in muscle biopsy analysis and genetic characterization. The recognized CMDs are listed in Table 94-1.

Clinical Findings in the CMDs

There is significant overlap in clinical presentation of the various CMDs. Most present at birth or in the following months with hypotonia and generalized weakness. Muscle wasting and/or hypertrophy are often not apparent at presentation. Tongue fasciculations are absent. The deep tendon reflexes are depressed or lost, and sensation is normal. Joint contractures may be present at birth or may develop later in life. The timing and distribution of contractures are often useful in classification of the CMDs. There is no organomegaly. Respiratory insufficiency and bulbar dysfunction are common findings in the muscle dystrophies, which may also be associated with hypertrophy of the tongue and limb muscles, progressive scoliosis, distal joint laxity, and skin changes.

A major determinant of phenotype in the CMDs is the presence or absence of CNS involvement. Some CMDs, generally those associated with abnormal glycosylation of α-dystroglycan ([α-DG] the α-dystroglycanopathies), are associated with structural brain abnormalities including cobblestone lissencephaly, cerebellar dysgenesis, and white matter signal changes. These conditions are typically associated with significant cognitive deficits in addition to motor delay.

Classification of the CMDs is predicated on the presence and severity of CNS involvement and changes on muscle immunohistochemistry for the extracellular matrix protein merosin (laminin-α2) and α-DG. Subclassification is based on clinical findings (rigid spine, joint contractures and/or laxity, muscle hypertrophy), neuroradiologic abnormalities, and muscle pathology, which guide specific genetic testing.

Diagnosis

In a floppy infant or child with delayed motor milestones, the diagnosis of CMD is suggested by a significantly raised (100s–1,000s) serum CK. Neurophysiologic testing is diagnostically useful. Nerve conduction studies are

TABLE 94-1. Congenital Muscular Dystrophies

Biochemical Defect	Protein	Neuromuscular Phenotype(s)	Gene	Gene Locus
Extracellular matrix protein	Merosin (laminin-α2)	Merosin-deficient CMD (MDC1A)	LAMA2	6q22-23
	Collagen VI	UCMD	*COL6A1, A2*	21q22.3
		Bethlem CMD (AD)	*COL6A3*	2q37
	Integrin α7	Merosin-positive CMD	*ITGA7*	12q13
Sarcolemmal protein	Plectin	CMD with epidermolysis bullosa	*PLEC1*	8q24.3
Glycosyltransferases	Fukutin	Fukuyama CMD	*FCMD*	9q31
		Walker-Warburg syndrome		
	Protein-O-mannose β1.2 N-acetylglucosaminyltransferase 1	Muscle-eye-brain disease	*POMGnT1*	1q33-34
	Protein-O-mannosyltransferase 1	Walker-Warburg syndrome	*POMT1*	9q34
		LGMD2K		
	Protein-O-mannosyltransferase 2	Walker-Warburg syndrome	*POMT2*	14q24.3
		Muscle-eye-brain disease		
	?	MDC1B	?	1q42
	Fukutin-related protein	Limb-girdle muscular dystrophy type 2I	*FKRP*	19q13.3
		MDC1C		
		FCMD, MEB, WWS		
	LARGE	MDC1D	*LARGE*	22q12.3-13.1
	SIL1	Marinesco-Sjögren syndrome	*SIL1*	5q31
Endoplasmic reticulum protein	Selenoprotein N	Rigid spine muscular dystrophy	*SEPN1*	1p35-36
		Minicore myopathy		
		Congenital fiber-type disproportion		
		Myofibrillar myopathy		
Nuclear envelope protein	Lamin A/C	Emery-Dreifuss MD (AD, AR)	*LMNA*	1q21.2-22.3
		LGMD1B		
		Congenital muscular dystrophy		
		Dilated cardiomyopathy		
		Charcot-Marie-Tooth disease type CMT2B1		
Unknown	Locus known, protein unknown	CMD linking to 4p16.3		
		CMD with joint hyperlaxity (chromosome 3p23-21)		
Unknown	Gene and protein unknown	CMD with cerebellar hypoplasia		
		CMD and muscle hypertrophy		
		CMD with mitochondrial structural abnormalities		
		CMD with arthrogryposis and absent limb muscles		
		CMD with cardiomyopathy and conduction block		
		CMD with pseudohypertrophy, macroglossia and respiratory insufficiency		
		CMD with CNS atrophy and loss of myelinated axons		
		CMD with adducted thumbs and ophthalmoplegia		
		CMD with rigid spine unlinked to 1p		
		UCMD with mental retardation		

CMD = congenital muscular dystrophy; FCMD = Fukuyama congenital muscular dystrophy; MEB = muscle-eye-brain; UCMD = Ullrich congenital muscular dystrophy; WWS = Walker-Warburg syndrome.

generally normal in the CMDs, but a moderately severe demyelinating neuropathy is seen after early infancy in merosin-deficient CMD and rarely in other forms of CMD. Electromyography (EMG) usually demonstrates "myopathic" abnormalities—low amplitude, polyphasic motor units with early recruitment—and may show repetitive discharges reflecting muscle membrane irritability.

Muscle biopsy in the CMDs shows dystrophic changes: increased fibrosis, connective tissue, fiber-size variation, and internal nuclei. Immunohistochemical staining of muscle biopsies is important for quantitative and qualitative analyses of merosin, α-DG, collagen VI, and other muscle proteins. Specific genetic testing is generally required for exact diagnosis.

Neuroimaging with magnetic resonance imaging (MRI) may demonstrate neuronal migration anomalies, white matter signal change, and other abnormalities useful in narrowing the differential diagnosis. Where possible, imaging should be deferred until after age of 6 months, as these changes may not been apparent on scans undertaken in the first few months.

Differential Diagnosis

The differential diagnosis of the CMDs includes the congenital myopathies, which are caused by genetic defects in the contractile apparatus of the muscle fiber. Congenital myopathies have a similar clinical presentation to the CMDs but are generally not associated with structural CNS anomalies. The serum CK is normal or slightly elevated. Diagnosis is contingent on recognition of specific abnormalities on muscle histochemistry and electron microscopy.

Spinal muscular atrophy, a recessively inherited neuronopathy, presents in infancy with hypotonia, motor delay, and weakness. There is facial sparing and tongue fasciculations. Nerve conduction studies show low-amplitude motor responses with normal sensory responses while EMG demonstrates neuropathic (high amplitude, polyphasic) motor units, with or without fibrillation potentials. Diagnosis is confirmed by genetic testing.

Congenital myotonic dystrophy is almost invariably maternally inherited. Affected neonates have marked facial and limb weakness and respiratory and feeding difficulties. The serum CK, EMG, and muscle biopsy are normal or show nonspecific abnormalities. Diagnosis is suggested by typical findings in the mother and confirmed by genetic testing, which shows an expanded trinucleotide repeat sequence on chromosome 19q13.3.

Common CMDs

CMDs Without Structural CNS Involvement

Primary Laminin-α2 (Merosin) Deficiency (MDC1A)

About 50% of all cases of CMD are due to deficiency of merosin, an extracellular muscle protein. Infants with merosin-deficient CMD present at or soon after birth with marked hypotonia and generalized weakness. Feeding and respiratory difficulties are common, as are joint contractures. Weakness is generally static or slowly progressive. Severe motor delay is virtually universal in merosin-deficient CMD. Most children with this disorder do not stand without support or walk. Occasional cases with later presentation and milder weakness are reported.

Merosin-deficient CMD is invariably associated with white matter signal changes resembling a leukodystrophy on T_2-weighted brain MRI (Figure 94-1). These changes are seen by 6 months of age, and persist throughout life, but are generally not associated with significant cognitive changes or long-tract signs. A minority of patients have additional CNS abnormalities, such as occipital polymicrogyria or cerebellar dysgenesis. As many as 30% of patients experience seizures.

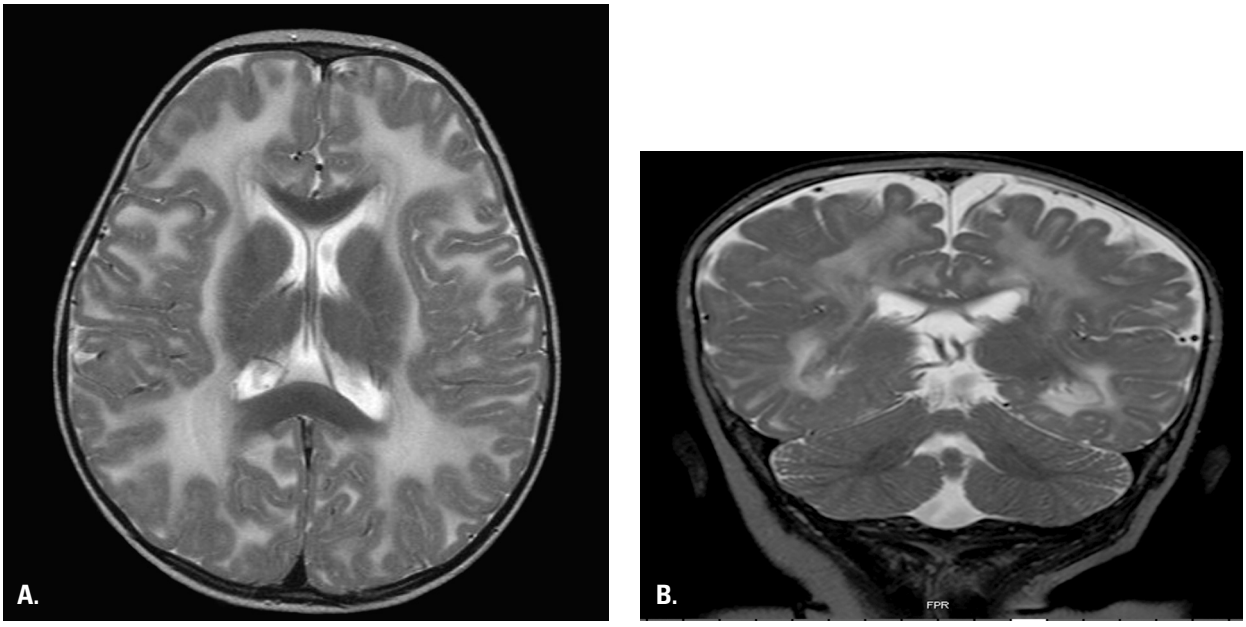

FIGURE 94-1. Brain magnetic resonance imaging in merosin-deficient muscular dystrophy. Axial (A) and coronal (B) T_2-weighted images showing high-signal changes in cerebral white matter. In a minority of cases of merosin-deficient CMD, these changes are associated with migrational anomalies.

Children with merosin-deficient CMD have markedly elevated serum CK levels. The muscle biopsy is severely dystrophic and may show "inflammatory" changes in early infancy. Merosin staining is markedly reduced or absent on muscle immunohistochemistry and Western blot analysis. Merosin deficiency can be primary (as in merosin-deficient CMD) or secondary to other disorders, such as the α-dystroglycanopathies, which tend to cause a reduction rather than complete absence of merosin. Distinction between primary and secondary merosin deficiency is facilitated by use of antibodies against multiple portions of the protein on immunohistochemistry.

Rigid Spine Muscular Dystrophy

This interesting disorder is increasingly recognized in recent years and has a characteristic phenotype with slowly progressive, primarily axial weakness, early respiratory failure, and marked spinal rigidity. There may be proximal contractures. Patients may develop respiratory failure while still ambulant. There is a characteristic facial appearance with midface hypoplasia and a "tubular" nose, with marked long of muscle bulk from the extremities. Cognition and neuroimaging are normal.

Rigid spine muscular dystrophy (RSMD) is caused by recessive mutations in the selenoprotein N gene (*SEPN1*). *SEPN1* mutations also cause minicore myopathy and congenital fiber-type disproportion, which may have a similar clinical phenotype to RSMD but are associated with a normal or only slightly raised CK and less dystrophic changes on muscle biopsy.

Ullrich CMD

Ullrich CMD (UCMD) is probably the second most common CMD and has a very characteristic clinical phenotype with generalized weakness, proximal contractures, and marked distal hyperextensibility. Muscle weakness and joint contractures are severe and progressive, with most patients never walking independently or doing so for only brief periods. Children with UCMD have a typical "pixie" facies, with follicular hyperkeratosis (an erythematous "sandpaper"-like rash most prominent over the face and the extensor surfaces), velvety skin over the hands and feet, and tendency to keloid scars. Orthopedic complications in the first year of life include torticollis, kyphosis, and hip dislocation. Posteriorly protruding calcanei are seen later in life. Cognition is normal. There may be spinal rigidity and respiratory involvement. Muscle biopsy shows typical dystrophic changes, with markedly decreased or absent collagen VI staining on immunohistochemistry of muscle and/or skin biopsies. The diagnosis is confirmed by testing for mutations in one of the three genes encoding components of the collagen VI protein (*COL6A1*, *2,* and *3*) (Figure 94-2). UCMD is generally inherited in a recessive fashion but is occasionally dominantly inherited.

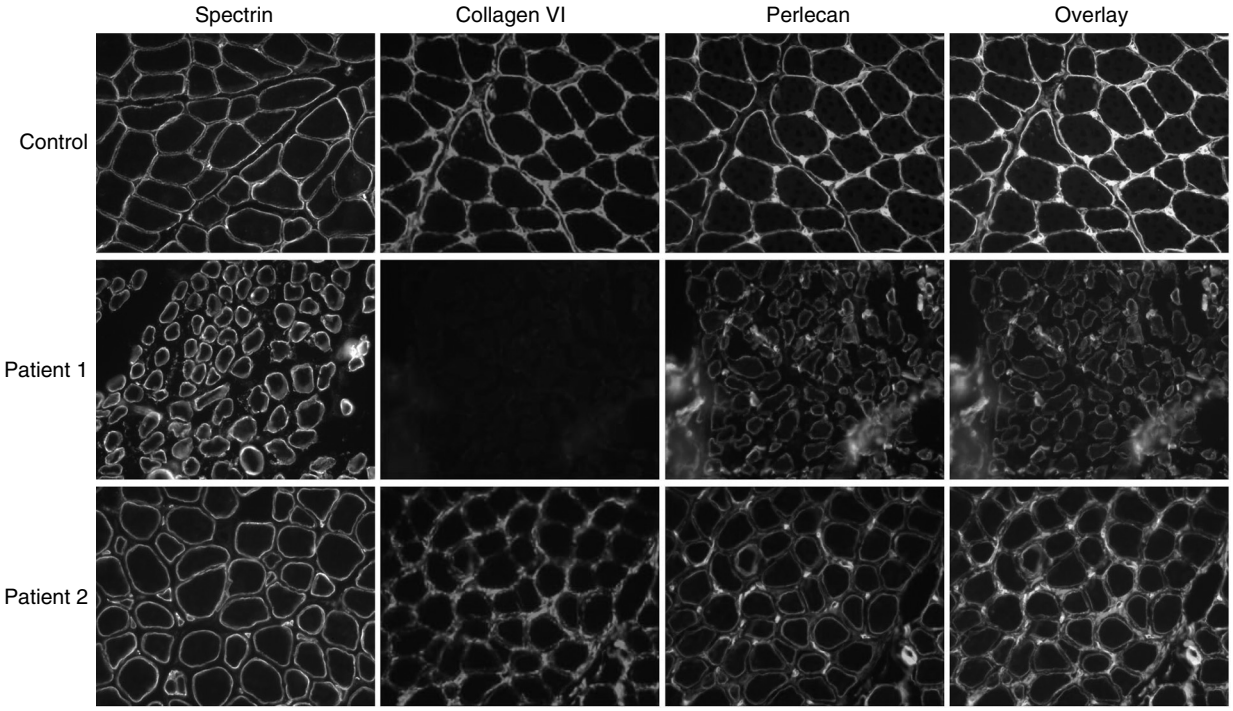

FIGURE 94-2. Muscle immunohistochemistry (IHC) in Ullrich congenital muscular dystrophy (CMD). IHC in a control subject shows normal immunostaining with antibodies to spectrin, collagen VI, and perlecan. Patients with Ullrich CMD show absent collagen VI (patient 1), or collagen VI present in interstitial tissue but absent at muscle sarcolemma (patient 2) (Courtesy Prof. Kathryn North and Dr Rachel Peat).

Bethlem myopathy is a similar disorder presenting with less severe muscle weakness, proximal contractures, and distal hyperlaxity. Both UCMD and Bethlem myopathy can be caused by recessive or dominant mutations in the genes for collagen VI, and increasingly look to be on a disease continuum, the distinction between the two being largely academic.

CMD with Epidermolysis Bullosa (EBS-MD)

This unusual CMD presents with skin blistering at birth or soon thereafter and is commonly associated with nail deformities and urethral, dental, and respiratory complications. Muscle weakness generally presents later in the first decade of life and is slowly progressive, most patients eventually losing independent ambulation. EMS-MD is caused by recessive mutations in the gene for plectin, a cytoskeletal protein linking intermediate and thin filaments at the level of hemidesmosomes (skin) and the sarcolemma and Z-discs (muscle). Mutations in this gene result in aberrant anchorage of cytoskeletal structures in keratinocytes and muscle fibers, leading to cell fragility. Diagnosis is suggested by the combination of skin abnormalities and muscle weakness and confirmed by plectin immunofluorescence and genetic testing.

CMDs with CNS Involvement: The α-dystroglycanopathies

Several CMDs are caused by mutations in the genes encoding glycosyltransferases, enzymes important in the posttranslational modification of α-DG, and other (as yet unknown) muscle proteins. α-DG is a key component of the dystrophin-associated glycoprotein complex, which stabilizes muscle cells during contraction and relaxation (Figure 94-3). α-DG is also expressed in the CNS, retina, and cochlea. Glycosylation of α-DG is a stepwise process involving several enzymes, referred to as glycosyltransferases.

Abnormal glycosylation of α-DG impairs its localization to the muscle membrane, causing reduced or absent staining of α-DG on immunohistochemistry. As laminin-α2 normally binds to α-DG in the basal lamina, this causes a secondary reduction in laminin-α2; immunohistochemical staining can be normal or patchy, but the protein is often markedly reduced on Western blotting.

A number of glycosyltransferases have been identified in the last decade. Mutations in these enzymes cause a variety of clinical phenotypes with variable involvement of the CNS, eyes, and muscle. All are inherited in an autosomal recessive fashion.

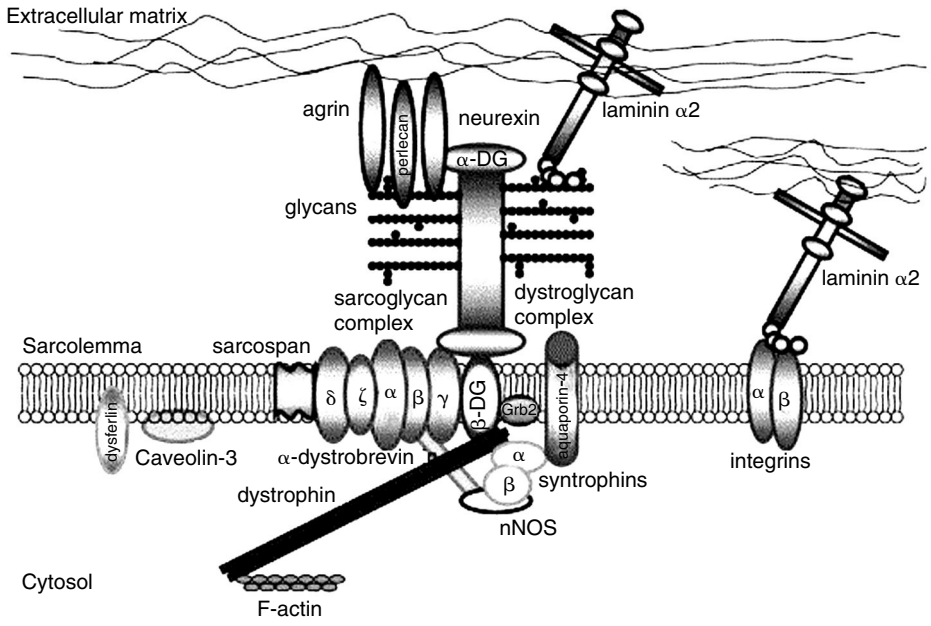

FIGURE 94-3. The dystrophin-associated glycoprotein complex. Dystrophin, the protein product of the Duchenne muscular dystrophy (*DMD*) gene, is a cytoskeletal protein tightly associated with a large oligomeric complex of sarcolemmal glycoproteins, the dystrophin-associated proteins (DAPs). The DAP complex includes clusters of sarcoglycans (α-ζ-sarcoglycans) and α- and β-dystroglycan. Inherited deficiencies of these proteins cause muscular dystrophies with a reduction in α-dystroglycan staining at the cell membrane. Adapted from Cohn RD. "Dystroglycan: important player in skeletal muscle and beyond." Neuromuscul Disord. 2005;15(3):207–17. Copyright (2005), with kind permission of Elsevier.

CMD Type 1C (MDC1C)

MDC1C is a heterogeneous disorder presenting in the neonatal period with hypotonia and severe muscle weakness. Affected children develop calf hypertrophy, macroglossia, cardiomyopathy, and respiratory impairment later in life. Most children have normal cognition and neuroimaging, but in recent years, there have been numerous reports of children with MDC1C and mental retardation with or without structural changes including cerebral or cerebellar atrophy and white matter signal changes.

The serum CK is moderately or markedly elevated, and muscle pathology is typically dystrophic. Muscle immunohistochemistry shows decreased staining for merosin and α-DG.

MDC1C is caused by recessive mutations in the gene for *FKRP* (fukutin-related protein), a muscle glycosyltransferase. *FKRP* mutations cause a number of other disease phenotypes, including muscle-eye-brain (MEB) disease, Walker-Warburg syndrome (WWS), and limb-girdle muscular dystrophy type 2I. Some genotype-phenotype correlation has been established.

Fukuyama CMD

Fukuyama CMD (FCMD) is most commonly seen in the Japanese population and presents at birth with severe weakness and decreased responsiveness. CNS anomalies reported in FCMD include polymicrogyria and pachygyria of the cerebrum and cerebellum. About 50% of patients have structural eye abnormalities, such as retinal hypoplasia, microphthalmos, or optic atrophy. Most have severe cognitive impairment and epilepsy. Children with FCMD are not ambulant. Early contractures, respiratory and cardiac involvements are common, with later development of hypertrophy of the tongue, quadriceps, and calves. The life expectancy is significantly decreased. Muscle pathology is typically dystrophic, with reduced immunostaining for merosin and α-DG. FCMD is generally caused by mutations in the *fukutin* gene on chromosome 9q31 but has also been associated with the *FKRP* gene.

MEB Disease

MEB disease is similar to FCMD but is most commonly seen in Finnish patients. Clinical features include marked muscle weakness, cerebral and cerebellar dysgenesis (pachygyria or polymicrogyria, cerebellar cysts, and hypoplasia), and ocular defects (microphthalmia, retinal defects, and anterior chamber anomalies). Most patients have severe cognitive defects and epilepsy. MEB is most commonly caused by recessive mutations in the gene encoding the glycosyltransferase protein-O-mannose β-1, 2-*N*-acetylglucosaminyltransferase (*POMGnT1*) gene on chromosome 1q33 but can also be due to mutations in *FKRP*.

WWS

WWS is the most severe of the α-dystroglycanopathies. WWS is characterized by severe CMD, eye anomalies (cataract, microphthalmia, buphthalmos), and structural brain defects (type II lissencephaly, occipital encephalocele, and callosal agenesis) (Figure 94-4). Mortality from respiratory failure or refractory epilepsy is common in infancy. WWS may be caused by recessive mutations in *POMT1*, protein-O-mannosyltransferase-2 (*POMT2*), and *fukutin* or *FKRP*.

Management of the CMDs

Improved genetic characterization of the CMDs has enabled specific diagnoses to be made in as many as 50 to 60% of cases. In many affected children, however, a specific diagnosis cannot be made, and treatment remains symptomatic and empirical.

The cornerstones of management of muscle diseases in childhood are maintenance of strength and joint range of motion by exercise, physiotherapy, and avoidance of prolonged periods of immobility. Lightweight polypropylene splints or orthoses, with appropriate surgical correction of contractures, can preserve independent ambulation for prolonged periods. The surgical correction of scoliosis makes sitting more comfortable and helps preserve lung function. The CMDs have not been associated with malignant hyperthermia, but surgery on affected children should be undertaken only in centers with appropriate anesthetic expertise, with facilities for postoperative ventilatory support and intensive physiotherapy.

Respiratory impairment is common, especially in disorders associated with spinal rigidity, such as RSMD and UCMD. All children should undergo regular respiratory function tests and/or sleep studies, with consideration of noninvasive ventilatory support in those with nocturnal hypercapnia or hypoxemia. Artificial ventilation via tracheostomy may be considered for those with severe respiratory insufficiency. Subclinical ventilatory failure may be unmasked by anesthesia, immobility, and postoperative atelectasis. Perioperative monitoring of respiratory function in children undergoing surgery is, therefore, vital. Respiratory infections should be treated early with postural drainage and antibiotics.

Bulbar insufficiency predisposes to aspiration and malnutrition, and many children benefit from caloric supplementation by gastrostomy feeds. The diet should be monitored to ensure adequate fiber intake, as constipation is often problematic, and to prevent excessive weight gain, which exacerbates muscle weakness.

Antenatal diagnosis may be possible in those CMDs with a defined genetic basis. In cases of merosin-deficient or UCMD with complete absence of merosin or collagen,

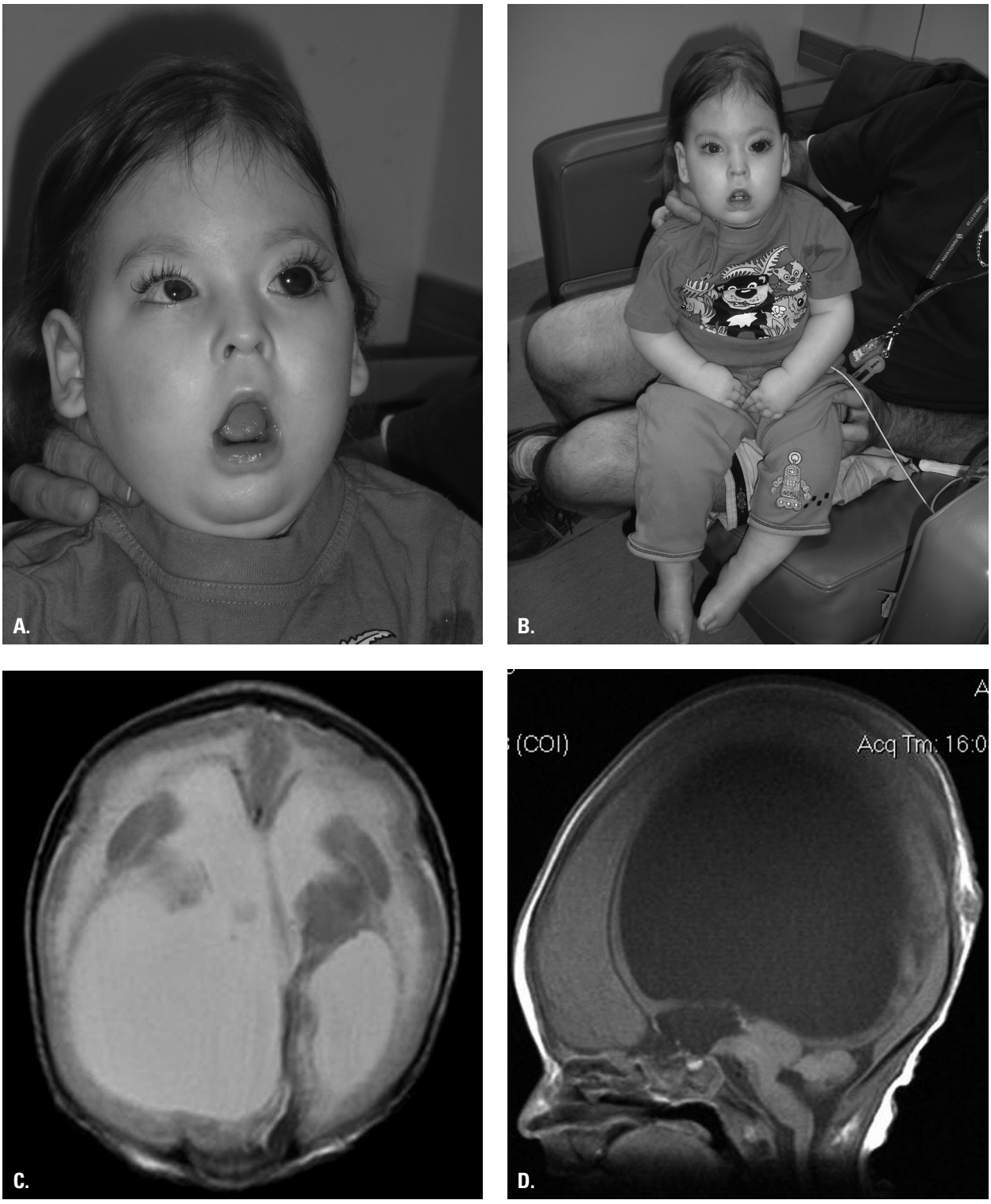

FIGURE 94-4. Walker-Warburg syndrome in a 2-year-old boy. There is marked weakness with facial diplegia and left-sided glaucoma (A), loss of muscle bulk and distal contractures (B). On brain magnetic resonance imaging (axial T_2- and sagittal T_1-weighted images [C, D]), there is severe hydrocephalus and cobblestone lissencephaly (MR images courtesy of Dr Rick Leventer).

respectively, immunocytochemistry on chorionic villus sampling may also be informative.

Suggested Readings

Muntoni F, Voit TC. The congenital muscular dystrophies in 2004: a century of exciting progress. Neuromuscul Disord 2004;14:635–49.

Quijano-Roy S, Renault F, Romero N, et al. EMG and nerve conduction studies in children with congenital muscular dystrophy. Muscle Nerve 2004;29:292–9.

Practitioner and Patient Resources

Neuromuscular Diseases Research Centre, Washington University, St Louis
An invariably up-to-date resource for clinical, neuropathologic, and genetic data on neuromuscular disorders.
<http://www.neuro.wustl.edu/neuromuscular/>

Gene Clinics
Excellent review articles on genetic neuromuscular conditions
<http://www.geneclinics.org/profiles/cmd-overview/>
Muscular Dystrophy Association of USA <http://www.mdausa.org/>

CHAPTER 95

INJURY TO THE PRETERM BRAIN

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The brain of the preterm infant is selectively vulnerable to injury because of developmental differences in structure and physiology related to immaturity. With advances in obstetric and neonatal care, 85% of very low birth weight infants (500–1,500 g) now survive, but 10% have cerebral palsy, and 50% require assistance with academic work and/or behavior problems at school age. While basal ganglia, thalamus and cortex show selective patterns of vulnerability in the term infant, the major lesions in preterm infants are intraventricular hemorrhage (IVH), cerebellar hemorrhage, periventricular white matter injury including cystic periventricular leukomalacia, and restricted growth of cortical and basal ganglia gray matter. IVH has diminished due to the introduction of antenatal steroid administration and other changes in care, but the recognition of white matter injury has increased. White matter is especially vulnerable to injury at 23 to 32 weeks gestation due to the immaturity of blood vessels and the susceptibility of oligodendrocyte progenitors to attack from oxidative stress, excitotoxic injury from glutamate, and inflammatory cytokines. Advanced imaging techniques such as diffusion tensor imaging provide a more complete picture of the patterns of white matter injury including damage to specific tracts. Quantitative magnetic resonance techniques have also demonstrated impaired growth of gray matter structures that is associated with white matter injury. Insights into the pathogenesis of injury in the preterm brain may lead to improved prevention and treatment.

More than 12% of newborns in the United States are born prematurely at less than 37 weeks and 2% are born at less than 32 weeks gestation. Modern obstetric and neonatal interventions, including routine antenatal administration of corticosteroids, advanced techniques for mechanical ventilation, and administration of artificial surfactant, have markedly improved the survival of these infants. The Vermont Oxford Network Database reported that more than 85% of very low birth weight (VLBW) infants (500–1,500 g, mean gestational age 28.5 weeks) survived the neonatal period in 1999. Data from the same period showed that survival of extremely preterm infants less than 26 weeks gestation (<800 g) falls to approximately 40 to 60% depending on the center reporting. However, the enhanced survival of VLBW infants is also associated with a 10% rate of cerebral palsy (CP), which is 5-fold higher than the rate in term infants. In addition, approximately half of the school age children from the VLBW group have impaired academic achievement and/or behavioral disorders that require additional educational assistance. Understanding how to prevent and treat the brain-based developmental disabilities associated with premature birth is one of the most important areas in pediatric neurology.

Major Brain Lesions Associated With Premature Birth

Injury to the brain of the preterm infant causes special patterns of pathology and functional disability that reflect the brain's rapidly changing organization and physiology at the time of the insult. As a general rule, the immature periventricular white matter in the preterm brain is more vulnerable than neuron-rich structures such as the cerebral cortex and basal ganglia to injuries such as hypoxia-ischemia. The term periventricular white matter injury (PWMI) is used to describe a spectrum of injuries, including cystic periventricular leukomalacia (PVL), the most prominent lesion of the white matter in the premature infant, and more diffuse, noncystic injury to myelin (noncystic PVL).

The vulnerability of the white matter in preterm infants is related to several biologic features of rapidly myelinating

pathways from 24 to 32 weeks gestation. In contrast, the vulnerability of neuronal circuits in the cortex and basal ganglia lags behind that of the periventricular white matter and is linked to establishment of synapses among neurons closer to term. Preterm infants are also far more vulnerable to intraventricular hemorrhage (IVH) than term infants due to the greater prominence and fragility of the vascular germinal matrix at mid-gestation. Extremely premature infants are also vulnerable to hemorrhage in the immature cerebellum. While the incidence of IVH in premature infants has fallen, the recognition PWMI has risen. Both IVH and white matter injury are important targets for potential interventions to reduce developmental disabilities associated with preterm birth.

IVH

IVH occurs in approximately 20% of neonates with birth weights of 1,000 to 1,500 g but is uncommon in infants greater than 32 weeks gestation. However, the incidence is higher in less mature infants, affecting more than 40% in infants with birth weights less than 500 g. Most hemorrhages occur within 3 days after birth. Surveillance for hemorrhage is generally performed by bedside head ultrasound examination on days of life 1 to 3 or by day of life 7, when greater than 95% of all hemorrhages will be detected.

A modification of Papile's standardized classification system is widely used to grade IVH. Grade 1 (subependymal) hemorrhages carry little risk for later developmental disorders, while grade 2 (intraventricular without distention of ventricles) or grade 3 (ventricles distended with blood) hemorrhages lead to neurologic sequela in 15 to 35%, respectively. IVH grades 1 to 3 occur following rupture of the fragile immature blood vessels of the germinal matrix. They are usually precipitated by wide swings in perfusion in the pressure passive cerebral circulation associated with fluctuations in systemic blood pressure. High intrathoracic pressures secondary to mechanical ventilation, cardiac instability, sepsis, and clotting disorders can also contribute to the pathogenesis of IVH.

Grade 4 IVH (also called periventricular hemorrhagic infarction) differs from lower grade hemorrhages because it results from venous infarction in the draining terminal vein circulation, often leaving an extensive cavity or porencephalic cyst in periventricular white matter and adjacent gray matter. Grade 4 hemorrhages are more common in the most premature infants, are often extensive, and are bilateral in 25% of cases. Grade 4 hemorrhages with large intraparenchymal echodensities seen on ultrasound are associated with a 90% chance of major motor deficits and more than 50% incidence of cognitive impairment. Extensive white matter involvement and subsequent connectivity derangements in gray matter may account for much of the increased morbidity of grade 4 IVH.

Approximately one third of premature infants with IVH, made up mostly of smaller infants with grade 3 to 4 hemorrhages, develop posthemorrhagic hydrocephalus (PHH) due to inflammatory changes in the cerebrospinal fluid (CSF) pathways. Periodic evaluation using ultrasound and measurement of head circumference is used to follow infants with IVH for this complication. Progressive ventricular dilatation may be rapid and requires CSF drainage through a shunt, but ventricular enlargement that progresses more slowly can sometimes be managed with serial lumbar puncture without shunting. Of the patients in whom ventricular dilation arrests, a small number will develop late PHH, with rapid head circumference increases around 3 to 6 months of age, and will require shunting.

PHH should be distinguished from low-pressure ventriculomegaly, which is a slowly evolving process due to white and gray matter atrophy. The ventriculomegaly will stabilize and will not show rapid head circumference growth as in PHH but is associated with increased risk of cognitive and motor deficits.

Severe PHH appears to add to the morbidity of the underlying IVH by impairing the perfusion of brain tissue, especially periventricular white matter. However, the effects of PHH alone are difficult to distinguish from the effects of factors that contribute to PHH, such as extreme prematurity and direct injury to white by matter by early periods of ischemia and infarction.

Strategies for Prevention of IVH

The observation that IVH is usually caused by fluctuations in cerebral blood flow within a few days after birth has stimulated a search for preventive strategies. The incidence of IVH has declined by half over the last two decades, and some of this decrease is believed to be due to improved nursing techniques in newborn intensive care units as well as improved mechanical ventilation and the use of surfactant. Phenobarbital was one of the first pharmacologic agents to be used antenatally to reduce IVH in impending premature birth. This strategy showed some promise in clinical trials but is not widely used now and has been supplanted by the use of antenatal corticosteroids. Multiple trials of postnatal administration of phenobarbital to prevent IVH have failed to show any benefit and may increase the need for assisted ventilation.

In contrast to phenobarbital, several controlled randomized trials have shown that corticosteroids given to mothers at risk for preterm delivery reduce infant mortality as well as the risk of respiratory distress syndrome and IVH. A National Institutes of Health consensus statement issued in 1994 recommended routine administration of

corticosteroids between 24 and 34 weeks gestation when there is a risk of preterm delivery. A complete steroid course of betamethasone (or dexamethasone), ideally administered to the mother at least 24 hours prior to delivery, can reduce the incidence of IVH by approximately 50%, and an incomplete course is partially protective. Multiple courses provide no added benefit.

Postnatal administration of steroids has also been shown to benefit premature infants by shortening the time needed for assisted ventilation, reducing the incidence of chronic bronchopulmonary dysplasia, and correcting hemodynamic failure. Although no adverse effects on brain development have been demonstrated with a single antenatal course, the benefits of more prolonged postnatal regimens may be gained at the cost of an increase in the incidence of CP and impaired brain growth. Magnetic resonance imaging (MRI) of premature infants treated with dexamethasone in the postnatal period showed impaired brain development that primarily affects gray matter rather than white matter. Multiple courses of prenatal steroids have also been associated with a reduction in cortical surface complexity in VLBW infants.

Several molecular mechanisms for these toxic effects of corticosteroids on brain development have been suggested based on work in experimental models, including atrophy of dendrites in the hippocampus, decreased neurogenesis, and alternations in excitatory mechanisms. It has been suggested that dexamethasone may be more harmful than other corticosteroids. The timing and duration of treatment with steroids in relationship to gestational age also appear to be important determinants of outcome. This is an active and controversial area of investigation, as the benefits of steroids are weighed against potential long-term risks.

Indomethacin, an anti-inflammatory drug that inhibits prostaglandin synthesis via the cyclooxygenase pathway and decreases fluctuations in cerebral blood flow in animal models, has also been studied for prophylaxis. Postnatal administration of indomethacin within 6 hours after birth has been shown to decrease the incidence and severity of IVH, particularly grade 4 hemorrhages. Although the drug reduced the incidence of IVH, initial follow-up of infants studied in a controlled trial of indomethacin prophylaxis when they had reached school age did not show a protective effect on cognition or motor function.

However, later reanalysis of this data showed that the response to indomethacin is markedly gender dependent. Indomethacin reduced the incidence of IVH by half and raised later verbal skills in boys but had no significant effect in girls. This evidence of sexual dimorphism in the effects of indomethacin on prevention of IVH is consistent with other evidence that male infants are more vulnerable to brain injury associated with prematurity and have a higher rate of CP. The success of antenatal steroids in addition to concerns about potential side effects of indomethacin has limited its clinical use at this time.

Cerebellar Hemorrhage in Extremely Preterm Infants

Hemorrhage occurs in the lateral regions of the cerebellar hemispheres in preterm infants less than 28 weeks' gestational age and may be unilateral or bilateral. Cerebellar hemorrhage may be associated with IVH, but an increasing number is being described as isolated bleeds. Cerebellar hemorrhages in extremely preterm infants are associated with destruction of portions of the cerebellum and later severe motor and cognitive disabilities. The cerebellum is one of the last parts of the brain to develop, and neurogenesis continues well into the postnatal period in term infants. It is noteworthy that the cerebellum is involved in learning and memory as well as coordination of motor activity.

PWMI

Immature white matter is one of the most vulnerable targets of injury in the preterm brain. Cystic PVL, which is at the most severe end of the PWMI spectrum, is strongly linked to the spastic diplegia form of CP in which all four extremities are affected, but the upper extremities are less impaired than the legs. Cystic PVL typically appears on cranial ultrasound at more than 2 weeks after an acute injury. The cysts usually collapse over the ensuing weeks leading to shrinkage of the periventricular white matter and secondary enlargement of the ventricles.

Serial cranial ultrasound scans are helpful in the diagnosis and follow-up for cystic PVL. Bilaterality of echogenic foci and smaller cyst size of ≤ 2 mm are associated with a >30% incidence of CP, whereas PVL with large cysts ≥ 3 mm carries a risk for CP of approaching 90% and greater likelihood that all four extremities will be impaired. More posteriorly located cysts confer a worse prognosis for multiple impairments, including visual, cognitive, and motor deficits.

The more common pattern of PWMI seen in nurseries today is noncystic PVL, with shrinkage of periventricular myelin and ventriculomegaly without cyst formation. While cranial ultrasound is very sensitive to cystic PVL, and usually shows echogenicity in the acute period after injury in noncystic PVL, it is less reliable in the identification of the more diffuse injury that commonly surrounds the PVL lesion. MRI signal change on T2-weighed images, termed diffuse excessive high signal intensities, has been shown to represent diffuse white matter abnormality and to correlate with later developmental impairments.

Later in childhood, MRI is a sensitive method for detecting the spectrum of PWMI, which is variably seen as white matter loss, periventricular gliosis, enlarged, scalloped ventricles, and thinning of the corpus callosum. However, the ability of conventional MRI to identify specific white matter tracks is limited. Recently, the relatively new technique of diffusion tensor imaging (DTI) based on diffusion MRI has been used to examine specific white matter tracks in children born prematurely with CP. These studies showed a group of white matter tracks that are highly susceptible to injury, including the posterior internal capsule, posterior thalamic radiation, superior coronal radiata, and commissural fibers. Although PVL is strongly associated with motor dysfunction and CP, DTI tractography indicates that sensory and association fibers are generally more affected than periventricular corticospinal pathways. Further study of specific pathways affected may be useful for understanding the pathogenesis of PWMI.

Pathogenesis of White Matter Injury

The major insults that have been implicated in white matter injury in premature infants are cerebral hypoxia-ischemia, infection/inflammation, and endocrine/metabolic disturbances. These insults place metabolic stress on the immature oligodendroglia (preoligodendrocytes) that are especially vulnerable to injury from 23 to 32 weeks gestation, leading to disrupted myelination and secondary axonal damage in periventricular pathways. Immaturity of the cerebral vasculature and special features of the immature preoligodendrocytes are important contributors to the time-dependent selective vulnerability of white matter in the preterm brain. The blood vessels serving the periventricular white matter before 32 weeks gestation are immature, creating areas of marginal perfusion in watershed regions if blood pressure drops. The premature infant's cerebral circulation may also lack the autoregulation that usually protects the mature brain from fluctuations in systemic blood pressure. Prolonged need for support on a ventilator, pneumothorax, persistent ductus arteriosis, and sepsis are some of the insults that have been reported to cause fluctuations in systemic blood pressure leading to white matter injury in sick premature infants. These factors are similar to those that predispose premature infants to IVH.

Hypoxia-ischemia exposes preoligodendrocytes within the white matter to combinations of oxidative stress due to elevated production of nitric oxide and other oxygen free radicals and elevated levels of the excitatory neurotransmitter glutamate. Neurochemical studies of postmortem tissue from infants with white matter injury and cells isolated from experimental models indicate that preoligodendrocytes are deficient in oxidative defense molecules such as superoxide dismutase, catalase, and glutathione. Depletion of glutathione in preoligodendrocytes is worsened by inward transport of glutamate in exchange for cystine. Elevated levels of glutamate in white matter also activate AMPA/kainate type glutamate receptors on the cell surface of preoligodendrocytes. Preoligodendrocytes are more vulnerable to glutamate-mediated excitotoxicity than more mature oligodendrocytes because their AMPA/kainate receptors contain subunits that allow them to flux toxic levels of calcium as well as because of inadequate oxidative defenses.

Therefore, both the immaturity of the premature infant's cerebral circulation and the biochemical characteristics of the immature preoligodendroglia create a temporal window of white matter vulnerability. Drugs that block AMPA/kainate receptors, such as the clinically used anticonvulsant topiramate, have been shown to reduce white matter injury from hypoxia-ischemia in experimental models and could potentially be useful to prevent white matter injury in preterm infants.

Infection and inflammation also attack preoligodendrocytes through mechanisms that interact with those activated by hypoxia-ischemia. Sepsis from endotoxin containing bacteria, such as occurs in premature infants with necrotizing enterocolitis, is a potent cause of PVL, and purified lipopolysaccharide associated with endotoxin causes white matter injury in animal models. This injury is mediated by toll-like receptors located on microglia, which become activated and produce oxygen free radicals and cytokines, including tumor necrosis factor-α and interleukin-1β. Hypoxia-ischemia also activates microglia and other inflammatory processes. Both chorioamnionitis and uteroplacental dysfunction have been linked to initiation of premature labor as well. A wide range of cytokines, chemokines, soluble receptors, and growth factors in amniotic fluid, cord blood, and CSF have been associated with the development of white matter injury and CP. The role of infection and inflammation in the pathogenesis of white matter injury remains an active area of investigation.

Endocrine and metabolic disturbances of the fetus, including factors that cause intrauterine growth retardation, are also potentially important causes of white matter injury and CP. Maternal thyroid dysfunction has been associated with pregnancy induced hypertension, preterm birth, low birth weight, placental abruption, and fetal death. The fetal thyroid does not secrete hormone until 20 weeks gestation, and there is evidence that maternal thyroid hormone is important for brain development early in gestation. Iodine deficiency during pregnancy associated with maternal hypothyroidism with goiter is one of the most common causes of spastic CP and mental retardation in less developed parts of the world. Transient hypothyroxinemia is common in premature infants and has been associated with IVH, PVL, and poor neurodevelopmental outcomes. Gestational diabetes may be associated with fetal white matter injury through the mechanism of uteroplacental dysfunction.

Severe hypoglycemia has also recently been shown to produce a pattern of selective damage to subcortical white matter in the occipital region. These endocrine/metabolic disturbances constitute a third important group of disorders that contribute to the pathogenesis of white matter injury.

Abnormal Gray Matter

Advances in three dimensional MRI methods have made it possible to measure white matter, gray matter, and CSF volumes independently in the brains of children born prematurely. Several research groups have found significant reductions in the volume of gray matter in cerebral cortex and basal ganglia and increases in CSF volumes in children born prematurely. These changes were associated with short-term neurodevelopmental deficits. Gestational age at birth and the presence of white matter injury were important predictors of altered cerebral volumes, and one study showed differences based on gender. These changes in gray matter volumes were difficult to detect on routine imaging with ultrasound or MRI but point to an important lesion in the brain of premature infants.

The explanation for impaired gray matter development in premature infants is unclear. One hypothesis that has been proposed is that the changes are secondary to loss of subplate neurons, which populate the immature white matter. This transient population of neurons peaks during the second half of gestation and disappears by apoptotic cell death by adulthood. They play an essential role in thalamic-cortical as well as intracortical connectivity, and their loss in damaged white matter could reduce the volume of synaptic networks in the cerebral cortex. Loss of neuronal connectivity from damage to commissural pathways, as suggested by lesions visualized by DTI described above, could also restrict the growth of cerebral gray matter. Far-reaching developmental deficits may, therefore, result from regions undersupplied by connecting white matter that are important in coordination of different cortical functions. Other factors, such as effects of steroid administration in the postnatal period, could also contribute to these changes. This new information based on sophisticated new imaging techniques is providing new insight into the effects of injuries on development of the preterm brain.

Future Directions

A better understanding of the mechanisms involved in white matter injury in the premature infant may contribute to strategies for prevention. These include ways to reduce fluctuations in cerebral blood flow and better therapies to treat infections and inflammation that may contribute to injury by attacking preoligodendrocytes. Recent evidence from experimental models suggests that glutamate receptors on immature oligodendrocytes may be targets for neuroprotective therapy to reduce injury to preoligodendrocytes. Drugs that block production of nitric oxide and other oxygen free radicals or repair deficits in oxidative defense molecules might also be useful. Since some of the injury to white matter in the premature infant occurs in the postnatal period, these strategies may be useful for neuroprotection in the nursery. It will be equally important to understand the pathogenesis of impaired growth of gray matter structures in the preterm brain and to determine if medications or early intervention educational strategies could help repair these deficits.

Acknowledgment

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CHAPTER 96

INJURY TO THE TERM BRAIN

REBECCA N. ICHORD, MD

Acute brain injury due to hypoxic-ischemic insults in term newborns remains an important disease, causing death or lifelong disability in a significant number of infants. This chapter reviews recent advances in definitions, incidence, pathophysiology, diagnostic approach, and treatment.

Acute brain injury remains an important cause of mortality and long-term morbidity for neonates born at term. The causes of acute neonatal brain injury are numerous and diverse, including hypoxic-ischemic events, trauma, infection, hemorrhage, stroke, and metabolic disease. This chapter focuses on acute hypoxic-ischemic brain injury in term newborns, the aim being to describe new knowledge and progress regarding incidence, pathophysiology, clinical features, approach to diagnosis and management, and outcome.

Definitions and Diagnostic Criteria

There is now growing consensus that use of the term "neonatal asphyxia" invites misunderstanding, inaccurate assumptions, and ill-founded expectations. Strictly speaking, "asphyxia" refers to a systemic physiologic perturbation leading to failure of gas exchange and a combination of hypoxemia and hypercarbia. When systemic hypoxemia and hypercarbia persist sufficiently long to compromise systemic circulation, then hypotension develops and the physiologic perturbation includes an element of ischemia or, in the worst cases, complete circulatory arrest. This is a systemic process distinct from the brain injury that may be caused by an asphyxial exposure and which is more properly referred to as hypoxic-ischemic encephalopathy (HIE). It is rare that the disruption of circulation and gas exchange can be objectively measured, forcing clinicians to rely on signs and symptoms in the newborn that may have multiple possible causes.

Problems arise when attempts are made to causally connect an acute brain injury to a specific physiologic perturbation, such as exposure to asphyxia, around the time of birth. First of all, the physiologic perturbation occurs prenatally, and as such cannot be directly measured. Second, the impact of physiologic perturbations on the fetus or newborn are highly variable, depending on numerous factors such as genetic and maturational vulnerabilities to oxidative stress and the duration and amplitude of the physiologic perturbation. Third, the neurologic manifestations of hypoxic-ischemic injury such as seizures and depressed mental status are nonspecific, and may be caused by any of a wide array of other pathophysiologic processes. This uncertainty as to cause and effect has led to increasing use of more descriptive terms such as perinatal depression or neonatal encephalopathy.

A number of investigations in recent years have aimed to provide more solid evidence-based diagnostic criteria for neonatal HIE. The Apgar score remains a marker of risk, but is only weakly predictive of neurologic injury. A recent prospective cohort study found that a 1-minute Apgar score of 3 or less predicted neonatal encephalopathy in only 11% of cases. Intrapartum fetal acidosis with a base deficit exceeding –12 or initial cord pH < 7.0 are fairly sensitive markers that predict which infants with abnormal fetal heart rate (FHR) profiles will go on to have clinical evidence of hypoxic-ischemic injury. However, the application of population-based statistics to the prediction in an individual patient of a cause-and-effect relationship between adverse perinatal events and neurologic injury must always be undertaken with caution. In some cases, the sequence of events clearly defines an episode of severe fetal circulatory compromise, such as uterine rupture or complete placental separation. In less obvious cases, existing literature shows there is considerable variability in outcomes, and there are always exceptions to generalizations.

What then is the incidence of neonatal HIE? A recent population-based cohort study of 23,000 deliveries estimated 20 to 25 newborns per 1,000 live births develop metabolic acidosis of intrapartum origin. Of these, only 3 to 4/1,000 were severe enough to be associated with acute encephalopathy (HIE) and multiple other organ injury. Of those with HIE, about 1/1,000 went on to have chronic static encephalopathy or neuropathologic evidence of cerebral injury.

In 1999, the College of Obstetrics and Gynecology published a consensus statement regarding risk factors: cord pH < 7.0, a base excess of –12 or worse, and the occurrence of associated other organ injury particularly of the kidney and liver. It seems clear, however, that there are many pitfalls to attributing neonatal encephalopathy to intrapartum hypoxia-ischemia without direct and persuasive evidence.

Pathophysiology: Cellular and Molecular Events

The "Decade of the Brain" has brought an explosion of knowledge resulting from spectacular advances in basic neuroscience research (Figure 96-1). However, relatively few studies have addressed developmental aspects of cell injury and death or the mechanisms involved in recovery and adaptation in surviving systems. A comprehensive review of this subject is beyond the scope of this chapter (Martin et al, 1998).

The immature brain is distinguished by highly dynamic systems of activity-dependent interconnected circuits, in which excitatory and inhibitory processes are in an ever-changing dynamic equilibrium. Figure 96-2 depicts a highly simplified schematic of events at the cellular level leading to neuronal dysfunction and ultimately cell death in this dynamic milieu. Failure of adequate energy substrate delivery (oxygen and glucose) during a hypoxic-ischemic event leads to adenosine triphosphate (ATP) depletion, failure of ion pumps, and widespread neuronal depolarization. Normal synaptic function fails, and there is abnormal ion flux and an excess accumulation of extracellular glutamate. GABAergic inhibitory systems fail, and there is over activation of glutamatergic receptors, with calcium influx, activation of calcium-dependent proteases, lipoxygenases, endonucleases, and nitric oxide synthase. There is widespread damage to all subcellular systems and damage to mitochondria, which if sufficiently severe will prevent recovery of the cell. Cell death ensues, largely by necrosis in regions most severely affected and secondarily by apoptosis in regions less severely affected and in systems affected by target deprivation or other activity- and connectivity-dependent mechanisms of cell survival. Cell death and the processes associated with cell death, particularly by necrosis, induce an inflammatory response that

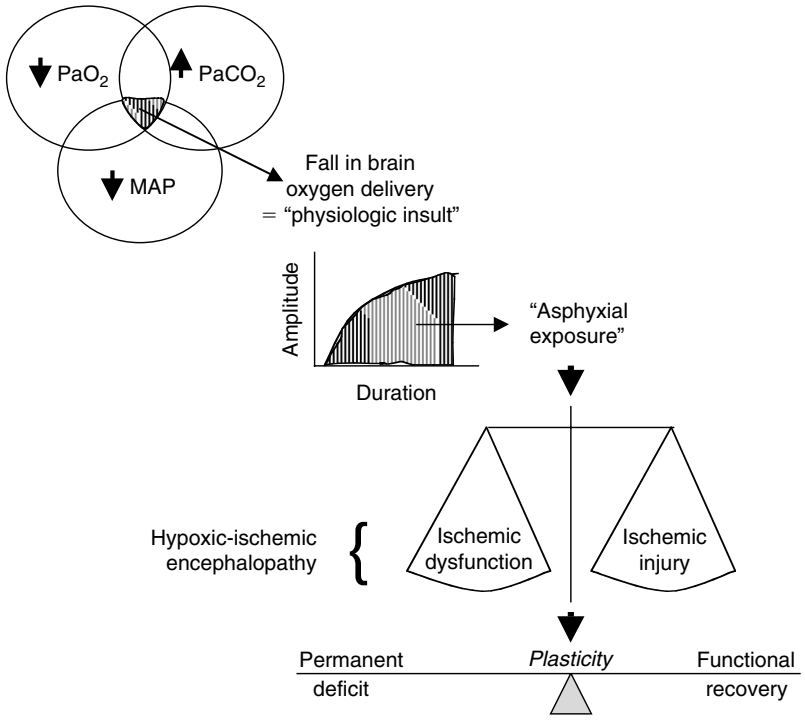

FIGURE 96-1. Physiology of perinatal hypoxic-ischemic brain injury. MAP = mean arterial pressure.

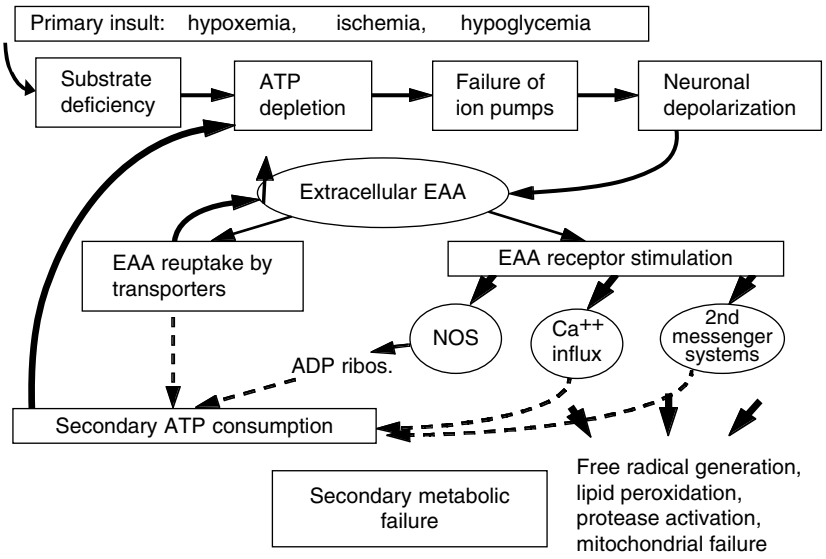

FIGURE 96-2. Pathophysiology: cellular and molecular events. ADP = adenosine diphosphate; ATP = adenosine triphosphate; EAA = excitatory amino acids; NOS = nitric oxide synthase.

plays a key role in the fate of marginally viable cells and perhaps in the function of surviving cells. Pathways involved in the cellular response to oxidative stress are important mediators and potential sites of intervention in the acutely injured neonatal brain.

The advent of genome-based and proteomic technologies has brought new insights regarding the complexity and temporal-dependence of hypoxic-ischemic brain injury. An example of this is the study of sublethal hypoxia-induced gene expression and protein markers, exemplified by hypoxia-induced factor-1 (HIF). After exposure to sublethal hypoxia, dozens of genes are upregulated for variable durations (seconds to hours), at various times during the first 24 hours, some of strictly neuronal origin and others of astroglial or endothelial origin. Examples of upregulated genes that have been implicated in the response to hypoxic injury through other lines of study include the glucose transporter, cytokines and inflammatory markers, lipoxygenases, endothelial nitric oxide synthase, erythropoietin, and vascular endothelial growth factor. Advances in the understanding of the preconditioning phenomenon may lead to identification of candidate interventions for ameliorating hypoxic-ischemic injury. For a detailed review of mechanisms related to preconditioning and hypoxia-induced factors, see Sharp and Bernaudin (2004). As is the case in many developmentally determined neuronal processes, oxygen sensing and adaptation to variable levels of tissue oxygen content may be built into the immature brain as a part of the mechanisms that match structure with function in the transition from in utero to extrauterine life. For example, neonatal hippocampal neurons have *N*-methyl-D-aspartate receptors that respond to hypoxia by decreased calcium influx, as compared with normoxia through a mechanism involving altered receptor subunit composition. This is associated with decreased glutamate-induced cell death in hypoxic conditions, and is age-dependent, disappearing in older brain. This is one of potentially many mechanisms that confers tolerance to hypoxia in the immature brain and a means of "oxygen sensing" to the developing brain.

Assessment: Clinical Features

The literature describing clinical features of neonatal hypoxic-ischemic encephalopathy dates back many years. It is exemplified by the staging system proposed by Sarnat in 1976, which classifies encephalopathy in term newborns as mild, moderate, or severe on the basis of presence and severity of abnormalities in level of consciousness, tone, neonatal reflex behaviors, seizures, and autonomic function. Infants with mild encephalopathy, or moderate encephalopathy of < 1 week duration, have a low risk of long-term disability, whereas infants with severe encephalopathy of any duration or moderate encephalopathy of > 1 week duration have a high risk of disability. More recently, Kaufman and colleagues have shown the predictive utility of a detailed newborn neurologic exam. Predicting outcome for infants with moderate encephalopathy can be improved by adding information from imaging and electrophysiologic studies.

Seizures are another important and distinctive clinical feature of acute HIE in term newborns. Miller and colleagues showed that the severity of clinical seizures was a predictor of metabolic indicators (brain magnetic resonance spectroscopy) of injury, independent of illness severity or need for resuscitation. As with clinical staging, the predictive significance of seizure severity score was greatest in the infants with mild and severe seizures, whereas intermediate seizure severity scores were associated with indeterminate risk of metabolic injury on magnetic resonance imaging (MRI). The role of seizures in exacerbating hypoxic-ischemic injury and contributing to the evolution of the final neurodevelopmental impairment after newborn encephalopathy remains uncertain.

Assessment: Imaging and Electrophysiology

MRI has proved to be a powerful tool in detection of the extent and severity of acute hypoxic-ischemic brain injury in newborns. Diffusion-weighted imaging (DWI) in particular has increased the sensitivity and predictive utility of MRI. In a prospective cohort study of term infants with HIE published in 2001, Barkovich showed that DWI in the first 24 hours of life is sensitive to, but underestimates the extent of, ischemic injury. However, others have shown that DWI is relatively insensitive during the first 24 hours, is maximally abnormal between 2 and 4 days of age, and is increasingly unreliable after day 7 because of pseudonormalization of the diffusion coefficient.

The weight of evidence relating MRI findings to later outcome was sufficient to provide the basis for a recently published Child Neurology Society/American Academy of Neurology practice parameter (Ment et al, 2002). This suggests that encephalopathic term infants should undergo computed tomography first to exclude hemorrhage and that MRI should be performed later in the first postnatal week to establish the pattern of injury and assist in predicting neurologic outcome.

Electroencephalograms (EEGs) have long been viewed and used as an important tool in the assessment of acute brain injury in term neonates. The utility of EEGs has gained additional support from studies performed in the past 5 years, confirming earlier observations that the severity of EEG abnormality is related to the severity of clinical encephalopathy and, in turn, is related to prognosis. The most severe burst suppression, defined by voltage $< 5\ \mu V$ with prolonged interburst intervals, is consistently associated with very poor outcome, predominantly severe disability, or death in almost all cases. However, "modified" burst suppression, defined by voltage $> 5\ \mu V$ in the suppressed segments and shorter interburst intervals, was associated with normal outcome or only mild impairment in 70% of the cases.

The advent of a clinical trial of hypothermia has prompted increased interest in bedside EEG technologies for purposes of rapid identification of candidates for treatment. Amplitude integrated EEG (aEEG) is such a technology and has been found to have good sensitivity and predictive validity for later disability with recordings made as early as 3 to 6 hours after birth. The significance of mild or moderate abnormalities in background EEG is less clear, and caution is warranted in the interpretation of background EEG abnormalities in the presence of sedating drugs.

Assessment: Biomarkers

Interest in identifying serum or cerebrospinal fluid (CSF) markers of brain injury is long-standing and has grown in recent years with the advent of new technologies to study genomics and proteomics. Traditionally, studies have focused on brain cellular markers of glial and neuronal injury. Results to date have been mixed (Nagdyman et al, 2003). Neurotrophic factor S100® and creatine kinase BB-isoenzyme levels are elevated as early as 2 hours after birth in babies with moderate or severe encephalopathy, when compared with normal babies. However, their predictive value is poor. Brain proteins are elevated in CSF in asphyxiated newborns in a manner correlating with outcome at 1 year. A novel marker of oxidative stress, non–protein-bound iron, may hold more promise as a biomarker. In a study of 384 newborns, plasma non–protein-bound iron was a good early predictive marker of neurodevelopmental outcome, with 100% sensitivity and 100% specificity for good neurodevelopmental outcome at 0 to 1.16 μmol/L and for poor neurodevelopmental outcome at values $> 15.2\ \mu mol/L$. Inflammatory markers are elevated in infants with asphyxial exposure, but overlap with elevations occurring with infection. Cytokines IL-6 and IL-1b as well as sICAM-1 serum levels may not differ between asphyxiated and infected neonates; however, at most time periods, their values were significantly higher than controls. The use of biomarkers remains a research tool at this point, and may be more helpful in elucidating the time course of different components of the injury cascade, thereby guiding the timing of interventions in trials of novel neuroprotective agents.

Treatment

Understanding of the cellular and molecular mechanisms of neonatal acute brain injury has advanced rapidly in the past decade. Despite this progress, there are few prospects for new therapies that can ameliorate or reverse acute brain injury. Small single-center trials of putative neuroprotective agents have proceeded for calcium-channel blockers and magnesium, both terminated early because of dangerous

systemic toxicity. Animal studies of glutamate antagonists were initially promising but failed to move to human clinical trials because of direct neurologic toxicity. The paucity of proven interventions leaves care providers with the same approach as 10 years ago, consisting of supportive care to optimize perfusion and oxygenation, prevent hyperthermia, and maintain salt and fluid balance. Treatment of neonatal seizures in this setting has traditionally been viewed as part of "supportive" care. The knowledge that more seizure activity correlates with an increased risk of a bad outcome amplifies the importance of addressing the efficacy of treatment in a multicenter trial. Hypothermia has been the focus of multicenter trials in the past 5 years, and the results of such trials await publication.

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Practitioner and Patient Resources

March of Dimes Birth Defects Foundation
1275 Mamaroneck Avenue
White Plains, NY 10605
Phone: (914) 428-7100 or 800-663-4637
E-mail: resourcecenter@modimes.org
http://www.modimes.org
The mission of the March of Dimes is to improve the health of babies by preventing birth defects and infant mortality. It carries out this mission through research, community services, education, and advocacy to save babies' lives.

Brain Injury Association (BIA)
105 N. Alfred Street
Alexandria, VA 22314
Phone: (703) 236-6000 or 800-444-6443
http://www.biausa.org
The mission of the BIA is to create a better future through brain injury prevention, research, education, and advocacy. The BIA seeks a world where all preventable brain injuries are prevented, all unpreventable brain injuries are minimized, and all individuals who have experienced brain injury maximize their quality of life.

Exceptional Parent Magazine
P.O. Box 3000, Department EP
Denville, NJ 07834
Phone: (800) 562-1973
Provides practical guidance and support for parents of children with disabilities and special health care needs. Informs parents about current and changing rights and laws and provides programs for children with disabilities.

CHAPTER 97

BIRTH BRACHIAL PLEXUS PALSY

MAUREEN R. NELSON, MD

This chapter describes birth brachial plexus palsy (BBPP), including its incidence, the mechanism presumed to underlie the condition, associated risk factors, and level of neurologic involvement. Early and late treatment options will be presented, both therapeutic and surgical

Birth brachial plexus palsy (BBPP) injury occurs in approximately 1 to 2/1,000 live births. This number has not changed significantly over the years. In most infants, clinical symptoms eventually resolve. As reported in the literature, between 50 and 95% of affected infants will recover.

In this chapter, we review risk factors and describe the anatomy involved. We also discuss the clinical evaluation and describe treatment approaches. Plain radiography and electrodiagnosis, including nerve conduction studies and electromyography, may be useful in clinical Decision making. Early treatment and immediate education of the family are essential. For a child with a flaccid, anesthetic arm, surgery is typically performed when he or she is 3 or 4 months old. If the child is capable of some arm movement, surgery is usually done when he or she is 6 to 9 months of age. Surgical intervention with nerve grafting has been available for more than 100 years. A multitude of muscle and tendon procedures also exist. In addition, more traditional orthopedic procedures, such as arthrodesis and derotational osteotomies, may be undertaken.

History

BBPPs have been described in the literature since the 1700s. In 1768,W.A. Smellie first published a description of BBPP. Then, in 1872, Duchenne first reported a unilateral BBPP in an article on electrical stimulation. Shortly thereafter, in 1874, Erb described the upper brachial plexus point, where there is a lower threshold for electrical stimulation of the plexus. Madame Klumpke described an adult with C8-T1 BBPP with Horner syndrome in 1885. In the 1890s, primary brachial plexus explorations with nerve grafts began and proceeded through the 1920s. The first publication describing the approach, in this case involving a C5-6 rupture and repair, was in 1903 by Kennedy in the *British Medical Journal.* Unfortunately, technical deficiencies at the time led to significant mortality secondary to the positioning of the great vessels close to the brachial plexus; therefore, the surgical procedures were, for the most part, stopped after the 1920s. The 1970s brought dramatic microsurgical advancements. Shortly thereafter, Dr. Alain Gilbert began performing these procedures routinely on infants with BBPP in Paris, and the procedure's popularity spread from there.

The incidence of BBPP is approximately 1 to 2/1,000 live births. BBPP is frequently associated with shoulder dystocia at the time of delivery. The next most common associations are multiparity and large infants who are large and mothers who are multiparous. There is increased risk with higher birth weight, especially with a diabetic mother. It has been reported that 10% of birth weights are prenatally underestimated by over 20%.

The most common description of an etiologic mechanism of action is a stretch, most commonly lateral. This is anatomically logical, as the site of the brachial plexus is just lateral to the sternocleidomastoid and just superior to the clavicle, leading to potential stretch of the brachial plexus in shoulder dystocia. Some intrauterine mechanisms also have been recently proposed, but they have not had wide support. Some infants clearly have anatomic variations or anomalies, including vascular, tendinous, or bony, which either cause BBPP or increase the susceptibility to it.

In any consideration of nerve injury, classification is useful. In the Seddon classification, the mildest type of injury is neurapraxia, in which there is no anatomic change and there is reversible loss of electrical conduction. This will completely resolve. The most severe type of nerve injury is neurotmesis,

in which there is complete physical disruption of the nerve. This is called an avulsion when it is preganglionic or proximal to the dorsal root ganglion and, therefore, immediately adjacent to the spinal cord. It is called a rupture when it is postganglionic. This distinction has pertinent surgical indications, but both require surgical repair. Axonotmesis is the third type of injury and it is the most difficult for evaluation because of variable severity. With this, the axon is disrupted, but there is preserved endoneurium.

The brachial plexus anatomy involved includes roots, trunks, divisions, cords, and the peripheral nerves. The roots are actually the anterior primary rami of C5, C6, C7, C8, and T1, with C4 sometimes involved. There are upper, middle and lower trunks, as well as dorsal and ventral divisions and posterior, medial, and lateral cords (Figure 97-1). An infant with BBPP will have variability in the level of the roots involved. *Erb's palsy* or C5-C6 palsy is the most common, occurring in approximately 75% of infants (Figure 97-2). This is anatomically logical, considering the position of the brachial plexus itself and the position of the baby during delivery. *Klumpke's palsy* is a C8-T1 palsy with frequent concurrent Horner syndrome. There are many who question whether Klumpke's palsy actually exists in BBPP, except as an anatomic anomaly, because of the lack of a plausible mechanism to involve C8 and T1 without involving the more superior roots during birth.

If a child presents with Klumpke's palsy, there are three possibilities to consider. First, and by far most likely, is that the entire plexus was initially involved in the injury. C4, C5, C6, and, sometimes, C7 are held in the transverse process spinal nerve gutter by connective tissue, which is protective positioning for them. C8 and T1 do not have this protection and, therefore, are more at risk for a severe nerve injury, given equal amounts of force to all roots. Therefore, it is quite likely that an infant who presents for evaluation with C8-T1 brachial plexus palsy with a thorough history will have had a complete plexus involvement initially, with resolution of the better-protected fibers prior to evaluation. The dorsal roots are also at relatively less risk than the ventral, secondary to them being more cohesive and staying together into the dorsal root ganglion, as opposed to the ventral roots, which have the ganglion within the spinal cord and, therefore, are separated prior to leaving the cord. Because of this, sensory fibers are relatively better protected than motor fibers. The second possibility is spinal cord injury. The third possibility is an anatomic variation that changes the forces applied to the roots, such as a blood vessel, tendon, or anomalous rib that selectively affects C8-T1. There may be other combinations of plexus involvement, due to variation of types of nerve injuries that may have occurred and the various levels that may be injured. In the most severe case, the complete plexus is

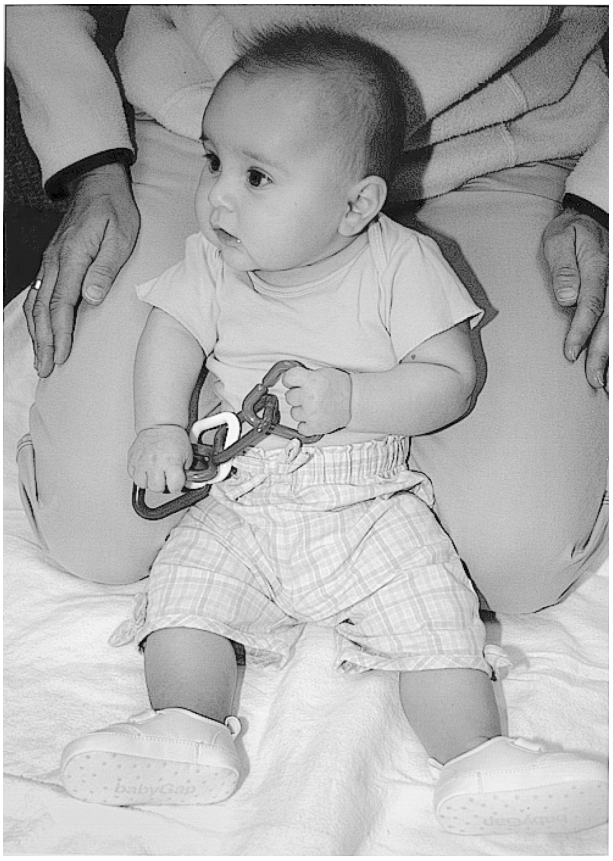

FIGURE 97-2. Infant with Erb's palsy of right arm.

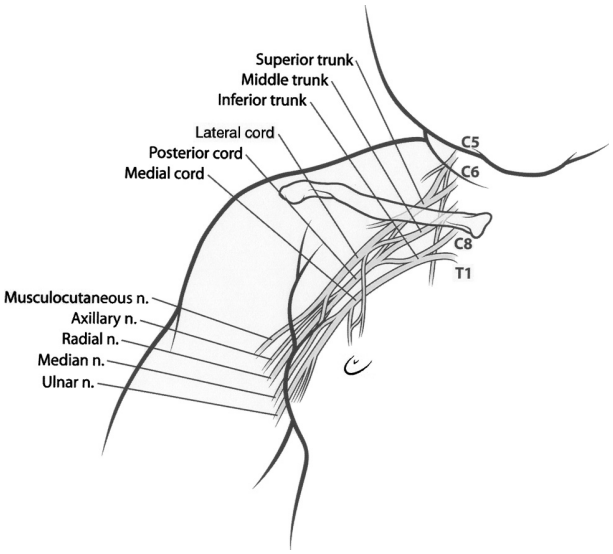

FIGURE 97-1. Anatomy of the brachial plexus.

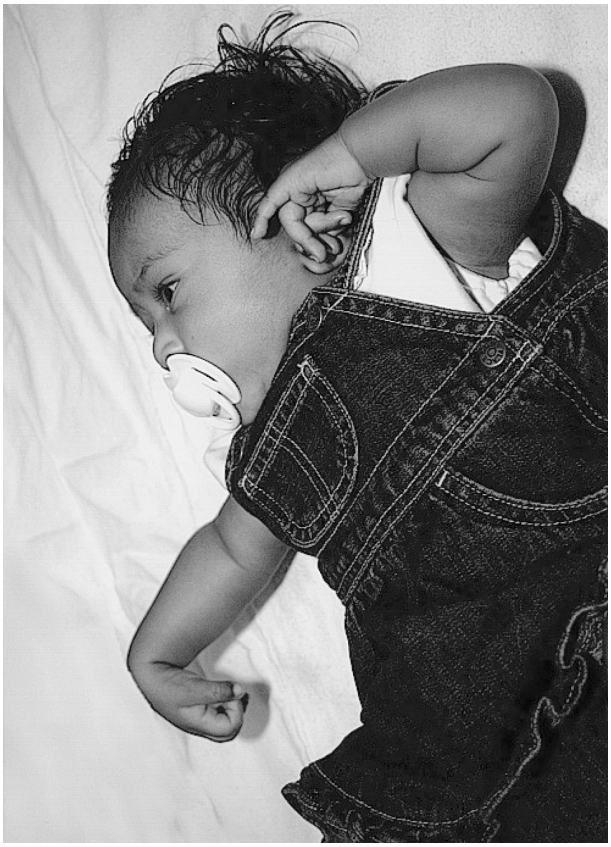

FIGURE 97-3. Complete brachial plexus injury on the right.

involved (Figure 97-3). Other diagnostic considerations in an infant with a weak or flail arm include infection, a very rare hereditary neuropathy or congenital lack of bicep development, neurofibromatosis, infection including osteomyelitis, or fracture. These should be differentiated by their time course & physical presentation.

Evaluation

Primary questions to be asked when taking the medical history include the parity of the mother, the infant's birth weight, and the presence of shoulder dystocia. Additionally, significant questions are the size of previous infants and their ages, presence or absence of gestational diabetes, and the clinical course since the time of birth, with any improvements or changes seen.

The physical examination includes sensory evaluation for any dermatomal or nerve root distribution deficits. A sensory exam in an infant may help with the motor exam by stimulating the child to move. A motor exam in an infant may be assisted by generating interest in reaching for toys or treats and by positioning the infant. Testing the primitive reflexes, particularly the Moro response, will help in showing the infant's active proximal physical movement. Tendon reflexes will be absent or decreased in all infants with BBPP. Range of motion must be evaluated in the arm due to the common presence of contractures, which may be seen in shoulder adduction, internal rotation and extension, and finger flexion. Later, wrist flexion and elbow flexion contractures are frequently seen. The elbow flexion contracture is even found, ironically, in infants and children who do not have active elbow flexion and do have active elbow extension. This appears to be due to our natural frequent positioning in flexion. The pronated position is frequently overlooked. The size of the involved arm may give clues to the specific deficits and is frequently decreased, with both atrophy in the muscle and smaller bony structure. The shoulder joint is very frequently underdeveloped compared with the other side, as is quite common in infants with many motor problems involving the shoulder or hip. Occasionally, temperature may be asymmetric in the arms, particularly if there is Horner's syndrome. Torticollis is commonly seen, with the neck rotated away from the involved arm the vast majority of the time.

Radiographic Evaluation

Plain radiographic films are an important part of early evaluation to rule out fracture of the clavicle or humerus. There are very rare instances of a bone tumor or osteomyelitis clinically mimicking BBPP; however, the history and time course differ. Computed tomography myelograms or magnetic resonance imaging (MRI) is routinely done for older patients for brachial plexus palsy. This has been evaluated and there are significant false-positives and false-negatives in doing these studies in infants with the current technology. As the infants must be sedated for these studies and studies have a low degree of reliability, these are currently not a recommended part of the evaluation. I believe it is likely that as the technology improves MRI will become a very useful study.

Electrodiagnosis

Electrodiagnostic evaluation can give crucial information about an infant with BBPP by revealing clinically problematic areas. This evaluation is a combination of a nerve conduction study (NCS) and electromyography. The NCS consists of a motor NCS, in which roots or nerves are stimulated for evaluation of subclinical electrical activity of muscle for indication of electrical continuity and potential for clinical recovery. This is useful because the electrical activity returns prior to having sufficient activity for clinical movement. Sensory NCS gives significant information if there is clinical sensory deficit. In this diagnosis, if sensation is intact in the arm, sensory NCS is not useful. If there is an area that is insensate and the sensory NCS shows a normal response, then there is a preganglionic

neurotmesis (avulsion). This is due to the continuity between the peripheral nerve and the dorsal root ganglion. Somatosensory evoked potentials (SEPs) are generally not performed as part of clinical evaluation both because of the overlap of innervation, making it less specific than ideal, as well as the fact that the child would need to be placed under general anesthesia for this study. Information on proximal portions of the roots can instead be obtained from F waves and H reflexes during the NCS. The F wave is easily obtained and there is no significant difference in the comfort level for the patient. H reflexes require increased duration of stimulation and are, therefore, more uncomfortable and less well tolerated. They are more technically challenging to obtain as well. The H reflexes are potentially available in testing of all motor nerves during infancy, decreasing over time so that only the median nerve, C5-6, may be present in older children and adults.

Preparation is essential so that both the parents and the infant can tolerate the study with minimal discomfort. I gather all equipment needed first so that everything will be within reach, including toys for distraction. I tell the parents that the child will get a mild electrical shock, similar to that experienced after rubbing one's feet on carpet and touching someone, and that we will then be able to measure the electrical activity of the nerves and muscles. Some children describe this stimulus as a ticklish feeling, whereas others do find it uncomfortable. Next, I show them both a sensory level and motor level response on my wrist and then encourage the parents to feel a sensory level stimulation, as well.

I then initiate the study with the child as comfortable as possible, very commonly with the infant on the parent's lap. I perform the sensory nerve conduction study first, then the motor nerve conduction study. I then tell the parents that I will not be putting any more electrical input into the child but will use a wire electrode to look at the child's muscle electrical activity. I tell them that I will be putting the electrode through the skin into the muscle and that, very likely, the child will find this uncomfortable. If this is the case, however, and they fight the study, it gives the optimal electrical view of the functioning motor units. We discuss that there will be no after-effects of the study. I then perform the electromyography using a wire electrode in muscles that have motor deficit. Both NCS and electromyography are done in an individualized manner with only selective studies performed. Therefore, because approximately 75% of infants will have clinical involvement of the upper trunk, it is quite likely that the hand will be excellent and we will do no median or ulnar studies. Erb's point stimulation is commonly performed in the NCS of this group of children to evaluate the axillary and musculocutaneous nerves.

Recommendations for timing of the performance of EMG and NCS in these infants are variable. Classically, studies are performed at least 14 to 21 days after a nerve injury as this is the EMG timing described for adults to show positive sharp waves and fibrillations, which indicate denervation of the muscles. The timing for positive sharp waves and fibrillations has been reported as earlier after injury in infants than in adults. Some advocate immediate EMG and NCS after birth to look for indications of possible intrauterine onset versus during delivery, which may be a legal question. It is important during the EMG to search for the presence of motor units in muscles which do not show clinical activity to determine if they do have electrical activity. This will help guide possibilities expected for clinical recovery period.

Early Treatment

The treatment approach is presented to the family after the child has been examined. We first discuss the anatomy of the brachial plexus and pertinent surrounding structures. I present the related issue of the risk of repeat birth brachial plexus palsy due to size issues and recommend considering future scheduled cesarean section prior to going into labor. I stress the importance of a passive range of motion program that keeps the baby's joints in excellent position as well as the importance of maintaining awareness of the baby's involved arm. I recommend use of a wrist rattle on the involved arm as well as to have the family move the involved arm and hand up into a child's field of vision and replicate movements the child does on the uninvolved arm. The parents are then given a prescription for occupational therapy (OT) or physical therapy (PT), depending on who is available in their area and their insurance coverage. The therapist then works on positioning the child immediately. The range of motion program is started at 2 weeks of age. Orthoses are frequently required, particularly for wrist extension early on and later for supination. Precautions are given to avoid overly strenuous shoulder abduction and external rotation or forearm supination to prevent shoulder dislocation and subluxation or dislocation of the radial head at the elbow. Seeing the therapist regularly and doing a home program several times a day to work on range of motion increase awareness of the arm and increase active use of the arm, which are crucial to gaining functional use of the arm. The importance of the parents consistently promoting the active use of the involved arm cannot be overemphasized.

Electrical stimulation to the level of muscle twitch is frequently used to attempt to gain the maximum strength possible. When muscles become extremely tight, to the degree of malpositioning or inhibiting the opposing muscle function, botulinum toxin injections may be useful. This may be combined with serial casting to stretch a tight muscle, most commonly the biceps.

Surgical Decisions

In most infants, BBPP spontaneously resolves, but findings reported in the literature vary dramatically. Those who report that up to 95% of their patients recovered counted any trace movement as recovery. Those who report that 50% or less recover demand perfect symmetry of the arm.

There are many reasons for attempting surgical intervention early. The primary one pertains to child development: a desire to have the child learning all bimanual activities with two hands from the beginning. The contractures also may progress over time, so that early intervention to minimize this is an aim. Quite frequently, growth is asymmetrical, with a decrease in arm length and atrophy. Lack of awareness may be a significant problem for these children, as they may grow up paying attention to one side and not having the other arm in the field of vision, leading to functional loss with daily activities. Shoulder asymmetry is extremely common, as is scapular winging. Pain is not usually an issue as it is in older patients. There are common reports of tenderness about the shoulder for approximately the first 2 weeks, particularly when changing clothes or bathing. Hand dominance may be affected, with one report noting that 90% of the general population is right handed, but that is true for only 17% of those with a right sided BBPP.

Surgical intervention was begun on nerve roots on individuals with BBPP in the 1890s. The proximity of the great vessels made this technically quite difficult at the time. Advances in microsurgical techniques in the 1970s made this a relatively common procedure, and technical improvements continue to this day. Electrical stimulations are generally done on the nerves to determine electrical continuity. Nerve grafts are performed, most commonly using the surely nerve to join together proximal functioning, electrically connected fibers with distal nerve fibers. Neurolysis is regularly done to remove scar tissue that lacks functioning nerves. Nerve grafts are then done, ideally with direct end-to-end anastomosis. This is not generally possible, so donor nerves, such as the sural, are used. Combinations of these procedures are done in most cases. Nerve growth will follow in the months after surgical intervention. If no functioning nerve roots are found, C7 may be partially taken from the contralateral side and tunneled under the skin, with ulnar nerve or sural nerve graft. This approach, of course, leads to a longer time for nerve growth. Intercostal nerves are sometimes used, but because they are smaller, it is more difficult to have sufficient nerve fascicles for grafting.

The infants will then continue with therapies and a home exercise program while health practitioners monitor nerve and muscle recovery. Secondary procedures include the ulnar or median nerve transfer to musculocutaneous nerve. If there are continued deficits, muscle transfers may be performed.

Muscle imbalance and internal rotation contractures, especially during development, can lead to shoulder deformity and decreased function. Accessory nerve to suprascapular nerve grafting may improve shoulder abduction. Latissimus dorsi and teres major release and transfer have been shown to improve shoulder function and range of motion but does not remodel the glenohumeral joint. Derotational humeral osteotomies have been performed for these deficits that show also significant glenohumeral deformity. Similarly, results of this procedure have been increased shoulder function but continued glenohumeral abnormalities. Transfer of motor fascicles from the ulnar nerve or the median nerve to the musculocutaneous nerve as it enters the biceps can be effective in gaining biceps function in those with no elbow flexion. Muscle and tendon transfers may be done for wrist and finger flexion extension or thumb positioning. Another possibility is a muscle transfer of the free gracilis to the forearm with nerve grafts. Advances continue to be made in this area with fine tuning of muscle, tendon, and nerve transfers.

Summary

Birth brachial plexus injury occurs in 1 to 2/1,000 live births, though approximately 75 to 80% of these recover spontaneously. It is important for therapeutic intervention to be undertaken early with education for the parents, including consideration of cesarean section for any future deliveries. A home exercise program is vital. Many surgical options are available if a child does not show recovery by 6 months of age when they show some motor activity, or at 3 to 4 months of age when they have a flaccid, anesthetic arm.

Suggested Readings

Nelson MR: Birth brachial plexus palsy. PM&R State of the Art Reviews, 14:2; 237–246, 2000.

Slooff AC: Obstetric brachial plexus lesions and their neurosurgical treatment. Clin Neurol Neurosurg, 95:S73–7, 1993.

Sundholm LK, Eliasson AC, Forssberg H: Obstetric brachial plexus injuries: assessment protocol and functional outcome at age 5 years. Devel Med Child Neurol 1998;40:4–11.

Waters, PM: Comparison of the Natural history, microsurgical repair, operative reconstruction in brachial plexus birth palsy. JBJS(A) 1999;81 A:649–659.

Waters PM, Bae DS: The effect of derotational humeral osteotomy on global shoulder function in brachial plexus birth palsy. JBJS(A) 2006;88 A:1035–42.

Practitioner and Patient Resources

United Brachial Plexus Network (UBPN)

http://www.ubpn.org
The UBPN is a registered non-profit 501(c)3 organization devoted to providing information, support, and leadership for families and those concerned with brachial plexus injuries worldwide.

National Institute of Neurological Disorders and Stroke (NINDS)

http://www.ninds.nih.gov

The mission of NINDS is to reduce the burden of neurological disease—a burden borne by every age group, by every segment of society, by people all over the world. NINDS seeks to lead the neuroscience community in shaping the future of research and its relationship to brain diseases, build an intramural program that is the model for modern collaborative neuroscience research, develop the next generation of basic and clinical neuroscientists through inspiration and resource support, seize opportunities to focus its resources to rapidly translate scientific discoveries into prevention, treatment, and cures, and be the first place the public turns to for authoritative neuroscience research information.

CHAPTER 98

ALTERED STATES OF CONSCIOUSNESS

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Child neurologists are often consulted to evaluate the child with an altered state of consciousness. This chapter introduces terms and concepts crucial to understanding altered states of consciousness and to providing a standard approach for early management, and describes patterns and common diagnoses. Many specific causes of coma in children are covered elsewhere in this text; however, we will discuss a few. This chapter concludes with a discussion of the prognosis for comatose children and for those with metabolic illnesses associated with alteration of consciousness.

Consciousness requires the normal function of both cerebral hemispheres as well as the ascending reticular activating system (ARAS), which extends from the level of the midpons to the anterior hypothalamus. Neuronal projections continue from ARAS into the thalamus, where they synapse and then project to the cortex. Consciousness requires both arousal, which is the appearance and preservation of wakefulness, and some degree of cognitive function. Plum and Posner state "arousal does not guarantee cognition"; therefore, the appearance of wakefulness does not imply consciousness.

Because many pathologic processes can affect the parts of the central nervous system (CNS) that mediate consciousness, alteration in the state of consciousness often is a common feature of many neurologic diseases. Impairment of consciousness represents a continuum that spans from mild confusion to coma. The degree of impairment of consciousness is determined by the pathological process and the severity of the condition. Other neurologic signs, such as hemiparesis or cranial nerve dysfunction, are often seen in the patient with altered consciousness, as the same process that can affect level of consciousness also may interfere with other CNS functions.

Rapid changes in the level of consciousness often occur, which highlight the need for charting specific clinical observations accurately and precisely. A child with altered consciousness will often lie still with the eyes closed and will not respond normally to vigorous or noxious stimulation. With a noxious stimulus, instead of arousing, the child might become alert for a brief time, become combative, or demonstrate pathologic extensor or flexor postures. When the stimulus is removed, the child will return to a quiet state. Early in the disease process, the appearance of agitation may surpass any concern about lack of normal consciousness. The term "coma" should be reserved for the patient that either has no response or one that includes a patterned movement that indicates release of the lower neuronal systems.

Although patients with altered consciousness also may appear vegetative, the actual condition termed *the vegetative state* usually evolves from a coma a month or more after a severe CNS injury, when sleep-wake cycles tend to reestablish in the setting of severe bilateral cortical injury. The vegetative state will be characterized by eye opening during wakefulness, a return of normal brainstem and cranial nerve function, but without evidence of self-awareness or awareness of the environment. It is often tempting to use descriptive phrases such as "obtunded," "stuporous," or "psychotic delirium," but because these terms are open to subjective interpretation, they should be avoided, and instead, the actual exam should be documented.

Examination

Glasgow Coma Scale

The Glasgow Coma Scale (GCS) was developed to provide a rapid, consistent, and easy system to quantify the impairment of consciousness. The prognostic significance of the GCS has been verified for head trauma in adults, but cannot be used to prognosticate for other causes of altered consciousness. It assigns numerical values for best eye opening, motor function, and verbal response (Table 98-1). The scale ranges from 3 to 15, with a value of < 8 defined as a coma. The simplicity ensures minimal intraobserver differences and allows for a meaningful appraisal of brainstem and cortical functions. This scale has been adapted for use with young children. Recording the GCS never replaces a narrative description of the neurologic examination, which remains of quintessential importance.

Vital Signs

Aside from the obvious need to respond to abnormal blood pressure, respiratory rate, and pulse rate, vital signs can sometimes provide clues about the possible causes for the underlying illness. Table 98-3 lists some of the more common causes of blood pressure and heart rate changes.

Level of Central Nervous System Function

The level of brain injury can usually be established by performing a complete neurologic examination. A detailed discussion is provided by Plum and Posner (1982).

State of Consciousness

In altered states of consciousness, higher cortical functions are always impaired. The best verbal response of the GCS is one measure of higher cortical function. This function is obviously difficult to evaluate in the infant, and modification in the interpretation is required in the nonverbal patient. In the child who has acquired language, the ability to use language to communicate is often the first skill to be lost and the last to return after neurologic injury.

Pattern of Breathing

Normal respiratory patterns require the normal interaction between the brainstem and cortex. Although the brainstem itself can produce a respiratory drive, the cortex will modulate the respiratory pattern. Therefore, a loss of normal cortical function will result in a variety of abnormal respiratory patterns. Metabolic control, or maintenance of normal oxygenation and acid—base balance, is controlled by the lower brainstem centers situated between the medulla and midpons. Behavioral control over respiration is maintained mainly in the forebrain. Although metabolic derangements, such as acidosis and hypoxia, can interfere with normal respiratory patterns, these can be easily tested for, and once eliminated as the etiology, abnormal breathing patterns should be considered indicative of severe neurologic dysfunction. The localizing value for the abnormal patterns is not exact, but recognition of these patterns is important in alerting the clinician to recognize the severity of the process. Some characteristic respiratory patterns are listed in Table 98-4.

Size and Reactivity of Pupils and Eye Movements

Pupillary reactions are controlled by both the sympathetic and parasympathetic nervous systems and are relatively unaffected by metabolic insults. The absence of a pupillary light reflex is the strongest argument for a structural, as

TABLE 98-1. Glasgow Coma Score for Adults and Infants

Response	Adults and Children	Score	Infants
Eye opening	Spontaneous	4	Spontaneous
	To verbal stimuli	3	To speech
	To pain	2	To pain
	None	1	None
Verbal	Oriented	5	Coos, babbles
	Confused	4	Irritable
	Inappropriate words	3	Cries to pain
	Nonspecific sounds	2	Moans to pain
	None	1	None
Motor	Follows commands	6	Normal spontaneous movements
	Localizes pain	5	Withdraws to touch
	Withdraws to pain	4	Withdraws to pain
	Decorticates to pain	3	Decorticates to pain
	Decerebrates to pain	2	Decerebrates to pain
	Flaccid	1	Flaccid

Reproduced with permission from James HE, Trauner DA. The Glasgow Coma Scale. In: James H, editor. *Brain insults in infants.* Orlando (FL): Grune and Stratton; 1985.

TABLE 98-2. Causes of Coma in Children

Infectious	Metabolic	Traumatic	Vascular	Other
Meningitis	Hypoxic-ischemic	Hemorrhage	Hypertension	Intussusception
Bacterial		Epidural		
Viral		Subdural		
Tubercular		Subarachnoid		
Protozoan		Parenchymal		
Encephalitis	Toxin ingestion	Contusion	Fat embolism	Hyperthermia
Viral				
Bacterial				
Protozoal				
Nematodal				
Acute demyelinating encephalomyelitis	Acidosis	Concussion	Aneurysm	Hypothermia
Sepsis	Renal failure	"Shaken baby" syndrome	Vasculitis	Postictal state
Abscess	Hepatic failure		Lupus	Conversion reactions
Reye's syndrome	Adrenal insufficiency		Henoch-Schönlein purpura	Atypical absence seizures
Toxic shock syndrome	Electrolyte imbalance Na^+, K^+, Ca^{++}, Mg^{++}		Post-pump encephalopathy	
Progressive multifocal leukoencephalopathy (papovavirus)	Central pontine myelinolysis			
	Hypoglycemia			
	Hyper- and hypo-osmolar states			
	Thiamine deficiency			
	Inborn errors of metabolism			

opposed to a metabolic, etiology for altered mental status. Asymmetry is more often seen with structural causes of coma. The pathways that control eye movements are regulated through the medial longitudinal fasiculus, which connects cranial nerves III, IV, and VI in the brainstem. Eye movement abnormalities are often found in patients with altered mental status, as their pathways share a similar anatomic location as the caudal portion of ARAS. Details of pupil testing and oculomotor testing are described in standard neurology textbooks.

TABLE 98-3. Common Causes of Blood Pressure and Heart Rate Changes in Comatose Children

Blood Pressure		
High	Low	
Increased ICP	Spinal shock	
Subarachnoid hemorrhage	Adrenal failure	
Intoxication-amphetamines	Poisons-narcotics	
Anticholinergics	Cyanide	
Sympathomimetics	Sedatives/hypnotics	
Heart Rate and Rhythm		
Irregular	Slow	Fast
Amphetamines	β-blockers	Alcohol
Anticholinergics	Narcotics	Amphetamines
Tricyclics		Theophylline
Digitalis		Sympathomimetics (OTC, prescription medicines, illicit drugs)

ICP = intracranial pressure; OTC = over-the-counter.

Motor Response

Abnormalities in motor function can provide much information about the localization of the lesion. Patterns,

Table 98-4. Respiratory Patterns with Decreasing Level of Central Nervous System Functioning

Cheyne-Stokes
: Alternating apneas and hyperapnea, bilateral cerebral, or diencephalic (*metabolic or impending herniation*)

Hyperventilation
: Diffuse metabolic acidosis, hypoxia, or poisons (*amphetamine or cocaine*), neurogenic pulmonary edema (*carbon monoxide, hydrocarbons, organophosphates [midpons to midbrain]*)

Apneuristic
: Pause at full inspiration (*pons or medulla*)

Ataxia
: No pattern (*medulla*)

Hypoventilation
: Alcohol, narcotics, or sedatives (*ascending reticular activating system*)

such as hemiparesis and abnormal muscle stretch reflexes, quickly localize the lesion to the contralateral decending corticospinal pathways. Cortical release phenomena, which occur with injury at or above a specific brainstem nucleus, cause the following syndromes:

- Decorticate or flexor posture (arms flexed and pulled up) is caused by injury to the corticospinal tracts at or above the red nucleus.
- Decerebrate or extensor posture (arms extended and internally rotated) is caused by injury near the vestibulospinal tract, as well as by toxins.
- Opisthotonus (head back, back arched, and arms at side) is caused by bilateral severe cortical injury.

Early Management

Regardless of the mechanism of injury, the most critical aspect of emergency treatment remains maintenance of the airway, breathing, and circulation (the ABCs of emergency management). The algorithm displayed in Figure 98-1 outlines the thought processes necessary for diagnosis and treatment. Unless the ABCs are addressed and treated, secondary neurologic injury will result from hypoxia or hypotension. Early aggressive airway management by means of intubation and supportive ventilation is preferred to decrease any risk of organ damage from hypoxia. The use of sedatives and paralytics is often necessary and should be carefully charted and timed so the neurologic examination can be interpreted appropriately. The examination should include determination of vital signs, a general survey examination, evaluation of respiratory pattern (if the ventilation is not controlled), determination of the GCS, evaluation to determine the best level of cognitive function, evaluation of pupillary light response and extraocular eye movements, and motor examination. The preservation of pupillary light responses in a nontraumatic coma most likely represents a toxic or metabolic derangement. Repeated neurologic examinations, imaging studies, and electrophysiologic studies may reveal dynamic processes that are not obvious on initial studies. Recognition of the characteristic patterns of underlying processes can provide support for both the localization and the etiology of altered consciousness.

Emergency Imaging

After the initial evaluation, most children should undergo computed tomography (CT) or magnetic resonance imaging (MRI) of the brain. Most centers have CT scanners in the emergency department, and scan times are reduced to under a minute with the newer machines. The value of the CT is not limited to only those children in a coma; CT should be used in any child in an altered mental status due to an unknown cause. When CT is not available, only clinical judgment can determine whether to transport a child to a facility with this technology. In one study, 31% of noncomatose children (GCS > 12) who suffered head injury and who had no focal abnormalities on neurologic examination had abnormal CT scans.

In some circumstances, MRI would be preferred to CT. MRI provides a better image of cerebellar, brainstem, and spinal cord pathologies. Abnormalities in gray–white matter differentiation, demyelinating lesions, early ischemia, and encephalitic processes are better visualized with MRI. The use of newer techniques, such as diffusion sequences, can provide valuable information about the etiology of the coma. However, MRI takes considerably longer and is generally located farther from the emergency department, so only clinical judgment can determine whether an MRI is justified.

Causes of Altered Consciousness and Coma

The history and a brief examination usually provide a narrow differential diagnosis for the altered consciousness or coma (Table 98-2). Although discussion of each possible cause is beyond the scope of this chapter, a few merit consideration.

Trauma

In the United States, about 5 million children sustain a head injury every year, and 200,000 require hospitalization. The approach to the patient who has a head injury is stabilization of vital signs with cardiovascular and ventilatory support, rapid neuroimaging with neurosurgical intervention, if appropriate, intracranial pressure (ICP) monitoring, and the use of hyperventilation, hyperosmolar therapy, and cerebrospinal fluid (CSF) drainage to keep the ICP within acceptable limits. An in-depth discussion is presented in Chapter 99, "Increased Intracranial Pressure."

Meningitis and Encephalitis

Meningitis and encephalitis are common causes of coma in children. Infections also can occur after a basilar skull fracture secondary to a CSF leak.

Bacterial meningitis should be presumed in children with fever and alteration of mental status. Meningeal signs are variable and can be strikingly absent, especially in younger children. In the infant or child with a fever and altered mentation, antibiotics should be given immediately, before lumbar puncture. The CSF will show pleocytosis, with a predominance of polymorphonuclear leukocytes. Treatment with a broad-spectrum antibiotic designed to cover the microorganisms common for the age of the

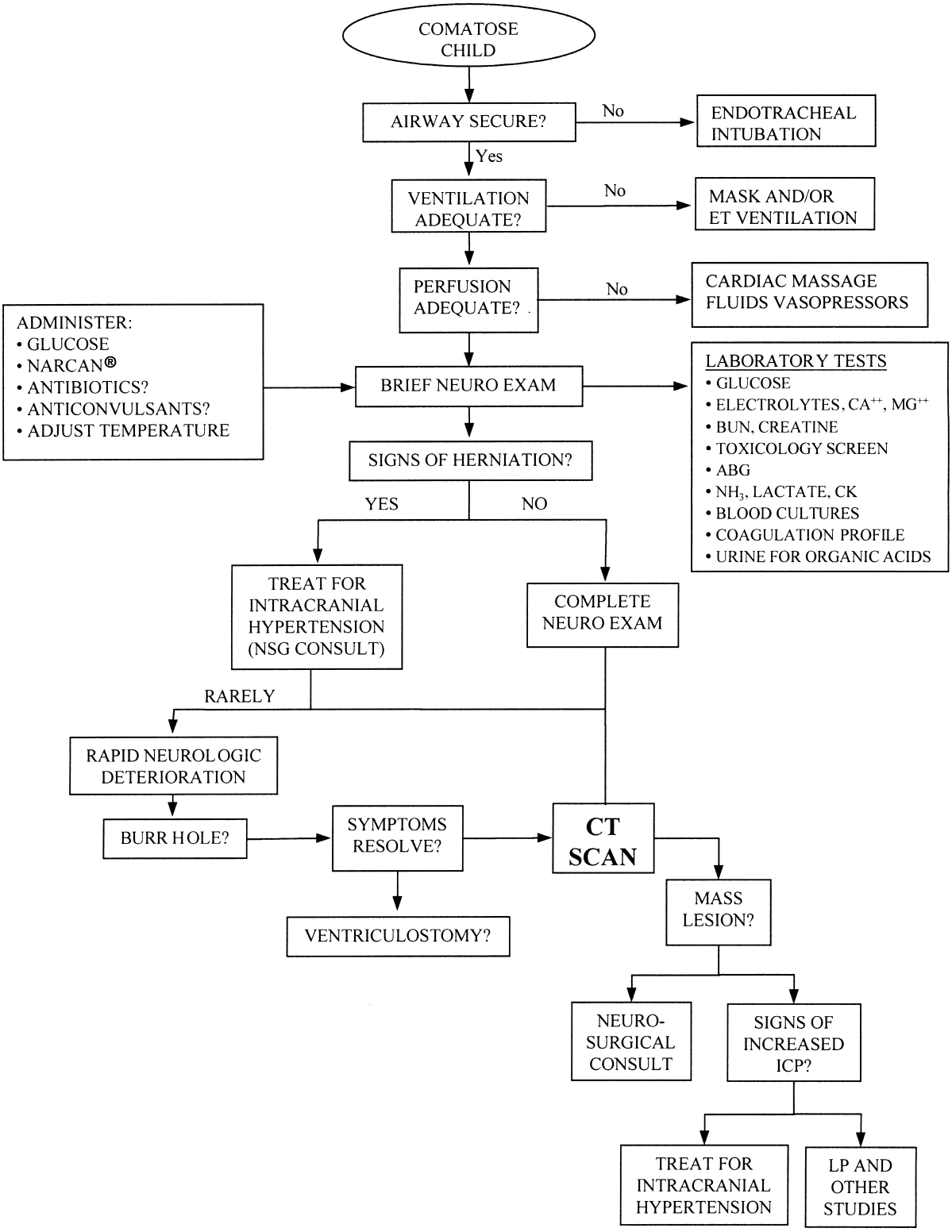

FIGURE 98-1. Algorithm for the management of children with altered consciousness or coma. ABG = arterial blood gas; BUN = blood urea nitrogen; CK = creatine kinase; CT = computed tomography; ET = endotracheal; ICP = intracranial pressure; LP = lumbar puncture; NSG = neurosurgery. Reproduced with permission from Goodwin SR. The comatose child: evaluation, treatment, and prediction of outcome. In: American Society of Anesthesiologists. 40th Annual Refresher Course Lectures and Clinical Update Program. Park Ridge (IL): American Society of Anesthesiologists; 1989.

patient should be initiated. The third-generation cephalosporins are the drugs of choice for children older than 1 month of age for treatment of the common microorganisms, including *Haemophilus influenzae, Pneumococcus,* and meningococcus. Dexamethasone provides protection against sensorineural hearing loss without morbidity when the meningitis is caused from *H. influenzae* or *Neisseria meningitides*. Dexamethasone should be given before or at the same time as the antibiotics and continued for 2 days. Acyclovir should be given when herpes simplex encephalitis (HSE) is suspected. Because it is now accepted that the clinical presentation of HSE is vast, it is appropriate to start both antibiotics and antiviral therapy initially and then discontinue the medications that are not necessary once laboratory data are available. The early phases of HSE will mimic most viral encephalitides and the characteristic electroencephalogram (EEG) and neuroimaging findings described in HSE may not be evident in all cases.

In the setting of possible CNS infection and increased ICP, performing a lumbar puncture should be done after a CT has excluded the possibility of a mass, intracranial shift, or tight cisternal spaces. If CT is unavailable and the clinician suspects a mass, antibiotics and antiviral agents should never be withheld while awaiting the results of neuroimaging.

Poisons and Metabolites

Toxic ingestion remains a frequent cause of emergency room visits. Nonintentional toxic ingestion in the toddler is common, despite educational efforts, the advent of childproof containers, and easy access to protective locks. Intentional use of alcohol, glues and other hydrocarbons, cannabis, organic and synthetic hallucinogens, and other drugs continues in the older child and adolescent. Over-the-counter medication and prescription medication are common methods of suicide and suicide attempts. An inventory of all such medications within the home should be elicited by a member of the health care team. The initial laboratory evaluation of a child with an altered mental status should be a urine and blood screen for toxins. Because not all toxins are routinely tested for, additional blood and serum should be frozen for further analysis. If ethanol ingestion is even a remote possibility, a blood level should be obtained. Organic acid analysis of urine using gas-chromatography–mass spectroscopy is an underutilized test when the nature of the ingestion remains a mystery, as many organic and commercial substances can be rapidly identified; because inborn errors of metabolism can sometimes mimic toxic ingestion (as well as present with alteration in consciousness), this test can be of great diagnostic value in the differential diagnosis. Intravenous glucose is routinely given in the urgent situation but is only beneficial in the setting of hypoglycemia. Hyperglycemia can be associated with poor outcome; capricious administration of glucose may worsen the outcome. Although narcotic overdose is rare in children, naloxone should be administered if the cause of the coma is unknown. Flumazenil may be administered if benzodiazepine overdose is suspected; however, the clinician should be aware that this drug might precipitate seizures in some patients. Support of the vital signs and hydration is a mainstay of therapy, with the use of acidification or alkalization becoming an important aspect of treatment if the toxin can be identified.

Seizures

The importance of aggressive treatment of seizures in comatose patients cannot be overstated, as prolonged seizures can result in hypercarbia and hypoxemia as well as primarily precipitate further damage. Identifying the etiology of the seizures is crucial, as specific treatment can be initiated, for example, in the setting of mass lesion, hypoglycemia, hyponatremia, or toxic ingestion. There are many acceptable protocols for treating status epilepticus. Patients should immediately be given a loading dose of fosphenytoin (20 mg/kg infused at up to 3 mg/kg/min intravenously, or intramuscularly when intravenous access is not available) or phenobarbital (20 mg/kg). Ativan® may have a faster onset of action and therefore may be used before or after fosphenytoin (or phenobarbital) at a dose of 0.1 mg/kg intravenously, with a maximum dose of 4 mg, over 2 to 5 minutes (in neonates the dose is 0.05 mg/kg). If there is any question of the integrity of the airway or interference with respiration, the patient should be intubated and placed on mechanical ventilation.

Hyperthermia and Hypothermia

Hyperthermia increases both the ICP and the cerebral metabolic rate by approximately 6% for every degree Celsius. Acetaminophen at a dose of 10 to 15 mg/kg should be administered and active cooling measures undertaken to maintain normothermia. Shivering also can increase ICP and can be treated with neuromuscular blocking agents or phenothiazines. However, phenothiazines reduce the seizure threshold and depress the CNS, and therefore, these agents should be used with caution. Although iatrogenicinduced hypothermia remains controversial in practice, recent evidence demonstrates a potential benefit of mild hypothermia in the treatment of patients with head injuries. Hypothermia may impair the immune response and cause cardiac arrhythmia, and may not offer any therapeutic advantage.

Increased ICP

Any type of brain injury, traumatic or otherwise, can result in brain edema and, ultimately, increased ICP, which, if untreated, can result in additional brain injury. As long as CSF pathways remain patent, brain edema will usually first cause displacement of the CSF, which is easily identified

with CT or MRI. Early signs of increased ICP include irritability that may be mistaken for difficult behavior. Mental confusion or headaches can precede the onset of a depressed level of consciousness. The Cushing response of depressed pulse and increased blood pressure are late signs of increased ICP (some believe preterminal), and therefore, lack of this sign should never be used to eliminate increased ICP as a possibility.

Treatment of increased ICP is discussed in Chapter 99, "Increased Intracranial Pressure." The patient's head should be placed in the neutral position and elevated 30° to 45°. Hyperventilation, the use of blood pressure augmentation, fluid restriction, and diuretic therapy are discussed in more detail in Chapter 99, "Increased Intracranial Pressure."

Hyperventilation will reduce carbon dioxide tensions and result in cerebral vasoconstriction, which decreases cerebral blood volume. This is a very effective way to rapidly decrease ICP in the acute emergency setting. The $PaCO_2$ should be lowered to 30 to 35 mm Hg. Reductions in the $PaCO_2$ below 25 mm Hg theoretically may cause cerebral ischemia and are potentially dangerous but can be used to acutely lower increased ICP in critical situations. The use of continuous intra-arterial blood pressure monitoring and ICP monitoring is essential. There is no evidence that expectant hyperventilation prevents the development of cerebral edema.

Fluid restriction is often mentioned as treatment for increased ICP, but the most critical concern it to maintain an adequate mean arterial pressure that will ensure an acceptable cerebral perfusion pressure. Therefore, fluid resuscitation in the hypotensive patient, regardless of etiology, should never be delayed for fear of exacerbating cerebral edema. Isotonic saline can be used in emergency situations to maintain blood pressure.

Both osmotic (mannitol) and loop diuretics (furosemide) reduce ICP effectively. Osmotic agents initially create an osmolar gradient between the brain and blood, drawing water out of the brain. Loop diuretics, alone or in combination with osmotic agents, may effectively reduce ICP by decreasing total blood volume. Mannitol, 0.25 to 1.0 g/kg, should be administered intravenously, with repeated doses of 0.25 g/kg every 4 hours while monitoring serum osmolarity. Serum osmolarity should not exceed 340 mOsm/L.

Many comatose patients will have slit ventricles from the effects of cytotoxic edema, in which case a ventriculostomy may not be possible. In those patients with ventricles large enough to allow catheter placement through a burr hole, a ventriculostomy will allow both monitoring of pressure as well as the ability to remove CSF to reduce ICP. If cerebral edema is severe the imaging may show small ventricles (so-called slit ventricles) and absent or near-absent basilar cisterns, in which case a ventriculostomy may not be possible. There are a variety of ICP monitoring sensors that can be placed through a burr hole.

Corticosteroids reduce vasogenic edema, which occurs in the vicinity of mass lesions, such as tumors and hematomas. Cytotoxic edema, which is seen as part of the apoptotic injury that accompanies ischemia and anoxia, does not respond to corticosteroids. Although "high-dose" steroid therapy (3–6 mg/kg dexamethasone) has been reported to improve the outcome in patients with head injuries, few data support its routine use. Corticosteroids are not beneficial for the global edema caused by ischemia. An initial dose of dexamethasone, 1 mg/kg, can be given when vasogenic edema is suspected.

There is no question that barbiturates decrease ICP in many situations; however, the ultimate benefit is not proven. It is clear that outcome from ischemia (eg, near drowning and cardiac arrest) is not altered by barbiturate therapy, and therefore, barbiturates are not indicated for the primary injury. However, the secondary injury that occurs after brain trauma or surgery may be prevented and the outcome improved by controlling the ICP. Most clinicians continue to use barbiturate-induced coma for control of ICP in hopes of preventing secondary injury in these patients. This is especially true in children, in whom the prognosis from head trauma is better than in adults.

Herniation Syndromes

Uncal herniation is most often caused by unilateral cerebral edema caused by tumors, strokes, or hemorrhage. The syndrome results from the mesial temporal lobe structures slipping beneath the tentorium and compressing the posterior cerebral artery, third nerve, and lateral midbrain. Pupillary dilation with a third nerve palsy, hemiparesis (usually contralateral to the lesion), and altered respirations occurring in the setting of depression of consciousness are the hallmark clinical features. The hemiparesis also may manifest as flexor posturing (decorticate) and then extensor posturing (decerebrate).

Central herniation occurs in the setting of cytotoxic edema associated with infarction or anoxia, trauma, or mass lesions. The clinical features of this syndrome arise as a result of the downward displacement of both hemispheres, which compresses the diencephalon and midbrain. The respiratory pattern includes Cheyne-Stokes respirations, eupenic breathing, or breathing with deep sighs and yawns. The pupils are small but reactive and motor tone is paratonic, with abnormal posturing developing in later phases.

Diagnosis

The differential diagnosis of coma in children is extensive (see Table 98-5). The history, complete neurologic examination, CT scan, lumbar puncture, and laboratory test results will usually direct therapy into one of the major categories. Many causes of childhood coma are discussed extensively in other chapters. Within the

TABLE 98-5. Pupillary Response and Eye Movements in Comatose Patients

Pupils dilated
One: Ipsilateral (same side) rapidly expanding blood or tumor and impending herniation, postictal, or lesion of cranial nerve III
Both: Postictal, hypothermia, hypoxia (often from drugs), direct application drugs, irreversible damage, encephalitis, blood shock
Pupils constricted
Fixed: Pons and metabolic
Reactive: Medullary and metabolic
Pupils midsized
Fixed: Central herniation
Eye movements
Deviated toward hemispheric destruction, away from seizure focus, and away from brainstem lesion: Hemiplegia
Down and out: Neuropathy from diabetes, skull fracture, compression false localizing, increasing ICP, pons basilar meningitis
Reflexes
Doll's eye—Held open and head moved laterally (*contraindicated after cervical trauma*), brainstem intact, eyes opposite movement
Calorics—Ice water against intact tympanic membrane, eyes toward irrigated

ICP = intracranial pressure.

category of metabolic disorders, two specific situations deserve special mention.

Metabolic Disorders Causing Altered Consciousness or Coma

Poisoning is one of the most common causes for altered consciousness in children. The five most common poison-related hospitalizations are caused by acetaminophen, antidepressants, lead, caustic alkali, and antihistamines. The five most common poisonings are alcohol, opiates, carbon monoxide, street drugs, and anticonvulsants. Although aspirin poisoning is not as common, the routine use of this medication in the at-risk adult population has increased dramatically in recent years and should be considered in a child with metabolic acidosis and an increased respiratory rate. Gastric lavage is beneficial in the first hour after ingestion and particularly if there is delay in gastric emptying, as with tricyclic antidepressant and narcotic poisoning. However, gastric lavage is contraindicated in alkali ingestion. Gastric emptying should not delay institution of other measures such as *N*-acetylcysteine for acetaminophen overdose. Activated charcoal absorbs toxins and prevents further absorption and usually needs to be administered through a nasogastric tube. Activated charcoal treatment may need to be repeated.

The list of potential poisons, as well as interactions of medications and poisons, is enormous. Regional and statewide poison centers provide the most complete source of information, including treatment, and should be contacted for information.

Disorders of Energy Metabolism: Mitochondrial Cytopathies

Mitochondrial cytopathies are a diverse group of inherited or acquired disorders. Mitochondria are subcellular organelles, contained in all human cells except mature erythrocytes, whose main task is to generate adenosine triphosphate (ATP). Mitochondria are composed of an outer mitochondrial membrane, an intermembrane space, the inner mitochondrial membrane, and the matrix. The majority of the electron transport chain is embedded in the inner membrane, and the inner membrane space holds the electrochemical gradient generated by the electron transport chain. There are hundreds of mitochondrial enzymes, most of which are located in the matrix. In addition to these matrix enzymes, normal metabolism also requires normal integrity of membranes, normal transport channels and translocases, and enzymes located within the membranes themselves. The terminal phase of energy generation, the process of oxidative phosphorylation (OXPHOS), occurs in the five enzyme complexes referred to as the electron transport chain, where reducing equivalents are passed from one enzyme complex to the next and protons are translocated into the inner membrane space. Complex IV reduces molecular oxygen into water and complex V phosphorylates adenosine diphosphate (ADP) into ATP as protons move from the inner membrane space, through a channel in complex V, back into the matrix. The energy stored in the third phosphate bond of ATP provides the bulk of the body's energy needs, including the energy to perform mechanical work, biochemical synthesis, and membrane pump function. Inadequate production of ATP results in organ dysfunction, and patients with mitochondrial cytopathies often have cognitive problems, seizures, and alterations in level of consciousness.

There are hundreds of reported inborn errors of energy metabolism, and these may affect normal CNS function in a number of ways. Disorders of electron transport chain activity can deprive the brain of necessary energy (ATP) to ensure proper functioning of the sodium-phosphorus ATPase. In addition to the disorders that result in deficient oxidative phosphorylation, numerous disorders proximal to the electron transport chain result from deficient mitochondrial and cytoplasmic enzyme function. These include disorders of fatty acid oxidation, citric acid cycle, urea acid cycle, amino acid metabolism, carbohydrate metabolism, and organic acid metabolism. Disorders of amino acid synthesis or degradation can cause a toxic build-up of neurotransmitters, such as seen in nonketotic hyperglycinemia. Furthermore, because some of these disorders are pathologically active before birth,

they can lead to an embryopathy that can result in a baseline encephalopathic state.

Intuitively, those inborn errors that present during the first few weeks of life tend to have a more malignant course than those that present later in life. Although the most common cause of coma in an infant is infection, an evaluation for an inborn error of metabolism should always be considered in an infant with an altered mental status. Because bacterial sepsis is a common presentation of a child with an inborn error of metabolism, consideration of an inborn error should not be excluded solely because of a proven infection. Screening laboratory tests should include blood glucose, lactate, ammonia, electrolytes, and a blood count. Urine should always be obtained at the time of acute illness and frozen for organic acid analysis, if necessary. Blood and CSF amino acid analysis can detect most serious amino acid disorders. Although low CSF glucose is seen with bacterial meningitis, it can occur in a rare but treatable condition in the transport of glucose across the blood-brain barrier (glucose transport defect). A low blood urea nitrogen, especially in the setting of dehydration, should automatically trigger consideration of an organic acid disorder or urea acid cycle defect, and an ammonia level should be obtained. Ammonia levels are physiologically elevated in the first few days of life but return to normal within 5 to 7 days of life. Neutropenia, anemia, and thrombocytopenia are often seen in the organic acidurias and other inborn errors. Fasting hypoglycemia is seen in glycogen storage diseases, disorders of fatty acid metabolism, disorders of gluconeogenesis, and electron transport chain disorders. Galactosemia can present with *Escherichia coli sepsis* or meningitis, along with hypothermia and an elevated direct bilirubin.

Lactic acid is generated in abnormal amounts in numerous metabolic disorders, as well as during anoxia, poisoning, and sepsis. Lactic acidosis is, therefore, frequently observed in the setting of altered level of consciousness, although an elevated lactic acid itself is not the cause for the abnormal sensorium. In most laboratories, a lactate above 2.2 mM is considered abnormal. A number of technical factors are crucial when obtaining blood and urine for metabolic studies. The blood obtained for lactate and pyruvate determination must be free-flowing. If the tourniquet is applied too tightly or is in place for more than 30 seconds before blood is obtained, the lactate can be falsely elevated. When obtaining blood pyruvate determination, it must be instantly (within seconds) denatured in an 8% perchloric acid solution, otherwise the red blood cells will consume glucose and produce pyruvate, resulting in a false elevation in pyruvate. Cooling the blood will not prevent the pyruvate concentration from increasing after the blood is removed from the body. Furthermore, an elevated pyruvate in the presence of a normal lactate is meaningless and occurs only because of technical difficulties. The ratio of lactate to pyruvate reflects the redox state of the cells. An elevated lactate with the lactate-pyruvate ratio preserved at 10 to 20:1 suggests a defect in pyruvate dehydrogenase. An elevated lactate with an elevated lactate-to-pyruvate ratio (above 20:1) suggests a defect in pyruvate carboxylase or, more commonly a disorder of electron transport chain function. Both carbon monoxide and cyanide inhibit cytochrome oxidase (complex IV of the electron transport chain) and can cause lactic acidosis. Sepsis also can inhibit normal electron transport as well as cause hypotension, both of which can lead to lactic acidosis.

During infancy and early childhood, these typically present with altered levels of consciousness, often associated with global developmental delays, failure to thrive, recurrent episodes of vomiting, and poor immune function. Table 98-6 lists the common diagnostic tests that can be performed if a disorder of metabolism is suspected, with clinical insight into the meaning of the tests. Screening laboratory tests that can be performed in the emergency setting include glucose, electrolytes, complete blood count, lactate, ammonia, creatine kinase, blood, and urine ketones. Additional plasma and urine should be obtained and frozen for further testing, if indicated. Collecting blood and urine during the acute illness will more often show abnormalities that can lead to a definitive diagnosis than samples collected during stable periods. Aside from the child with pyruvate dehydrogenase (PDH) deficiency, a glucose-containing balanced salt solution (usually 5–10%) should be administered to ensure normoglycemia and reverse any catabolic state that is occurring. Lactate-containing solutions should be avoided. In the case of PDH deficiency, glucose is rapidly converted into pyruvate and then into lactate, without any further ability to be metabolized. In patients with known metabolic disorders, we will often add levocarnitine (100 mg/kg/d in three or four divided doses) to the intravenous solution.

A viral illness, with or without fever, is a common precipitant to a metabolic crisis. Varicella is particularly dangerous, but any infection can cause decomposition. In some situations, no precipitating factor can be identified. In the organic acidurias, fatty acid cycle disorders, and urea acid cycle defects, elevated ammonia or lactic acid levels will occur as part of a metabolic decomposition. Elevated lactic acid levels, usually without a severe elevation in ammonia, will occur in electron transport chain disorders. In critical situations, where lactic acid and ammonia levels are extremely elevated, the use of continuous infusion insulin (0.1 U/kg/h), with frequent glucose monitoring, may help reverse catabolism, decrease circulating toxic free fatty acids, and lower lactic acid and ammonia levels. The use of sodium benzoate, phenylbutyrate, and sodium phenylacetate can bind conjugate ammonia in the case of severe hyperammonemia. Enteral use of lactulose also can help lower ammonia levels.

TABLE 98-6. Laboratory Evaluation of Mitochondrial Disorders

Test	Tissue	Comment
Primary evaluation		
Glucose	B, CSF	Hypoglycemia is seen in numerous metabolic disorders that affect gluconeogenesis, including defects in pyruvate carboxylase, phosphoenolpyruvate carboxykinase, 1,6 diphosphofructase, glycogen storage diseases, ETC defects, fatty acid oxidation defects, and organic acidurias. Hyperinsulin states should also be excluded. Low cerebrospinal fluid glucose in the absence of infection should be an indication of a glucose transport defect.
Electrolytes	B	Calculate anion gap
Blood counts	B	Anemia, thrombocytopenia, and neutropenia are seen in a variety of metabolic diseases, especially the organic acidurias. Primary and secondary disorders of folate and B_{12} metabolism should be considered.
Lactate	B	Tourniquet must be released before blood is sampled (see text)
CK	B	Mild elevation common in myopathic forms
Urine analysis	U	High pH may suggest renal tubular acidosis
Ammonia	B	Fasting sample most useful; elevated ammonia (up to 150 μM) is normal in the first few days of life; elevated in urea acid cycle defects and organic acidurias.
Organic acids	U, CSF	Samples must be kept refrigerated or frozen. Urine collections may be random or timed, and may be collected after a fasting period or glucose load, depending on the clinical situation. Correct interpretation requires knowledge of the timing and composition of last meal and the age of the patient. The presence of abnor mal amounts of lactate, pyruvate, citric acid cycle intermediates, and 3-methylglutaconic acid suggests mitochondrial dysfunction. Dicarboxylic acids are seen in disorders of fatty acid oxidation and glutaric aciduria type II. Specific disorders of organic acid and amino acid metabolism can be diagnosed by a typical pattern of abnormal organic acid analysis. Note that 3-methylglutaconic acid can be seen in patients on progesterone, corticosteroids, or during extreme stress, and some organic acids (hippurate and benzoate) are found in preservatives and gelatin-containing products.
Ketones	B, U	Often present in fed individuals with respiratory chain dysfunction. Elevation in the β-hydroxybuterate/acetoacetate ratio is highly suggestive of a respiratory chain dysfunction. A fatty acid oxidation defect should be considered if ketones are absent during fasting, starvation, or an illness that results in vomiting, diarrhea, and dehydration.
Mitochondrial DNA Southern blot	B, M	If a patient fits into a specific, well-described mitochondrial phenotype, such as CPEO, KSS, or MELAS, Southern blot testing may lead to a rapid diagnosis.
Nuclear DNA Mutations	B	Assembly Genes: *SCO1, SCO2, SURF1, COX 10, BCLS1* mtDNA Depletion: *POLG1, MPV17, dGUOK, TK2* ADP-ATP Translocase: *ANT1* DNA Helicase: *TWINKLE* MNGIE: *thymidine phosphorylase* (low thymidine level also diagnostic)
Bone marrow biopsy	—	Perform only if indicated due to anemia. Sideroblastic anemia is part of Pearson syndrome
Brain MRI	—	Bilateral symmetric lesions of basal ganglia and brainstem, leukodystrophy, multifocal areas of hyperintense signal
Ophthalmology consult	—	Assess for retinitis pigmentosa or optic atrophy
Cardiac evaluation	—	Routine ECG and echocardiogram (see text)
Secondary laboratory evaluation		
Lactate	B, CSF	See above
Pyruvate	B	Proper determination of pyruvate requires the specimen be instantly deproteinized. Pyruvate not useful if lactate is normal. Disregard results if not properly corrected.
L/P ratio	B	The ratio of lactate to pyruvate can be very helpful in determining if lactic acidosis is due to an OXPHOS disorder (L/P > 20) or pyruvate dehydrogenase deficiency (L/P ~ 10)
Amino acids	B, U, CSF	Urine collections may be random or timed and may be collected after a meal or after fasting, depending on the clinical situation. "Generalized aminoaciduria" may indicate the presence of proximal renal tubular dysfunction due to mitochondrial cytopathy, as well as other medical conditions. Alanine is the amino acid precursor to pyruvate; therefore, an elevated alanine can be helpful in the diagnosis of an OXPHOS disorder. Because alanine can be elevated after a meal, one technique of compensating for dietary fluctuations is to calculate the ratio of alanine to lysine (which corresponds closely with dietary intake). An elevated alanine along with an alanine: lysine ratio > 3 suggests true hyperalanemia. Many specific amino acid disorders can be diagnosed with a specific amino acid profile.
Organic acids	U, CSF	Often worth repeating, especially during an acute illness, as abnormal organic acids profiles are not present at all times.
Carnitine analysis	B, U, M	Most laboratories determine the free carnitine and total carnitine. Fractionation into specific acyl carnitines may be helpful in some situations and can help determine disorders of long- and medium-chain acyl CoA dehydrogenase deficiency and GA II. Urine collections may be random or timed and may be collected after a fasting period or carnitine load, depending on the clinical situation. Serum carnitine deficiency is almost always a secondary

TABLE 98-6. Laboratory Evaluation of Mitochondrial Disorders (continued)

		phenomena due to a disorder of fatty acid oxidation or oxidative phosphorylation. Elevated urinary carnitines, especially in the setting of serum carnitine deficiency, is an indication of a metabolic disorder.
Ketones	B, U	Determining the ratio of β-hydroxybutyrate and acetoacetate may be helpful and offers a similar estimate of the redox state as does the lactate: pyruvate ratio. This test is most valuable if collected during an acute illness or after a fast.
Acyl glycines	U	Useful in detection of disorders of β-oxidation and electron transfer flavoprotein (glutaric aciduria type II)
Skin biopsy	—	Electron microscopy may reveal structural defects in mitochondrial structure. A fibroblast culture can be established with the skin obtained from a biopsy. This can be sent for testing ETC activity, β-oxidation disorders, as well as for various other specific enzyme-deficient disorders.
Tertiary laboratory testing		
Repeat testing		Repeating some of the above-listed tests, sometimes under different conditions (such as during an illness), may be helpful.
Provocative metabolic testing		Under monitored conditions, usually in the hospital, repeating some of the above tests after a glucose load, fructose load, protein load, and fasting may be helpful. Offered in very few centers.
ETC enzymology		This is the most commonly performed test for mitochondrial function. It can be performed on homogenates of whole tissue (muscle, liver), skin fibroblasts, or freshly isolated disrupted mitochondria. Provides indication of the activity of the catalytic component of ETC complexes I, II, III, and IV. It provides no information about nonenzy matic components of the ETC complexes, membrane integrity, or substrate transport defects. Improperly prepared tissue, especially in the case of tissue homogenate, is subject to false-positive results.
OXPHOS polarography		Performed only on freshly isolated intact mitochondria. Provides functional estimates of the integrity and efficiency of oxidative phosphorylation, fatty acid oxidation, citric acid cycle function, inner and outer mitochondrial membrane function, substrate transport, and respiratory control. Offered in very few centers. New and smaller polarographs may allow this testing to be performed on very small samples allowing more centers to offer this testing.
Specific enzyme function		Performed on skin fibroblasts, lymphocytes, and other tissues, depending on the laboratory and specific enzymatic test.
Light microscopy		The presence of ragged red fibers, ragged blue fibers, numerous COX-negative fibers is highly suggestive of a mitochondrial disorder. Abnormal lipid or glycogen accumulation is also indicative of a metabolic disorder.
Electron microscopy		The presence of pleomorphic mitochondria, paracrystalline inclusions, and mitochondrial proliferation is highly suggestive of a mitochondrial disorder. Abnormal lipid or glycogen accumulation are also indicative of a metabolic disorder.

B = blood; CPEO = chronic progressive external ophthalmoplegia; CSF = cerebrospinal fluid; ETC = electron transport chain; GA = glutaricaciduria; KSS = Kearne-Sayne syndrome; M = muscle; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome; MRI = magnetic resonance imaging; OXPHOS = oxidative phosphorylation; U = Urine.

Dialysis is required in extreme situations and referral to a metabolic center is often required.

Prognosis in Childhood Coma

The prognosis for recovery depends on the etiology and severity of the underlying illness. Mortality rates from head trauma vary enormously, depending on the series, from 6 to 40%, with 1 to 2% of comatose patients surviving in a chronic vegetative state. In one childhood series of patients with severe head injury requiring ventilation, 16% died, with 37% having normal or independent functioning at discharge, 40% partially dependent, and 7% totally dependent. In adults, mortality after head trauma is 95% with nonreactive pupils or absent oculocephalic responses 6 hours after the event.

Absence of pupillary responsiveness, transtentorial herniation, and GCS scores are helpful in predicting prognosis in adults with nontraumatic coma. In adults, coma beyond 48 hours after cardiac arrest is associated with almost certain chronic vegetative state or death. Outcome from childhood coma, independent of etiology, is better than with adults, especially after head injury. Reports show that 25% of children with a GCS score of 3 have a normal survival. In one series, flaccidity after trauma was associated with only 33% morbidity or mortality. In this study, children with nonreactive pupils or absent oculovestibular responses had only a 25% morbidity and mortality rates. Thus, the apparent resilience of the child's brain makes it difficult to determine the prognosis.

Summary

Children may present with an altered level of consciousness from any number of causes. In addition to treating the primary injury, another main goal is to prevent secondary injury. An ordered sequence of assessment and intervention is required to ensure the best outcome. The ABCs of basic life support in preventing secondary injury is the starting point. This is followed by a brief neurologic

examination, which assesses the GCS score, respiratory patterns, pupillary response, and extraocular muscle examination. Diagnostic tests, such as neuroimaging and other interventions, are done at the same time this examination is conducted. Interventions will then be guided by the information provided by this assessment, and therapy can be focused on the specific cause of the coma while preventing secondary injury.

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Practitioner and Patient Resources

The Brain Injury Association
105 North Alfred Street
Alexandria, VA 22314
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Fax: (703) 236-6001
http://www.biausa.org

National Institute of Neurological Disorders and Stroke
31 Center Drive MSC 2540
Building 31, Room 8806
Bethesda, MD 20892
Phone: (301) 496-5751 or 800-352-3424
http://www.ninds.nih.gov/health_and_medical/disorders/coma_doc.htm

Coma Recovery Association
807 Carman Avenue
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CHAPTER 99

INCREASED INTRACRANIAL PRESSURE

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The management of children with increased intracranial pressure (ICP) is aimed at recognizing the signs and symptoms of increased ICP and instituting prompt treatment so that potentially harmful and permanent neurologic sequelae do not occur. This chapter reviews the pathophysiology, evaluation, diagnosis, and treatment of increased ICP in children.

An understanding of the normal pathophysiology of intracranial pressure (ICP) and cerebral edema is essential to effectively manage pediatric patients with increased ICP.

Intracranial Contents

After closure of the cranial fontanelles and sutures by 2 to 3 years of age, the skull is a rigid container of fixed volume. The intracranial contents constitute the brain bulk (80%), blood volume (10%), and cerebrospinal fluid (CSF) (10%). According to the Monro-Kellie doctrine, intracranial volume is equal to the volume of the brain bulk, blood, CSF, and other mass lesions. Therefore, an increase in the volume of one of these compartments can raise ICP and subsequently reduce cerebral perfusion pressure (which is defined as mean arterial pressure minus ICP) and cerebral blood flow (CBF).

CSF volume appears to be the major compensatory mechanism, with the majority in the subarachnoid spaces of the spine and brain and only 10% in the intracranial ventricular system. This CSF volume compensatory mechanism can be expressed as the volume-pressure intracranial compliance ($\Delta V/\Delta P$ = compliance) or pressure volume index (PVI). The PVI is the volume of fluid injected or withdrawn that would result in a 10-fold change in ICP and is calculated as $PVI = \Delta V / \text{Log } P_f / P_o$, where ΔV = volume of fluid injected or withdrawn, P_f = final ICP, and P_o = initial ICP. The PVI varies in proportion to the estimated neural axis volume. The PVI is 8 mL in an infant and 25 mL in a 14-year-old; therefore, a 10 mL volume added to the neural axis of a 14-year-old may produce a modest elevation in ICP, whereas the same volume can be lethal in an infant (Figure 99-1). However, in infants and young children who have open cranial fontanelles and sutures, the Monro-Kellie doctrine does not apply, because the cranial vault will compensate by expanding.

CSF Dynamics

The CSF is normally secreted from the choroid plexus by active transport, and its rate decreases only when CBF begins to decline. Its absorption occurs passively by a hydrostatic gradient through the arachnoid granulations into the venous circulation. This rate is linearly related to ICP. Therefore, either an increase in CSF formation or a resistance to absorption will lead to an increased ICP. The

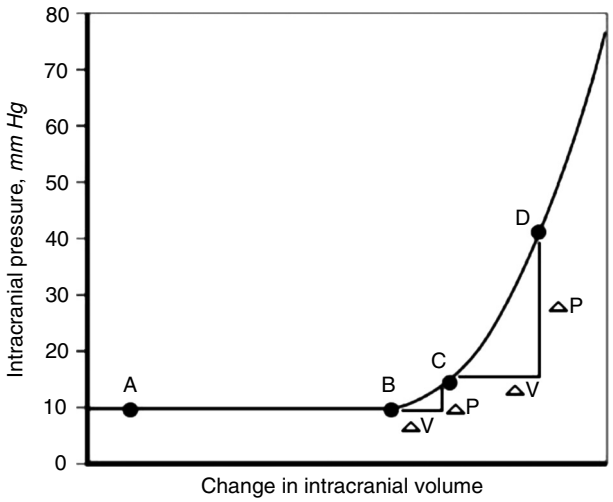

FIGURE 99-1. Pressure-volume curve.

normal rate of CSF production and total CSF volume during childhood varies as the child matures. It is estimated that the average total CSF volume in a neonate is 40 to 50 mL. In contrast, the average total CSF volume in an adult is 150 mL, with a secretion rate of about 20 mL/h (0.34 mL/min).

Cerebral Blood Flow

Adequate cerebral blood flow may be compromised when ICP is significantly elevated. Because CBF is difficult to measure clinically, cerebral perfusion pressure (CPP) is used as a guide to determine adequate cerebral perfusion. CBF is equal to the CPP divided by the cerebral vascular resistance while CPP is defined as the difference between the mean arterial blood pressure (MAP) and the ICP. Under normal physiologic conditions, CBF is autoregulated over a wide range of CPP by dilation and constriction of the cerebral vasculature. The optimal CPP treatment threshold is between 40–65 mm Hg. When ICP increases significantly, the CPP eventually falls below the critical value for tissue oxygenation, leading to a reduction in cerebrovascular tone, loss of autoregulation and subsequent brain ischemia. Certain pathologic conditions, such as head trauma or hypoxic-ischemic injury, may also disrupt autoregulation with blood pressure elevations aggravating ICP and resulting in diffuse cerebral edema.

Cerebral Edema

Cerebral edema can be classified into five different theoretical types. Each is caused by a different pathophysiologic mechanism on which each specific treatment is based:

1. *Vasogenic edema* results from the physical disruption of brain tissue with impairment of the blood-brain barrier. The pathophysiology of clinically significant vasogenic edema involves: (1) an increase in capillary permeability, (2) an increase in transmural capillary pressure, and (3) retention of the extravasated fluid in the interstitial space. First, an increase in capillary permeability may result from damage to endothelial membranes, activation of transendothelial pinocytosis, and disruption of the tight endothelial junctions. Damage to the endothelial membranes by direct injury or secondary edemagenic substances is probably the most likely mechanism.

   Second, an increase in the capillary transmural pressure by elevation of body temperature and hypercapnia has been shown experimentally to increase the rate and extent of cerebral edema formation by relaxing precapillary resistance vessels.

   Third, retention of extravasated fluid appears to be mediated by the electrical charge of the protein molecule. For example, albumin, an anionic protein that readily passes through the damaged blood-brain barrier, is subsequently cleared just as readily by pericytes and other cells. In contrast, immunoglobulin G (IgG) fraction, a cationic protein, remains within the interstitial space by adhering to anionic binding sites and, therefore, retains fluid. The complexity of the pathogenesis of vasogenic edema is highlighted by the fact that administration of glucocorticoid steroids improves the edematous process in brain tumors as well as in chronic subdural hematomas. Vasogenic edema occurs adjacent to brain tumors, traumatic lesions, intracerebral hemorrhages, inflammatory foci, and chronic subdural hematomas.
2. *Cytotoxic edema* is primarily caused by impairment of the sodium-potassium-adenosine triphosphatase pump due to the reduction of CBF below critical threshold levels. It is an intracellular process affecting astrocytes and neurons. The resultant ischemic process produces a cascade of biochemical reactions consisting of an increase in potassium in the extracellular space and an intracellular accumulation of calcium, which leads to irreversible cell damage from membrane dysfunction. Cytotoxic edema occurs adjacent to areas of focal or global ischemia and hypoxia, such as a cerebral infarction.
3. *Interstitial edema* is caused by high-pressure obstructive hydrocephalus, whereby CSF infiltrates the periventricular tissues by high hydrostatic pressure within the ventricular system. When this process does occur, the perifocal edema may lead to brain ischemia and neuronal dysfunction. It has been proposed that either the substances in the edema fluid or ischemic cellular cascade products may be responsible for the vascular and neuronal dysfunction that occurs. A representative example

is the child with a posterior fossa tumor who presents with high-pressure obstructive hydrocephalus causing neurologic deterioration secondary to hydrocephalus and increasing cerebral interstitial edema.

4. *Hydrostatic edema* is caused by an increase in the transmural vascular pressure (ie, the hydrostatic pressure gradient between the intravascular and extravascular spaces), which leads to an accumulation of extracellular fluid. Loss of cerebral autoregulation may also lead to an abruptly increased transmural pressure at the capillary bed. An example is the formation of diffuse hydrostatic edema of the ipsilateral cerebral hemisphere after an acute subdural hematoma has been evacuated, whereby the sudden reduction in ICP results in an abrupt increase in the cerebral vascular transmural pressure.
5. *Osmotic edema* is a complex process and results from a critical fall in serum osmolality and hyponatremia. Hyponatremia at serum sodium levels < 125 mEq/L may tip the osmotic balance, causing cerebral edema. At a given sodium level, women are more likely than men to suffer brain swelling, presumably due to the differential effects of sex hormones.

Evaluation

A rapid and complete history and physical examination as well as neuroimaging studies are crucial to making a definitive diagnosis of increased ICP. Once increased ICP is diagnosed, immediate treatment is essential to prevent potentially harmful neurologic sequelae. Children may present with increased ICP from a variety of causes, such as brain tumors, traumatic brain injury, hemorrhage (eg, vascular abnormalities), infarction (eg, stroke), infection (eg, brain abscess or encephalitis), metabolic factors (eg, electrolyte abnormalities), untreated craniosynostosis, and hydrocephalus due to ventricular shunt failure.

Seizures

Children with tumors of the cerebral hemispheres may present with seizures ranging from simple focal seizures to status epilepticus. Immediate management should include (1) control of seizures, (2) maintenance of a patent airway, and (3) maintenance of an adequate blood pressure. Control of seizures may be accomplished by both short-acting anticonvulsants in the acute setting (eg, lorazepam) or long-acting anticonvulsants (eg, phenytoin, carbamazepine, valproate, or phenobarbital). In children who have brain tumors, seizures may have been precipitated by (1) increased surrounding cerebral vasogenic edema, (2) tumor progression, (3) low anticonvulsant drug level, (4) electrolyte disorders, or (5) recent hemorrhage into the tumor. After the child is medically and neurologically stabilized, head computed tomography (CT) or magnetic resonance imaging (MRI), with and without contrast, is indicated to rule out an immediate need for surgical intervention.

Intracranial Hemorrhage

Brain tumors in children may present with intratumoral hemorrhage, leading to increased ICP and neurologic compromise. Examples of these tumors are glioblastoma multiforme, ependymoma, medulloblastoma (primitive neuroectodermal tumor), pontine astrocytoma, oligodendroglioma, and germ cell neoplasms. In addition, intracranial hemorrhages may result from ruptured vascular malformations and aneurysms as well as traumatic injuries. In these cases, emergent measures to stabilize the child medically must be undertaken and should include (1) maintenance of respiratory and circulatory status, (2) ICP management by medical (ie, hyperventilation and diuresis) or surgical (ie, placement of a ventriculostomy drain and hematoma evacuation) treatment, and (3) seizure control, if indicated. If the child is not taking antiepileptic drugs at the time of the cerebral hemorrhage, prophylaxis is also indicated.

Nonshunt-Related Hydrocephalus

Children with posterior fossa, brainstem, optic-chiasm, suprasellar (eg, craniopharyngioma), pineal, or ventricular (eg, choroid plexus papilloma and carcinoma) region tumors may present with acute hydrocephalus associated with neurologic deterioration secondary to hydrocephalus, increasing interstitial edema, or intratumoral hemorrhage. Preoperative unilateral or bilateral ventriculostomy drainage of CSF may therefore be indicated to relieve the hydrocephalus and for monitoring ICP. Although risks such as infection, hemorrhage, parenchymal injury, upward herniation, intratumoral hemorrhage, and porencephalic cavities in infants are associated with placement of a ventriculostomy drain, emergent ventriculostomy placement is essential in this life-threatening situation. Recently, antibiotic-impregnated catheters have shown promise in reducing infections associated with ventriculostomy placement. At the authors' institutions, obstructive hydrocephalus secondary to a posterior fossa tumor is initially managed with administration of glucocorticoid steroids (ie, dexamethasone) and ventricular drainage if the child is significantly symptomatic. A preoperative ventriculoperitoneal shunt is usually not indicated, as studies have shown that a substantial number of children with posterior fossa tumors will not require a permanent shunt after resection of the tumor.

Shunt Malfunction

A child with a ventriculoperitoneal–atrial–pleural shunt malfunction often presents with signs and symptoms of

increased ICP. Infants with a shunt malfunction usually present with irritability, poor feeding, increased occipital-frontal head circumference (OFC), and inappropriate sleepiness. Children with a shunt malfunction usually present with headache, irritability, lethargy, nausea, and vomiting. However, it is important to inquire if the signs and symptoms that the child is presenting with are the same as those during a past shunt malfunction. When a shunt malfunction is suspected, neuroimaging studies consisting of a head CT as well as anteroposterior (AP) and lateral skull, chest, and abdominal radiographs are obtained to evaluate for increased ventricular size and shunt hardware discontinuity. Even though most children with a shunt malfunction present with increased ventricular size on neuroimaging studies, there are those whose ventricular size does not change due to decreased brain compliance (ie, "stiff ventricles") secondary to scarring of the ventricular lining. In these children and other children with unclear presentations, a sterile shunt tap is indicated to test the proximal and distal shunt flow. Children who are diagnosed with a shunt malfunction must be taken urgently to the operating room for shunt revision.

Trauma

Traumatic brain injuries may result in intracranial hemorrhage and/or cerebral edema, producing signs and symptoms of increased ICP. Patients are at risk of brain herniation and although consciousness may be preserved in the initial minutes, a decreased state of consciousness invariably results. Familiarity with the clinical features of the herniation syndromes discussed below is imperative. ICP monitoring is appropriate in infants and children with severe traumatic brain injury (Glasgow Coma Score ≤ 8) but not routinely indicated with mild or moderate head injury. However, ICP monitoring may be necessary in certain conscious patients with traumatic mass lesions or in patients for whom serial neurological examination is precluded by sedation, neuromuscular blockade, or anesthesia.

Diagnosis

When diagnosing a child with increased ICP, initial neurologic documentation is critical to detect signs and symptoms of neurologic deterioration. The initial neurologic examination should assess cranial nerves (eg, examination of pupillary size and reactivity to light) as well as motor, sensory, reflex, and cerebellar functions.

In neonates and infants younger than 6 months of age, it is difficult to measure ICP invasively. Therefore, palpation of the open cranial fontanelles and sutures provides a rough estimation of the degree of increased ICP, on the basis of the fullness or increased tension of the fontanelles as well as the degree of metopic, coronal, sagittal, and lambdoid suture splaying. In addition, increased OFC, decreased level of consciousness, irritability, poor feeding, inappropriate sleepiness, and limited up-gaze or forced down-gaze (ie, sun-setting sign) are signs of increased ICP in neonates and infants. Papilledema is rare in infants.

In children, headache, nausea, vomiting, lethargy, decreased level of consciousness, papilledema, double vision secondary to compression of the abducens cranial nerve, and difficulty concentrating or maintaining attention are signs of increased ICP. Cushing's triad of bradycardia, hypertension, and an irregular breathing pattern as well as autonomic dysfunction secondary to brainstem compression are also indications of increased ICP in infants and children. Once increased ICP is diagnosed, urgent neuroimaging studies (ie, head CT, ultrasonography, or MRI) are critical to facilitate proper treatment.

If increased ICP is severe enough, herniation of portions of brain from their normal location into other compartments over the dural membranes may occur, leading to compression of adjacent brain structures. Uncal, central transtentorial, and downward herniations are three important brain herniation syndromes. Uncal or unilateral transtentorial herniation results when the uncus is compressed into the tentorial notch, and the midbrain compression leads to an ipsilateral dilated and fixed pupil, decreased consciousness, respiratory and cardiac irregularities, and decerebrate rigidity. Central or bilateral transtentorial herniation results when both cerebral hemispheres compress the diencephalon and midbrain into the tentorial notch, leading to pupillary constriction and then dilation, decreased consciousness, respiratory irregularities, and decerebrate or decorticate rigidity. Downward or cerebellar herniation results when the cerebellum is compressed into the foramen magnum and brainstem compression leads to neck stiffness or head tilt, impaired upward gaze, decreased consciousness, and lower cranial nerve palsies. A lumbar puncture should be carefully considered in any child suspected of having increased ICP, as it may increase the chance of brain herniation.

Treatment

Intracranial Pressure Monitoring

Routine monitoring of ICP is performed in certain clinical situations, as outlined in Table 99-1. Regardless of the method of ICP monitoring, vigilant clinical monitoring to prevent any untoward complications is essential. Invasive devices used to measure ICP in children older than 1 year of age include a fiber-optic intraparenchymal monitor (Camino fiber-optic catheter monitoring system), subarachnoid screw (Richmond bolt), epidural transducer, subdural catheter, and intraventricular

TABLE 99-1. Indications for Intracranial Pressure Monitoring

In a child with Glasgow coma scale score ≤ 8 (comatose)
In a child with rapid deterioration of neurologic examination
In a child who is chemically paralyzed
In a child who is ventilated with high airway pressures or positive end-expiratory pressure
In a child who is heavily sedated
In a child who underwent a small reception or biopsy of a brain tumor, with resultant increasing mass effect and cerebral swelling

catheter. All clinically available invasive ICP monitoring systems have their own recognized advantages and disadvantages. Noninvasive techniques are also available for the measurement of ICP in neonates and infants, in whom it is difficult to measure ICP invasively, including fiber-optic, strain gauge, and transfontanelle pressure transducer measurements.

The most commonly used ICP monitoring systems are the Camino fiber-optic intraparenchymal catheter and the mechanically transduced intraventricular catheter. The ICP monitoring system is routinely placed on the same side as the intracranial pathology, as a pressure differential may exist between the ipsilateral and contralateral sides. ICP monitoring is essential in children with elevated ICP so that appropriate treatment may be tailored to prevent brain herniation and secondary ischemia. Table 99-2 lists the normal ICP of neonates, infants, children, adolescents, and adults. Treatment should be initiated when the ICP is 10 mm Hg greater than the normal range for a specific age for more than 5 minutes.

Intracranial Pressure Treatment

Various treatments are available for the management of elevated ICP and act by (1) decreasing cerebral blood volume, (2) decreasing brain bulk and CSF, and (3) increasing intracranial volume (Table 99-3). Prior to initiating ICP reduction therapy, the respiratory and circulatory systems (ie, airway, breathing, and circulation [ABCs]) must be stabilized to ensure adequate oxygenation. One thing that is commonly overlooked in children with head injuries, who are brought into an emergency setting to be stabilized, is the cervical collar. Sometimes the cervical collar is on too tightly and this can impede venous return, thereby elevating ICP; therefore, it should be one of the first things that is checked.

Cerebral Blood Volume

In most instances, cerebral blood volume (CBV) is the compartment that can be most easily and rapidly altered.

TABLE 99-2. Comparison of invasive ICP monitor devices

Device	Advantages	Disadvantages
Intraventricular catheter	Low cost	May be difficult to insert
	Therapeutic CSF drainage	Inaccurate if fluid column is obstructed
	Accurate and reliable	Must moved as HOB raised/lowered to maintain fixed reference point
	Can be recalibrated to minimize drift	Highest risk of infection and hemorrhage
Fiber-optic intraparenchymal monitor	Ease of placement	Subject to measurement drift
	Relative accuracy regardless of head position	Inability to recalibrate
	Useful when unable to obtain ventricular access	Inability to drain CSF
		Fiberoptic system expensive
		Fiberoptics can be broken if cable stretched or kinked
Subarachnoid screw	Lower risk of infection and hemorrhage	More likely to malfunction or become obstructed
	Ease of placement	False readings at high ICPs
	Useful when cerebral edema prevents ventricular access	Inability to drain CSF
		Possible CSF leakage
Subdural catheter	Low risk of infection and hemorrhage	More likely to malfunction or become obstructed
	Direct measurement	Inability to drain CSF
		Poor accuracy & reliability over time
		Catheter may be compressed as brain tissue re-expands
Epidural transducer	Low risk of infection and hemorrhage	Indirect measurement
	Ease of placement	Questionable accuracy
		Inability to drain CSF

CSF = cerebrospinal fluid
HOB = head of bead
ICP = intracranial pressure

TABLE 99-3. Normal Intracranial Pressure by Age

Age	Range of ICP (mm Hg)
Neonate (< 4 weeks old)	< 2
Term Infant (< 1 years old)	1.5 to 6
Children (1–15 years old)	3 to 7
Adolescent & Adult (> 15 years old)	< 15

ICP = intracranial pressure

Hyperventilation to a $PaCO_2$ of 25 to 30 mm Hg leads to cerebral arteriolar vasoconstriction and a subsequent reduction in brain and cerebral blood volumes. For immediate reduction in ICP, acute hyperventilation is indicated, but chronic hyperventilation should be avoided. The head should be in the neutral position and elevated 30° above the heart to avoid cerebral venous outflow obstruction and an increased CBV, which will help reduce ICP without a concomitant compromise in cardiac function.

Administration of cerebral vasoconstricting anesthetic agents, such as thiopental, pentobarbital, or propofol, will reduce the cerebral metabolic rate of oxygen and, therefore, decrease CBF and CBV. However, thiopental and pentobarbital may cause significant cardiovascular instability (ie, hypotension). Therefore, it may be necessary to administer vasopressor therapy (ie, phenylephrine or dopamine infusion) in children with poor cardiovascular function. Mannitol may also reduce CBV by reflex compensatory vasoconstriction resulting from the transient increase in CBF.

Administration of analgesic, sedative, and paralytic agents can be used to decrease ICP by decreasing agitation, decreasing somatic stimulation, and preventing breathing against the ventilator. Because hyperthermia increases the rate of brain metabolism and the level of carbon dioxide, the child's temperature should be monitored closely; if elevated, surface cooling blankets and antipyretics should be used to return the temperature to normal. In experimental studies, hyperthermia has been shown to increase cerebral edema by up to 40%.

Brain Bulk and Cerebrospinal Fluid

Mannitol, an osmotic diuretic, or furosemide, a loop diuretic, is frequently used for the rapid reduction of ICP. Twenty percent mannitol at a dose of 0.25 to 1.0 g/kg is given as an intravenous infusion, and effective action occurs within 10 to 15 minutes and lasts for up to 8 hours. A decrease in brain tissue volume and CSF formation are two mechanisms that contribute to the rapid action of mannitol. The side effects of mannitol include (1) hemodynamic instability (ie, hypotension followed by hypertension), (2) dehydration and hypovolemia, (3) electrolyte disturbances, (4) hyperosmolarity, and (5) increased rebound ICP phenomena.

The administration of mannitol requires that the child's serum osmolarity and electrolytes (ie, sodium and potassium) be frequently measured. When serum osmolarity is > 320 mOsm/L, mannitol should be discontinued to avoid the potential complications of hypernatremia, hyperkalemia, low serum bicarbonate, metabolic acidosis, altered mental status, fluid overload, congestive heart failure in children with poor myocardial function, and acute renal failure, which usually occurs 2 to 4 days after mannitol treatment.

Furosemide is also used to reduce ICP by inducing a systemic diuresis and decreasing CSF production without producing significant changes in serum osmolarity. It is initially given as a large intravenous dose (0.5–1.0 mg/kg) alone or at a lower dose (0.15–0.30 mg/kg) in combination with mannitol. It has been demonstrated that the combined treatment with furosemide and mannitol has a synergistic action and prolongs the effect of lower doses of mannitol but may lead to more electrolyte abnormalities and severe dehydration. In a child with impaired cardiac function, furosemide may be preferable to mannitol.

Hypertonic saline is also effective for the control of increased ICP and acts like mannitol by establishing a constant osmolar gradient to draw fluid from the brain parenchyma. It may be advantageous in cases of a hypotensive and hypoperfused patient when use of mannitol may be deleterious. Three percent saline at a dose of 0.1 to 1.0 mL/kg/hr at a continuous intravenous infusion is administered on a sliding scale to achieve the minimum dose needed for maintaining an ICP < 20 mm Hg. The serum osmolarity should be maintained < 360 mOsm/L. Possible side effects of hypertonic saline include rebound ICP increase, central pontine myelinolysis and subarachnoid hemorrhage.

Acetazolamide (Diamox®), a carbonic anhydrase inhibitor, may be used to decrease CSF production both acutely and chronically. It has been shown that acetazolamide

TABLE 99-4. Treatment to Decrease Intracranial Pressure

To decrease cerebral blood flow
Hyperventilation ($PaCO_2$ of 25–30 mm Hg)
30° head elevation in neutral position
Administration of barbiturates
Administration of paralytics
Administration of sedatives
Prevention of hyperthermia
To decrease brain bulk and cerebrospinal fluid (CSF)
Osmotic diuretic (Mannitol)
Loop diuretic (furosemide)
Hypertonic saline—3% saline (0.1 to 1.0 mL/kg/hr)
Glucocorticoid steroids (Dexamethasone)
Surgical resection of a selected cerebral lobe or brain tumor
Acetazolamide to decreases CSF production
Intraventricular CSF drainage
Increase intracranial volume
Surgical decompression of adjacent brain, ie, lobectomy
Decompressive craniectomy and dural expansion to allow for cerebral swelling

can decrease CSF production by 16 to 66% in humans, and the effect of an intravenous dose appears to last for < 2 hours. However, a rapid intravenous dose of acetazolamide may have a cerebral vasodilative effect and, therefore, cause a transient increase in ICP due to tissue CO_2 release and a subsequent increase in CBV and CBF. It appears that acetazolamide may be useful as a temporizing measure or as an adjunct to definitive treatment in children with transient alterations in CSF absorption and without acute clinical signs and symptoms of increased ICP, such as clinical situations with slowly progressive hydrocephalus (eg, after resection of a posterior fossa tumor, repair of a myelomeningocele, germinal matrix and intraventricular hemorrhage in a premature infant, or meningitis). Lethargy, poor feeding, tachypnea, diarrhea, and electrolyte imbalances (ie, hyperchloremic metabolic acidosis) are potential side effects of acetazolamide treatment.

ICP can be decreased by glucocorticoid steroid (eg, dexamethasone) administration to decrease cerebral vasogenic edema. Intraventricular drainage of CSF by placement of an external ventriculostomy drain or by inserting a 23-gauge butterfly needle into a shunt reservoir in the presence of a distal catheter shunt malfunction also can also decrease ICP.

Moderate hypothermia (32–33°C) may also be a helpful therapeutic adjunct for managing increased ICP by reducing the cerebral metabolic rate for oxygen. This consequently reduces the cerebral blood flow through vasoconstriction of the cerebrovasculature and increasing blood viscosity. During this process, blood pressure and urine output usually decreases, while hyperkalemia may also develop. Proper physiologic monitoring of these parameters is imperative. In children with severe traumatic brain injury, reducing ICP with moderate hypothermia for 48 hours, instituted within 24 hours of injury, may reduce mortality and potentially improve functional outcome. Rewarming should be proceeded at a slow rate to avoid potential rebound in the ICP.

Conclusion

Caring for a child with increased ICP must include not only treatment for the child, but also support for the family through frequent and effective communication between the health care team and family members. Early recognition and treatment of increased ICP and attention to detail with regard to all organ systems at all times are essential to effectively manage a child with increased ICP and, ultimately, reduce morbidity and mortality.

Suggested Readings

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Practitioner and Patient Resources

Brain Injury Association of America (BIAA)
8201 Greensboro Drive, Suite 611
McLean, VA 22102
Phone: (703) 761-0750 or 800-444-6443
http://www.biausa.org
The mission of the BIAA is to create a better future through brain injury prevention, research, education, and advocacy.

American Brain Tumor Association (ABTA)
2720 River Road
Des Plaines, IL 60018
Phone: 800-886-2282
http://www.abta.org
The ABTA exists to eliminate brain tumors through research and to meet the needs of patients and their families.

Hydrocephalus Association (HA)
870 Market Street, Suite 705
San Francisco, CA 94102
Phone: (415) 732-7040 or 888-598-3789
http://www.hydroassoc.org
The HA provides support, education, and advocacy for individuals, families, and professionals.

CHAPTER 100

EVALUATION AND MANAGEMENT OF ACUTE HEADACHE

LAWRENCE P. RICHER, MD, FRCP(C)

While a small minority of headache in childhood or adolescents is urgent or life threatening, it is important for the practitioner to remain diligent in their evaluation and treatment. Thorough clinical evaluation will provide clues to guide further diagnostic and therapeutic decision-making.

Headache is a common problem in children and a frequent presentation in the emergency department (ED) or hospital setting. The majority of headaches are benign, self-limited, and non-life-threatening. However, it is critical that the practitioner recognizes the signs of more serious headaches and make appropriate diagnostic and management decisions. This chapter will review a general approach to the child presenting to hospital with a headache including the differential diagnosis, diagnostic evaluation, and management of the more common or important etiologies.

The Second Revision of the International Classification of Headache Disorders (ICHD-II, 2004) classifies headache as primary (Table 100-1) or secondary (Table 100-2). The aim of the practitioner evaluating a child with headache is to distinguish the various disorders from one another—a task made difficult by the absence of diagnostic markers for any of the primary headache disorders. Moreover, many of the secondary headache disorders may mimic other primary headache types. While serious and life-threatening causes of headache are infrequent, the evaluation of headache requires vigilance and attention to the clues that may suggest more ominous causes.

TABLE 100-1. Primary Headache Disorders

Migraine
Tension-type headache
Cluster headache and other trigeminal autonomic cephalgias
Cluster headache
Paroxysmal hemicrania
Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing
Probable trigeminal autonomic cephalalgia
Other primary headaches
Primary stabbing headache
Primary cough headache
Primary headache associated with sexual activity
Primary thunderclap headache
Hemicrania continua
New daily persistent headache

TABLE 100-2. Selected Secondary Headache Disorders That May Require Hospital-Based Evaluation and Treatment

Headache attributed to head and/or neck trauma (see text)
Headache attributed to cranial or cervical vascular disorder (see text)
Headache attributed to nonvascular intracranial disorder (see text)
Headache attributed to high cerebrospinal fluid pressure
Headache attributed to low cerebrospinal fluid pressure
Headache attributed to intracranial neoplasm
Headache attributed to a substance or its withdrawal
Medication overuse headache (eg, analgesic, triptan, opioid)
Defined as the use of substance > 15 d/mo for > 3 mo. May require detoxification.
Headache attributed to infection (see text)
Headache attributed to disorder of homeostasis (eg, hypoxia, hypercapnea, dialysis, hypertension)

Clinical Evaluation

History

The evaluation of child with headache depends largely on a detailed and careful history. The history should include a

Table 100-2. Selected Secondary Headache Disorders That May Require Hospital-Based Evaluation and Treatment (continued)

Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or facial or cranial structures
Localized pain (to structure) with referred pain to head; abolition of headache with treatment of source pain or blockade (eg, greater occipital nerve); chronic sinusitis is not a validated cause of headache.
Headache attributed to psychiatric disorder
Cranial neuralgias and central causes of facial pain (eg, trigeminal neuralgia, glossopharyngeal neuralgia, Tolosa-Hunt syndrome)

good description of the headache quality, severity, location, onset and temporal course, associated symptoms, and exacerbating features. Table 100-3 outlines clinical features that may help differentiate benign from more concerning causes. It is important to consider the information given by the child as well as the caregiver(s) and to determine if this is a new type of headache or a recurrence of previous similar headaches. Asking why the child was brought to hospital may also be revealing (ie, change in headache, persistence of long-term headache, worsening or new symptoms, poor access to ambulatory care, etc.).

TABLE 100-3. Clinical Features Important in the Evaluation of Child With Headache

Feature	Benign	More Concerning
Quality	Migraine headache is typically pulsatile. Meningeal inflammation may also cause pulsatile headache (eg, meningitis, SAH) so must look at other characteristics.	Diffuse or nonpulsatile headache may occur with raised intracranial pressure or other primary and secondary headache disorders.
Severity	Gradual onset with moderate to severe intensity	Rapidonset; "worst headache of my life"
Location	Frontal and/or temporal headache is the most common location of benign headache.	Occipital headache is less common and may be secondary to referred pain from the posterior fossa; diffuse headaches with other associated symptoms (eg, nausea) can occur with benign or concerning headaches.
Laterality	Migraine may be bilateral or unilateral in children, but the painful side will usually alternate.	Persistently localized and lateral headache may indicate a fixed abnormality (eg, vascular, neoplasm).
Onset	Migraine headaches are more gradual in onset.	Abrupt and severe "thunderclap" headaches may indicate a serious etiology (eg, SAH, raised intracranial pressure).
Course	Migraine and other primary headache are typically episodic in between in which the child is completely well.	Progressive (frequency or severity) or changing pattern of headache; associated symptoms (nausea, neurologic dysfunction) during and in between headache episodes (ie, child is not perfectly well in between).
Associated symptoms	Gradual onset nausea, photophobia, and sonophobia are suggestive of migraine; headache is commonly associated with other systemic infections (particular respiratory infection) and a common presenting complaint in emergency departments.	Similar clinical features may be present with meningitis or SAH and are differentiated by the rapid onset of symptoms, fever, and meningismus; other signs of systemic infection; altered consciousness; neck pain with arterial dissection
Preceding symptoms	Gradual onset symptoms of neurologic dysfunction are most in keeping with migraine aura.	Sudden onset symptoms that immediately precede the rapid onset of headache; vomiting followed by headache; headache immediately followed by seizure
Exacerbating features	May be worse with moderate to vigorous activity.	Marked worsening with all activity including coughing and straining; worse when lying down (high pressure) or standing (low pressure); nocturnal or early morning waking
Medical history	A history of episodic headache and completely well in between headache episodes; sleep apnea may be associated with daytime headache; medication overuse may contribute to headache frequency.	Other medical conditions (eg, neurofibromatosis type 1, Sturge-Weber syndrome, connective tissue disorder, immunocompromise); not well in between headaches (eg, anorexia, apathy, personality changes); recent head trauma; focal seizure; renal disease; hypertension; neurofibromatosis type 1

SAH = subarachnoid hemorrhage.

Severe headaches of sudden onset (thunderclap headache) generally raise concern for subarachnoid hemorrhage (SAH) and should prompt a careful evaluation for meningismus. A family history of aneurysms may raise suspicion and preceding symptoms of persistently localized headache, focal neurologic deficits, or painful ophthalmoplegia are ominous. Arterial dissection may also cause thunderclap headache with or without SAH as well as vascular malformations (eg, arteriovenous malformation). Meningitis or encephalitis may present with acute progressive headache but will normally be of more gradual onset and associated with fever. Trigeminal neuralgias are distinguished by the recurrence of trigeminal pain often in the 2nd and 3rd divisions and provocation with sensory stimuli. A history of substance use or exposure should be sought including, but not limited to, oral analgesics, triptan medications, opioids, caffeine withdrawal, cocaine, or carbon monoxide. A number of primary headaches may also cause thunderclap-like headache including primary thunderclap headache, cluster headache, other trigeminal autonomic cephalalgias, or primary exertional headache.

Examination

A neurologic examination must be conducted on children with headache. Important features of the examination include fundoscopy for papilledema, extraoccular movements for nystagmus or ophthalmoplegia, focal motor signs (weakness, hyperreflexia, and extensor toe sign) and tests of coordination for ataxia, intention tremor, or dysmetria. Head circumference (macrocephaly), temperature (fever), blood pressure (hypertension), and heart rate (component of Cushing triad) should all be recorded. Head and neck structures should be examined for localized sources of pain (eg, acute otitis media, dental abscess, acute sinusitis, and orbital pain) or neck pain with arterial dissection. Palpation of the cervical muscles may reveal myofascial pain. Tests for meningismus (ie, Brudzinski, Kernig, or tripod maneuvers) must be documented in the hospital setting. A general examination for signs of systemic illness (eg, respiratory infection), trauma, drug use, carotid bruit, and stigmata of neurocutaneous disorders (eg, café-au-lait spot or port wine stain) completes the assessment.

Signs of neurologic dysfunction may be present with primary (an aura) or secondary headaches, and there are clinical clues that may help differentiate one from the other. Migraine aura is of gradual onset (at least over 4 minutes) as opposed to the rapid onset of ischemic or hemorrhagic lesions. Aura symptoms may sometimes advance from occipital brain areas (visual symptoms) to anterior regions (ie, sensory symptoms followed by motor symptoms). The persistence of symptoms beyond 1 hour and recurrent symptoms consistently in the same distribution and side would raise the possibility of a brain lesion. Finally, migraine auras often produce positive symptoms (eg, visual scotomas) as opposed to negative symptoms (eg, visual loss) with ischemic lesions.

Investigations

Neuroimaging

Guidelines on the use of neuroimaging (Lewis and colleagues, 2002) suggest that neuroimaging is not necessary in most children with recurrent headache who have a normal neurologic examination. According to the guideline, a higher probability of detecting an abnormality is observed in the following:

1. headache of less than 1 month duration
2. absence of a family history of migraine
3. abnormal neurologic examination (focal or diffuse)
4. gait abnormalities
5. seizures (focal or generalized)

Clinical features suggestive of a secondary cause of headache may also prompt neuroimaging including:

1. thunderclap headache (severe headache of sudden onset)
2. persistently lateralized headaches
3. progressive course of headache (frequency/severity)
4. possible shunt malfunction
5. prior to lumbar puncture (LP)
6. change in pattern or type of headache
7. occipital headache (relative red flag given pediatric predisposition to posterior fossa tumors)

The choice between computed tomography (CT) scan and magnetic resonance imaging (MRI) is based largely on the problem to be assessed and the urgency of the test. CT scan remains a reasonable screening test for acute neurological problems for which hemorrhage, ischemia, neoplasm, or hydrocephalus may be the problem. MRI provides better definition and increased sensitivity for subtle changes involving white matter (eg, demyelination or ischemia) and brainstem structures. "Benign" abnormalities including (1) sinus disease, (2) Chiari type I malformation, (3) nonspecific white matter changes, (4) venous angiomas, (5) arachnoid cysts, (6) pineal cysts, and (7) mega cisterna magna are sometimes detected but infrequently alter management (Schwedt and colleagues, 2006).

Noninvasive angiography with CT angiography or magnetic resonance angiography may be very helpful in the safe evaluation of possible vascular disorders. The choice between the two modalities is predicated on the exposure to radiation with CT and preference or expertise within the institution. Both modalities are likely to visualize aneurysms greater than 4 to 5 mm. Vascular malformations are generally visible, but conventional angiography will

offer more information on the direction of flow and greater anatomical detail of feeder arteries. Nonetheless, the gain in information must be balanced by the risk of complications including a 1% risk of stroke.

LP

LP should be considered in selected patients. First, the diagnosis of idiopathic intracranial hypertension is dependent on measuring the opening pressure. The procedure should be performed in the lateral decubitus position with the lower extremities partly extended to relieve intra-abdominal pressure that may falsely elevate the recorded pressure. Other diagnostic considerations for an LP are meningitis or SAH. The presence of meningismus, fever, new onset seizures, altered mental status, or thunderclap headache may prompt cerebrospinal fluid (CSF) analysis. The immunocompromised patient with headache or patient with HIV risk factors should be investigated as well.

Evaluation and Management of Selected Primary and Secondary Headache Disorders

Migraine

The diagnosis of migraine is based on the presence of features as described in the ICHD-II (2004) and elsewhere in this text. Without a biological marker for migraine, the absence of features suggestive of another underlying cause for headache (ie, fever, meningismus, or thunderclap head ache) and a normal neurologic examination are also critical to appropriate diagnosis. However, neuroimaging is not routinely required. The patient presenting with their first migraine attack presents a diagnostic challenge, and the presence of an aura can be quite alarming as well. Clarifying the reason for presenting to hospital can enhance your understanding of the patient and focus ongoing evaluation and management.

Few randomized controlled trials on acute migraine therapy in children in the ED have been published (Brousseau and colleagues, 2004). Consequently, treatment recommendations are limited and often based on adult trials. If the child has not received abortive therapy, it is reasonable to begin with an oral analgesic (ie, ibupro fen, acetaminophen, or naproxen). Adding an antinauseant with prokinetic properties such as oral metoclopramide may be helpful in promoting absorption of the analgesic and treating nausea.

Parenteral therapy is recommended in patients whom have failed home or oral therapy. Intravenous (IV) prochlorperazine is more effective than ketorolac in one randomized trial in children (Brousseau and colleagues, 2004). Intramuscular (IM) prochlorperazine may also be used. Adult trials support the use of IV or IM metoclopramide or chlorpromazine. The use of IV fluids alone have not been studied, but given the nausea and vomiting with migraine as well as the hypotension that may be caused by prochlorperazine or metoclopramide, it is reasonable to include a fluid bolus with treatment. Extrapyramidal side effects with either medication may include akathisia (an unsettling feeling of needing to move) and dystonia (eg, occulogyric crisis). These side effects may be diminished or avoided altogether by administering diphenhydramine or benztropine prior to prochlorperazine or metoclopramide.

Triptan medications in children have not been studied in the ED setting. Intranasal sumatriptan and intranasal zolmitriptan may have an advantage over oral preparations presumably due to more rapid absorption (Rapoport and Winner, 2006). However, triptans are more effective when given early in the attack, and the delay in treatment for many children presenting to the ED may limit their effectiveness. Subcutaneous sumatriptan may be more effective than intranasal but has also not been studied in children.

Some combinations of medications with different mechanisms of action seem intuitive. For example, a triptan combined with a nonsteroidal anti-inflammatory drug (NSAID) such as naproxen or subcutaneous sumatriptan with IV/IM prochlorperazine. Similarly, prochlorperazine or metoclopramide may be combined with a parenteral NSAID such as ketorolac. Other considerations without proven efficacy in children include valproate. However, opioid medications should be avoided.

Chronic Migraine

Children with a long-standing history of frequently recurring migraine may also present to the ED. It is reasonable to provide a trial of abortive relief with parenteral therapy, but the intractable nature of the migraine may limit effectiveness and/or result in early headache recurrence. Also many children will also have comorbid medication overuse. No trials support a particular management approach. However, it may be reasonable to consider initiating migraine prophylactic therapy with appropriate outpatient follow-up. More immediate therapies to sustain headache relief or help with detoxification of medication overuse have not been studied in children, but one may consider the use of a longer acting NSAID (ie, naproxen) for 5 to 7 days or prednisone for 5 to 7 days. Opioid medications should especially be avoided in children with frequently recurring headache.

Cluster Headache

Cluster headache is a unique and painful primary headache disorder. The cluster headache attack will usually last 45 to 90 minutes but may recur numerous times in a cluster episode. Management will vary in part on the duration of the attacks and frequency of recurrence. Oxygen therapy may be helpful. Dihydroergotamine given intranasally/IV

TABLE 100-4. Medications Used in the Treatment of Primary and Secondary Headache (See Text for Indications)

Medication	Route	Dose per kg	Maximum
Dihydroergotamine	Intranasal	0.5 mg/spray (1 spray each nostril q15 min × 2; adult)	2 mg/attack; 4 mg/week
Sumatriptan	Intranasal	5 or 20 mg in one nostril × 1	40 mg/24 h
	SC	4–6 mg SC × 1 (adult)	12 mg/24 h
Zolmitriptan	Intranasal	5 mg in one nostril × 1	10 mg/24 h
Caffeine	IV	5–10 mg/kg	500 mg/dose
Valproate	IV	15 mg/kg	1,000 mg/dose
Chlorpromazine	IV, IM	0.2 mg/kg (may repeat once)	10 mg/dose
Dihydroergotamine	IV, IM	0.5–1 mg/dose (adult)	2 mg/dose
Diphenhydramine	IV, IM	1 mg/kg	50 mg/dose
Ketorolac	IV, IM	1 mg/kg	30 mg IM; 15 mg IV
Metoclopramide	IV, IM	0.2 mg/kg (may repeat once)	10 mg/dose
Prochlorperazine	IV, IM	0.2 mg/kg (may repeat once)	10 mg/dose
Acetazolamide	PO	10–30 mg/kg/d div tid-qid	2,000 mg/d
Furosemide	PO	1–6 mg/kg/d div bid	6 mg/kg/dose
Metoclopramide	PO	0.25 mg/kg (may repeat once)	15 mg/dose
Prednisone	PO	1–2 mg/kg/d	60 mg/d
Naproxen	PO	10–20 mg/kg/d div q8–12h	1,000 mg/d
Benztropine	PO, IV, IM	0.02–0.05 mg/kg	2 mg/dose

IM = intramuscular; IV = intravenous; OP = by mouth; SC = subcutaneous

or sumatriptan subcutaneously may also be effective. Some trigeminal autonomic cephalalgias are uniquely responsive to indomethacin. Prophylaxis with verapamil is the most established treatment. A 5-to 7-day course of prednisone may also be beneficial.

Acute Posttraumatic Headache

The characteristics of headache following head trauma vary but frequently have migrainous features in children. Children with a history of recurring headache or family history of migraine may be at greater risk. Dizziness, concentration difficulties, or personality changes often accompany the headaches. The child may also present with an unusual aura (eg, confusion and agitation) that may suggest a more serious underlying pathology. Neuroimaging is warranted in a child following head trauma with an altered level of consciousness or abnormal neurologic examination. Acute posttraumatic headache may respond to migraine therapy. Prochlorperazine or metoclopramide preceded by a fluid bolus and diphenhydramine may relieve the headache.

Headache Attributed to High CSF Pressure

Idiopathic intracranial hypertension presents with progressive, nonpulsatile, daily headache aggravated by coughing or straining. Papilledema is present in most cases while tinnitus, diplopia, or visual obscurations are variably reported. The diagnosis requires LP with measurement of the opening pressure. Abnormal opening pressures are > 200 mm H_2O for the nonobese child and > 250 mm H_2O for the obese child. CSF may be removed to lower the pressure with the following limitations: (1) lower the opening pressure by no more than half of the original pressure (ie, if the opening pressure is 40 cm H_2O lower to no more than 20 cm H_2O) and/or (2) do not remove more than 0.4 mL/kg. Headache is commonly relieved following the LP but may take 24 hours to achieve full benefit. Sustaining the lowered pressure is achieved with acetazolamide and furosemide. The patient must be referred to ophthalmology for visual field testing and follow-up care as blindness is a potential outcome.

Children with a ventriculoperitoneal or other intracranial shunt for hydrocephalus often report headache. Shunt malfunction or infections are two critical causes to consider, and neuroimaging is often required. Characteristics of the headache may vary, but it is typically diffuse, progressive, and associated with neurologic dysfunction (eg, altered consciousness, diplopia, and papilledema). However, migraine and other primary headache may also occur. A pattern of recurrent headaches with migraine features, normal neurologic examination, and nonprogressive course are suggestive. Specific migraine treatment may be effective.

Space occupying lesions or neoplasm may infrequently present with headache alone. The headache characteristics are typically diffuse but may also be localized. Tumors of the posterior fossa may present with occipital headache. The headache may be worse with activity, coughing, and straining and occur more frequently in the morning. Persistent nausea is often present. Vomiting prior to the onset of headache is an ominous sign that may be due to the location of the lesion or hydrocephalus.

Headache Attributed to Low CSF Pressure

Low CSF pressure may follow dural puncture (ie, LP), development of a CSF fistula, or occur spontaneously. Diffuse headache that is worse within 15 minutes of upright posture and improved within 15 minutes of lying

is suggestive of the diagnosis. Neck stiffness, tinnitus, hypacusia, photophobia, or nausea may also be present. MRI with gadolinium may show leptomeningeal enhancement. Symptoms usually resolve, and simple analgesics are often sufficient (eg, ibuprofen). However, if the headache persists beyond 5 to 7 days, treatment with caffeine or autologous epidural blood patch may be helpful.

Headache Attributed to Cranial or Cervical Vascular Disorders

Hemorrhagic vascular disorders including intracranial hemorrhage and SAH may present with very abrupt onset unilateral 'thunderclap' headache. SAH may include migrainous features such as nausea and vomiting. The presence of nuchal rigidity, abnormal neurologic examination, or altered level of consciousness will help differentiate the disorders. Urgent neuroimaging is warranted for 'thunderclap' headache or migraine-like headache with persistent focal neurologic symptoms or altered consciousness. LP may be necessary if the clinical index of suspicion is high and neuroimaging is normal.

Headache is uncommon with an unruptured aneurysm; however, thunderclap headache may precede rupture. Clues to the diagnosis include painful oculomotor palsy, focal neurologic signs, or persistently localized headache. Noninvasive CT or magnetic resonance angiography will detect most aneurysms over 4 to 5 mm. Consider screening if there are two first-degree relatives with cerebral aneurysms.

Vascular malformations may present with acute severe headache and hemorrhage but are often associated with migraine with aura-like symptoms. Persistently, localization, 'thunderclap' headache, or a persistent focal neurologic deficit may distinguish the disorders. Noninvasive angiography with CT or MR minimizes risk to the patient. Conventional angiography may be necessary for further risk assessment or surgical planning. Sturge-Weber syndrome (facial angioma, focal signs, seizures) associated with ipsilateral leptomeningeal angioma may present with migraine-like headache as well.

Cerebral ischemia may trigger headache. The acute onset of focal neurologic signs or diffuse neurologic dysfunction (eg, changes in concentration, cognition, mood/personality) may suggest an ischemic insult. Focal signs are usually negative phenomena (eg, weakness or numbness). Congenital heart disease or thrombotic risk factors may increase the risk. Neck trauma/pain or a Horner syndrome may suggest arterial dissection while systemic inflammatory symptoms may suggest a vasculitis.

Cerebral sinovenous thrombosis will present with diffuse and progressive severe headache and often with focal signs. Similarly, the presentation may mimic migraine or thunderclap headache. Symptoms of raised intracranial pressure and/or diffuse neurologic dysfunction are clues to the diagnosis. Thrombotic risk factors need to be explored. MRI and MR venography is the preferred diagnostic approach.

Headache Attributed to Infection

Diffuse, bilateral, progressive headache is frequently associated with intracranial infection and may be the presenting feature. Migraine-like features including nausea, photophobia, or sonophobia may also occur. Nuchal rigidity, meningismus, fever, focal neurologic signs, seizures, and altered consciousness help distinguish meningitis from other causes of headache. Systemic infections often of the respiratory tract may also present with diffuse headache. General malaise and symptoms of the underlying infection (eg, fever, cough, and rhinitis) will suggest the correct diagnosis.

Suggested Readings

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Schwedt TJ, Guo Y, Rothner AD. "Benign" imaging abnormalities in children and adolescents with headache. Headache 2006;46:387–98.

Practitioner and Patient Resources

The National Headache Foundation
428 W. St. James Place, 2nd Floor
Chicago, IL 60614
Phone: (800) 843-2256
<http://www.headaches.org>
The National Headache Foundation is a nonprofit organization dedicated to educating headache sufferers and healthcare professionals about headache causes and treatments.

American Headache Society
19 Mantua Road
Mt. Royal, NJ 08061

Phone: (856) 423-0043
Fax: (856) 423-0082
E-mail: ahshq@talley.com
<http://www.americanheadachesociety.org/>
The American Headache Society (AHS) is a professional society of health care providers dedicated to the study and treatment of headache and face pain. Founded in 1959, AHS brings together physicians and other health providers from various fields and specialties to share concepts and developments about headache and related conditions.

American Council for Headache Education
<http://www.achenet.org>
The American Council for Headache Education (ACHE) is a nonprofit patient-health professional partnership dedicated to advancing the treatment and management of headache and to raising the public awareness of headache as a valid, biologically based illness. ACHE was created in 1990 through an initiative of the American Headache Society.

MAGNUM: Migraine Awareness
113 South Saint Asaph, Suite 300
Alexandria, VA 22314
Phone: (703) 739-9384
Fax: (703) 739-2432
<http://www.migraines.org>
MAGNUM was created to bring public awareness, using the electronic, print, and artistic mediums, to the fact that migraine is a true biologic neurologic disease, to assist migraine sufferers, their families, and coworkers, and to help improve the quality of life of migraine and head-pain sufferers worldwide.

CHAPTER 101

BRAIN AND SPINAL CORD TUMORS

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Tumors of the central nervous system (CNS) together are the most common solid tumor in children and account for the highest rate of malignancy-related mortality and morbidity. This chapter reviews the diagnostic approaches to pediatric CNS tumors and the therapeutic considerations, which are tempered by risks of long-term neurologic sequelae.

Primary tumors of the pediatric CNS represent the most common solid tumor in this age group and the second most common childhood cancer. They are a notably heterogeneous group classified according to histology, location, and increasingly genetic and molecular characteristics (Table 101-1). Although recent decades have seen overall increases in survival rates, particular tumor types remain poorly treatable. Moreover, neurologic, neuroendocrine, and neurocognitive morbidity is often consequent of the various therapies used requiring long-term multidisciplinary care. Strategies are continually developing with the goal of eliminating the tumor while preserving as much function as possible. These strategies include advancements in neurosurgical and radiation therapy techniques, increased development of chemotherapy protocols, and promising molecularly targeted therapies.

Epidemiology and Etiology

In the United States, the incidence of primary brain tumors from ages 0 to 19 years is 4.28 per 100,000. This incidence is highest between 0 and 4 years and varies depending on histologic type. With the exception of ionizing radiation, no specific exposures have been proven as causative of pediatric central nervous system (CNS) tumors and the great majority (95%) occur sporadically. There are, however, a number of genetic syndromes and phakomatoses associated with a higher incidence of primary CNS neoplasia (Table 101-2).

Within the tumors themselves, consistent chromosomal rearrangements and molecular signatures have been associated with particular tumor types. These include isochromosome 17q (i17q) in medulloblastoma; monosomy 22 in atypical teratoid/rhabdoid tumor (ATRT), meningioma, and acoustic neuroma; and 1p loss with or without 19q loss

TABLE 101-1. Relative Incidence of Selected Tumor Subtypes

Subtype	Relative Incidence (%)
Neuroepithelial	
Embryonal tumors	15–20%
Medulloblastoma	10–20%
PNET	1–2%
ATRT	2–4%
Glial tumors	40–50%
Pilocytic	15–35%
Low grade	5–15%
Anaplastic and GBM	10–15%
Brain stem glioma	10–15%
Choroid plexus tumors	1–3%
Pineal parenchyma tumors	1–2%
Ependymoma	5–10%
Neuronal and mixed tumors	1–5%
Nonneuroepithelial	
Germ cell tumors	1–3%
Craniopharyngioma	5–13%
Spinal tumors	1–2%

ATRT = atypical teratoid rhabdoid tumor; GBM = glioblastoma multiforme; PNET = primitive neuroectodermal tumor.

TABLE 101-2. Familial Brain Tumor Syndromes

Syndrome	CNS Tumors	Systemic Tumors	Chromosome	Gene
Turcot	Medulloblastoma, GBM	Colon carcinoma	7p22, 5q21-22, and 3p21.3	*APC, MLH1, PMS2*
Gardner	Medulloblastoma, GBM	Colon carcinoma	5q21	*APC*
Gorlin	Medulloblastoma	Basal cell carcinoma	9q22.3	*PTCH*
Li-Fraumeni	Astrocytoma, PNET	Soft-tissue sarcomas, breast carcinoma, leukemia	17p13.1	*P53*
Von Hippel-Lindau	Cerebellar/spinal/retinal hemangioblastoma, glioma, choroids plexus tumors	Renal cell carcinoma, pheochromocytoma, neuroendocrine tumors	3p25	*VHL*
Lhermitte-Duclos/Cowden	Dysplastic gangliocytoma of the cerebellum	Skin, thyroid, and breast papilloma	10q23	*PTEN*
Ataxia-telangiectasia	Astrocytoma, medulloblastoma	Lymphoid and solid tumors	11q22.3	*ATM*
Trilateral retinoblastoma	Pineoblastoma	Retinoblastoma	13q14	*Rb1*
Neurofibromatosis type 1	Optic pathway and cerebral glioma, plexiform neurofibroma, ependymoma		17q11	*NF1*
Neurofibromatosis type 2	Bilateral acoustic schwannomas, meningioma, ependymoma		22q12	*NF2*
Tuberous sclerosis	SEGA, cortical tuber, astrocytoma, ependymoma, GBM	Renal hamartoma, cardiac rhabdomyoma	9q34, 16p13.3	*TSC1, TSC2*

GBM = glioblastoma multiforme; PNET = primitive neuroectodermal tumor; SEGA = subependymal giant cell astrocytoma.

in oligodendroglioma. Gene-specific alterations include *hSNF5/INI1* in ATRT. Loss or reduction of nuclear hSNF5/INI1 immunostaining is now routinely tested to confirm this diagnosis.

Of particular interest, high-throughput gene expression profiling of medulloblastoma has identified molecular signatures that are highly predictive of outcome at initial diagnosis. Thus, knowing the particular gene expression pattern of a tumor can allow for tailored therapy depending on risk stratification, reserving the most rigorous therapeutic regimens for those in the high-risk category. In addition, these studies have confirmed that medulloblastoma is distinct from supratentorial primitive neuroectodermal tumor (PNET) and other histologically similar embryonal tumors by highlighting the tumorigenic role of sonic hedgehog pathways that are also vital to cerebellar granule cell development. Finally, such studies provide a framework for the development of molecularly targeted therapies, outlining genes and genetic pathways important in tumor development and maintenance. Molecular characterization of other pediatric CNS tumor types should provide further insights across all aspects of management.

Clinical Presentation

The presenting symptoms of CNS tumors are largely dictated by their position along the neuraxis. Nearly half of all CNS tumors arise in the posterior fossa with 75% of these involving the fourth ventricle or cerebellum. Thus, obstruction of cerebrospinal fluid (CSF) flow can lead to signs and symptoms of increased intracranial pressure (ICP). These include moderate to severe headaches, which tend to occur at night or in the morning upon waking, with associated nausea, vomiting, and lethargy. Cranial nerve palsies may indicate an intrinsic brain stem lesion or extrinsic forces on the brain stem due to increased ICP, herniation, or mass effect. Problems with balance and coordination are common from lesions involving the cerebellum or brain stem.

Suprasellar tumors cause neuroendocrine dysfunction, visual disturbances, and changes in sleep wake cycle. Diencephalic syndrome typically occurs in children less than 4 years of age as a consequence of hypothalamic/chiasmatic tumors. It is characterized by severe emaciation, normal linear growth, normal or precocious intellectual development with or without hyperactivity, hyperalertness, euphoria, and visual disturbance. Tumors in the pineal region often result in Parinaud syndrome, characterized by failure of upgaze, impaired convergence, decreased pupillary reaction to light, lid retraction, and convergence or retraction nystagmus. Obstructive hydrocephalus is common with pineal region tumors due to compression of the cerebral aqueduct.

Tumors involving the cerebrum result in varying symptoms dictated by location and include seizures, cognitive or behavioral changes, speech or language difficulty, sensorimotor complaints, visual changes, headache, somnolence, and gait disturbances.

Symptoms from intrinsic spinal tumors may be slowly progressive. Spinal cord tumors whether the result of a primary cord tumor or drop metastases may present with pain if intradural or infiltrative. Sensory level, motor weakness, and bowel/bladder dysfunction are common. Scoliosis occurs in up to one third of children with spinal cord tumors.

Infants and toddlers present a special challenge. Classic symptoms of increased ICP are uncommon in infants with

open fontanelles and unfused sutures, who tend to present with irritability, poor feeding or lethargy, and rapidly expanding head size with a bulging fontanel.

Diagnostic Considerations

Neuroimaging

Magnetic resonance imaging (MRI) remains the standard imaging modality used to characterize tumors and assess disease burden. Pre- and post-contrast sequences are useful in defining the primary tumor and disseminated lesions. T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences also highlight the extent of disease and surrounding edema. Specialized sequences such as magnetic resonance (MR) spectroscopy and MR angiography can provide useful adjunctive information. T2 ECHO or susceptibility-weighted sequences exaggerate blood breakdown products indicating areas of new or old hemorrhage in addition to calcium deposits.

Disseminated disease, suspected by history, exam, or preliminary radiographic data, warrants imaging of the entire neuraxis. Pial-subarachnoidal, leptomeningeal, and/or linear enhancement along the spinal column confirm disseminated disease (Figure 101-1). Extraneural metastases are exceedingly rare with primary CNS tumors in children and therefore full body surveys are not routine.

For two specific diagnoses, neuroradiographic features alone can lead to a specific diagnosis without further need for a pathologic specimen. Diffuse intrinsic pontine glioma is an example where tissue diagnosis has to date not been shown to alter management or outcome. In addition, children with optic pathway tumors associated with neurofibromatosis type I (NF1) seldom require tissue diagnosis.

Serum and CSF Markers

In general primary CNS tumors do not elaborate specific or identifying serum or CSF markers. The exceptions are nongerminomatous germ cell tumors which may differentially produce α-fetoprotein (α-FP) and β-human chorionic gonadotropin (β-hCG), detectable in both serum and CSF.

Cytological analysis of CSF is necessary when disseminated disease is suspected. In general, embryonal, choroid plexus tumors (both papilloma and carcinoma), and germ cell tumors (both germinomatous and nongerminomatous) spread by seeding. Craniopharyngiomas rarely disseminate. Glial based tumors can rarely spread along CSF pathways, therefore MRI evaluation of the spine is necessary if symptoms of back or nerve root pain are present.

Cautionary comment should be made regarding lumbar puncture (LP) in any patient with an intracranial mass. Any suspicion of increased ICP by neuroimaging, symptoms, or clinical exam should preclude LP given the risk of potentially life threatening downward herniation. When LP cannot be safely performed, CSF sampling for cytology and tumor markers can be obtained at the time of neurosurgical intervention when indicated.

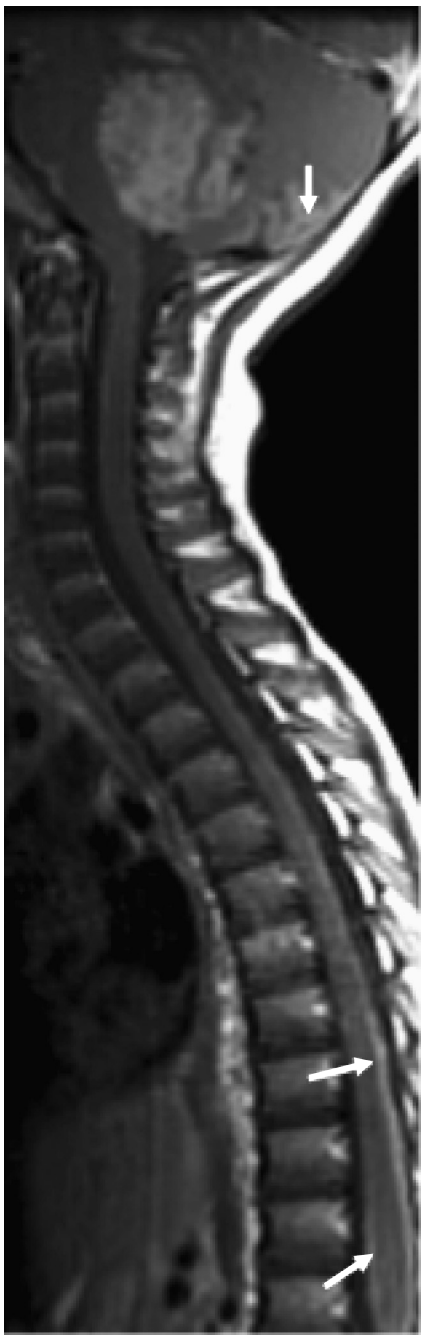

FIGURE 101-1. Postgadolinium, sagittal T1-weighted magnetic resonance imaging shows strong contrast enhancement of a medulloblastoma involving the fourth ventricle and diffuse subarachnoidal/leptomeningeal spread (arrows).

Electroencephalogram

There is little utility for electroencephalogram (EEG) as a diagnostic tool in neuro-oncology except to establish the presence of epileptic seizures. Some tumors tend to be particularly epileptogenic, including dysembryoplastic neuroepithelial tumors (DNTs), gangliogliomas, and oligodendrogliomas. Other tumors can cause seizures by mass effect, cortical irritation, or inflammation. In some cases, surgical resection of the tumor can be curative of medically refractory seizures.

Histopathology, Tumor Classification, Grading, and Staging

Histologic confirmation is a critical step in dictating the management of the majority of primary CNS tumors. The recently revised World Health Organization (WHO) classification of CNS tumors (2000) is predicated on several factors including histologic appearance (cell type and tissue pattern) and immunocytochemical markers. This schema divides pediatric brain tumors into those derived from tissues intrinsic to the brain (neuroepithelial) and those extrinsic (nonneuroepithelial; see Table 101-1).

The WHO grades tumors I-IV based on degree of anaplasia. Tumors that disseminate such as embryonal tumors are always considered high grade (IV) and are further staged on a modified Chang scale of M0-M4. M0 represents no evidence of metastatic spread, M1 denotes positive CSF cytology alone, M2 and M3 denote spread of disease seen on neuroimaging, and M4 designates systemic spread (rare in children).

Therapeutic Considerations

Acute Management

Occasionally patients with brain tumors present with increased ICP and signs of herniation warranting urgent or emergent management. In these cases, mannitol can be used as a temporizing measure to avoid cerebral herniation while taking the child emergently to the operating room. In most cases, symptoms from vasogenic edema surrounding CNS tumors can be managed with high dose steroids such as dexamethasone.

Central dysregulation of cardiac and respiratory drive can occur with intrinsic brain stem lesions or extrinsic forces compressing the brain stem. Thus, close cardiorespiratory monitoring if not intensive care monitoring may be necessary. In addition, strict monitoring of fluid intake and urine output is essential. Fluid and electrolyte imbalances are commonly seen with tumors involving the suprasellar region. These are usually the result of hypothalamic-pituitary axis dysfunction. Syndrome of inappropriate antidiuretic hormone and cerebral salt wasting both result in hyponatremia but should be differentiated as management differs (fluid restriction versus fluid and salt replacement). Diabetes insipidus (DI) is a frequent complication after craniopharyngioma or germ cell tumor therapy but can present in the preoperative period as well. DI is treated with desmopressin.

Seizures are the presenting symptom in up to 30% of cortical tumors but in their absence the use of antiepileptic drugs for prophylaxis is controversial. Phenytoin or fosphenytoin can be used in the immediate period with transition to a more appropriate long-term seizure medication once stabilized. Routine EEG can be informative in determining the need for and duration of antiepileptic drug therapy.

Tumor-Directed Therapy

Neurosurgical Approaches

The role of neurosurgery includes obtaining tissue for diagnosis, resection, or reduction of the tumor as treatment or as a precursor to other treatments, and CSF diversion to treat increased ICP. Gross total resection when possible has remained the treatment of choice for most tumors and in particular low-grade tumors, such as pilocytic astrocytomas.

Advances in neurosurgical techniques over recent decades, such as the development of dissecting microscopes, utilization of intraoperative MRI, cavitron ultrasonic aspirator, laser, and computed tomography-guided biopsy have made previously impossible resections possible and have benefited surgical outcomes. However, certain regions of the brain remain inoperable including the brain stem, thalamus, motor area, and deep gray matter structures.

For tumors causing obstructive hydrocephalus, ventriculoperitoneal (VP) shunting is sometimes necessary. However, for tumors that tend to spread through CSF pathways, dissemination via CSF shunting into the peritoneal cavity has been reported. For these patients, efforts are made to avoid VP shunt placement when possible. Other modes of CSF diversion, such as third ventriculostomy, may thus become necessary in cases of obstruction of the cerebral aqueduct or fourth ventricle. Nevertheless, certain patients will invariably require extracranial CSF diversion in which case placement of a shunt is recommended.

Radiation Therapy

Radiotherapy is a common adjuvant therapy. Despite recent advances in delivery technique, radiation treatment continues to have substantial neurologic morbidity and risk of secondary malignancy (Table 101-3). The developing CNS is particularly sensitive to radiation, which limits the use of radiotherapy in patients < 36 months of age and with caution up to 7 years of age.

TABLE 101-3. Radiation Toxicity

Acute (< 1 month)
Local alopecia
Erythema ± desquamation
Otitis externa, secretory otitis media
Sub-acute (1–6 months)
Somnolence syndrome: lethargy, anorexia, headache
Transverse myelitis/Lhermitte's sign
Late-effects (> 6 months)
Radiation necrosis
Moyamoya vasculopathy
Secondary malignancy
Neurocognitive impairment
Neuroendocrine impairment
Vision and hearing loss

Advances in radiation therapy over recent decades include fractionation techniques, stereotactic radiosurgery, stereotactic radiotherapy, radiation sensitizers, brachytherapy, and proton beam irradiation. Fractionation and hyperfractionation allow for an increased total dose of radiation by delivering the treatment in fractions over multiple days rather than one large dose. The advantage is that tumor cells are killed in proportion to the summed dose, whereas normal tissue is relatively spared. A large single fraction, as used in radiosurgery, kills both tumor and normal cells. This can only be used when the loss of normal neural tissue does not result in significant neurologic disability.

Conformal approaches, such as intensity-modulated radiation therapy, sculpt radiation-sparing critical neural structures from excessive radiation. This technique is widely available and limits dose exposures to normal tissue relative to conventional techniques. Brachytherapy is usually administered through implantation of radioactive seeds, but this technique can only be used in a limited number of cases and dosimetry is less certain.

Proton beam therapy offers some promise in addressing exit dose radiation. Currently, high-energy photons derived from x-rays or γ-rays are the commonest energy source used in radiotherapy. Protons have superior properties to photons in that they deposit their energy over a narrower area limiting exposure of tissue in front of and behind the target area. However, proton beams have to be generated in large cyclotrons, which are available in a limited number of centers worldwide.

Chemotherapy

Recent decades have seen chemotherapy increasingly incorporated as adjuvant or primary treatment in many tumors. Chemotherapy is the primary therapy for low-grade astrocytomas in children less than 10 years old. Infants with malignant tumors with metastatic potential are treated with chemotherapy to avoid craniospinal radiation. In the case of choroid plexus tumors, chemotherapy prior to surgical resection can decrease the risk of hemorrhage at the time of resection. Relapsed medulloblastoma and other embryonal, disseminating, and high-grade tumors are currently treated with myeloablative doses of chemotherapy followed by peripheral blood stem cell rescue.

In general, most chemotherapy protocols use multiple agents. In conjunction with surgical resection and radiation therapy (when age permits), standard and high-risk medulloblastomas are treated with vincristine, cisplatin, CCNU (Lomustine), and cyclophosphamide. Current low-grade glioma protocols include vincristine, carboplatin, and combinations of thioguanine, procarbazine, CCNU, vincristine (TPCV). Temozolamide is now widely used for high-grade glial tumors.

A variety of clinical trials are underway through large cooperative groups, including the Children's Oncology Group and the Pediatric Brain Tumor Consortium, as well as smaller multicenter and single-center groups. Agents being studied include molecularly targeted therapies, such as antiangiogenic compounds, differentiation factors, various receptor tyrosine kinase and tyrosine kinase inhibitors, cell cycle inhibitors, and gene therapy.

Management of Selected Tumors

Embryonal Tumors

Medulloblastomas

Medulloblastomas account for 10 to 20% of pediatric brain tumors and are the most common embryonal tumor of childhood. The peak incidence is from 5 to 7 years of age and they are rare beyond 20 years of age. They occur exclusively in the cerebellum and are thought in most cases to arise from cerebellar granule cell precursors. Clinical presentation is often related to increased ICP from obstructive hydrocephalus, namely headache and vomiting. Ataxia and cranial nerve deficits are other common presenting signs. Disseminated disease is evident in more than 20% of patients at diagnosis, with a particularly high incidence in infants.

Traditionally, medulloblastomas have been divided into two principal histologic subtypes, both with the potential to disseminate and considered WHO grade IV tumors. The majority are termed *classical medulloblastomas* and are highly cellular "small blue cell tumors" with compact nuclei and minimal cellular differentiation. Classical medulloblastomas tend to localize to the cerebellar midline/vermis. Approximately, 25% of medulloblastomas are of the desmoplastic variant, which typically localize to the cerebellar hemispheres and occasionally the cerebellopontine angle. MRI reveals a homogeneous hypointense T1-weighted signal and contrast enhancement (see Figure 101-1). Cyst formation, necrosis, and hemorrhage are not uncommon.

Because medulloblastomas as with all embryonal tumors tend to disseminate, treatment consists of surgical resection, radiation to the whole neuraxis with local "boost," and multiagent chemotherapy. Historically, standard risk and thus favorable prognosis has been associated with gross or near total resection, age > 3 years, and absence of metastasis at the time of initial diagnosis. Disseminated disease, subtotal resection, and age < 3 years are considered poor risk. For good-risk patients, the overall 5-year-survival rate approaches 80%, but unfortunately, survivors have significant learning and medical disabilities consequent of the rigorous treatment warranted by this aggressive cancer. Current standard risk protocols have reduced doses of craniospinal radiation in an effort to minimize some of the untoward effects of this aspect of treatment.

Recently, high-throughput gene expression profiling of medulloblastoma has identified molecular signatures that are highly predictive of outcome at the time of tumor diagnosis. Such data will eventually help direct treatment strategies reserving the most rigorous protocols for those who fall into the highest risk categories.

Supratentorial/Cerebral PNETs

Historically, the term *PNET* was used to describe a series of tumors sharing common histologic features and a tendency to disseminate throughout the nervous system. However, these tumors differed in their location and moreover in their prognosis after therapy. This subclass of CNS tumors included medulloblastoma, supratentorial PNET, ATRT, as well as retinoblastoma, ependymoblastoma, pineoblastoma, medulloepithelioma, and intracranial neuroblastoma. Advances in molecular characterization have made it clear that each is a distinct entity, likely arising from aberrations in developmental programs unique to the tissue in which the tumor develops. In this chapter, PNET will thus refer to all supratentorial/cerebral PNETs distinct from the other embryonal tumors.

PNETs account for 1 to 2% of childhood CNS tumors. They occur in the first decade of life and are thought to originate from primitive neural progenitors, possibly the multipotent cells of the subpial granular layer of the cerebral hemispheres. They commonly develop in the frontoparietal regions, arising either cortically or in the deep periventricular white matter. They can also develop in the suprasellar or pineal region. Thus, clinical presentation varies depending on location. Seizures and motor deficits can occur when the tumor involves the cortex, while symptoms of increased ICP, endocrinopathy, and visual deficits can result from suprasellar tumors. Infants may present with a rapidly increasing head circumference.

MRI shows heterogeneous features. Peritumoral edema is common though often minimal given the large size of these tumors.

All PNETs are considered high risk regardless of age, extent of resection, or the presence or absence of disseminated disease. As such, they are treated similarly to high-risk medulloblastoma, with surgical resection followed by radiation to the whole neuraxis and multiagent chemotherapy. Overall survival rates at 5 years are reported from 30 to 50% with the youngest children accounting for the lowest survival percentages.

ATRTs

First described in 1986 by Rorke and colleagues, ATRT is a relatively new classification of tumor and only in the last decade has it clearly become a distinct entity amongst other embryonal tumors. ATRT account for 2 to 4% of childhood CNS tumors. These high-grade tumors occur most commonly in children younger than 2 years of age and are evenly divided between the infratentorium and supratentorium. The infratentorial ATRT commonly involves the cerebellum with a predilection for the cerebellopontine angle. These tumors tend to be aggressive and frequently spread throughout the CNS. Presenting symptoms depend on location but include those resulting from increased ICP, cranial nerve involvement, or seizures, neuroendocrine, and visual disturbance from supratentorial lesions. Neuroimaging reveals heterogeneous enhancement, cyst formation, and sometimes hemorrhage. Loss or reduction of nuclear SNF5/INI1 antibody staining confirms the diagnosis of ATRT and distinguishes it from other embryonal tumors.

The usual age of presentation being less than 2 years precludes the use of craniospinal radiation therapy. Long-term survival is very poor with the overall survival rates of less than 10% in children 3 years of age and younger at diagnosis. Most patients die within 12 months of diagnosis. Older children fare better due to the addition of full neuraxis radiotherapy to the treatment regimen, with long-term survival nearing 70% in some series.

Pineal Parenchymal Tumors

Pineoblastomas, pineocytomas, and pineal tumors of intermediate differentiation account for 1 to 2% of childhood CNS tumors. It is thought that these tumors arise from pinocytes or their precursors. They are much less common than other tumors that tend to localize to the pineal region, such as germ cell tumors. Given their location, clinical presentation may manifest as Parinaud syndrome. In addition, their proximity to the cerebral aqueduct can cause an obstructive hydrocephalus and consequently increased ICP.

Pineoblastomas are highly malignant neoplasms, which occur at any age and have a tendency to disseminate early in their course. They appear as large, lobulated, generally solid tumors with areas of cystic necrosis on MRI and

enhance homogeneously with contrast. Imaging of the whole neuraxis should be performed given the tendency of pineoblastoma to disseminate. Treatment of pineoblastoma is similar to other high-risk embryonal tumors with gross or near total surgical resection, chemotherapy, and radiation therapy to the whole neuraxis when possible. The overall prognosis for patients with pineoblastomas is generally poor.

Pineocytomas are significantly less aggressive and typically present during adolescence.

Current management of patients with low-grade pineocytomas is complete surgical resection followed by careful surveillance with serial MRIs. Neither adjuvant radiation nor chemotherapy has been shown to provide any clear benefit for pineocytoma.

Glial Tumors

Astrocytomas

Astrocytomas are a large class of CNS neoplasms in which the predominant cell types develop along the astroglial lineage. They account for the largest group (greater than 50%) of CNS neoplasia in the pediatric population with the large majority (80–90%) being pilocytic or low-grade astrocytomas.

The WHO scheme classifies pilocytic astrocytomas as grade I, fibrillary astrocytomas as grade II, anaplastic astrocytomas as grade III, and glioblastoma multiforme (GBM) as grade IV. Grade I lesions predominate in childhood whereas GBM is far more common in adulthood.

Pilocytic or grade I astrocytomas are the commonest childhood astrocytoma. Peak incidence is around 10 years of age thus they are often referred to as juvenile pilocytic astrocytomas. The majority localize to the cerebellum (60%) with the second most common site being the diencephalon/optic pathway. However, pilocytic astrocytomas can be found anywhere along the entire neuraxis including the brain stem, cerebrum, and spinal cord. Cerebellar astrocytomas tend to arise in the cerebellar hemispheres and thus can present with lateralized ataxia. They can also cause obstruction to CSF flow resulting in signs and symptoms of increased ICP. Rarely, dissemination along CSF pathways can occur, which is usually associated with astrocytomas localized to the hypothalamus.

Grade II astrocytomas are classified as four histologic variants: fibrillary, protoplasmic, gemistocytic, and mixed. Fibrillary astrocytomas are the most frequent grade II subtype and can arise anywhere along the neuraxis. Those found in the cerebellum tend to have a predilection for the midline with extension into one or both cerebellar hemispheres. Protoplasmic and gemistocytic astrocytomas are usually cortically based.

Anaplastic astrocytomas are rare and likely represent an intermediary lesion transitioning from a low-grade tumor to a GBM. These tumors tend to localize to the cerebral hemispheres but have also been found elsewhere along the neuraxis. Anaplastic astrocytomas can progress to GBM.

GBM are usually found in the cerebral hemispheres but also arise in the brain stem as pontine gliomas. Despite being the most common primary brain tumor in adults, they are much less common in childhood with less than 10% of total GBMs occurring during childhood. Radiographically, they appear as a heterogeneous mass. Ring enhancement surrounding a necrotic center is the most common finding on postcontrast MRI sequences but multiple rings may be seen. Signs of recent and remote hemorrhage are common. Vasogenic edema can be impressive and adds significantly to the mass effect. Despite the apparent demarcation on neuroimaging, GBMs diffusely infiltrate into the brain, commonly crossing the corpus callosum.

Treatment protocols for astrocytomas are dictated by tumor grade, subtype, and location. In patients with pilocytic astrocytomas, total resection alone leads to > 95% long-term survival. Infiltrative cerebellar astrocytomas may be less amenable to total resection. However, patients with microscopic and even gross residual tumor after surgery may experience long-term progression-free survival without any postoperative therapy. Regardless, frequent surveillance imaging to monitor for disease progression is necessary in the immediate postoperative years. For residual or progressive disease in children less than 10 years of age, chemotherapy is currently the recommended primary treatment. Adjuvant radiation therapy is reserved for older children (> 10 years) or those younger children who fail chemotherapy.

High-grade gliomas are treated with radical surgical resection followed by radiation, which combined has been shown to improve prognosis. Temazolamide given concurrently and after radiation therapy has also been shown to improve outcomes. The 5-year survival for anaplastic astrocytoma may exceed 25% while for GBM it is no greater than 10%.

Visual Pathway Gliomas

Glial-based tumors of the visual pathway account for 5 to 10% of primary CNS tumors in children. Nearly, 75% occur during the first decade of life with a peak incidence at 3.5 years of age. In general, visual pathway tumors are low-grade astrocytomas, usually pilocytic, and they most often involve both optic nerves, the chiasm, and the optic tracts. Less often, they are confined to a single optic nerve. Gliomas involving the chiasm may also extend to invade the hypothalamus or the thalamic nuclei. NF1 is associated with 50 to 70% of isolated optic nerve tumors and 16 to 20% of patients with chiasmal or deeper optic tract tumors. Conversely, patients with NF1 have a 15% chance of developing a visual pathway tumor. Bilateral optic nerve gliomas are pathognomonic for NF1.

MRI reveals visual pathway gliomas as isointense to the cortex and hypointense to white matter on T1-weighting. On T2-weighted images a mixed appearance with isointense to hyperintense relative to white matter and the cortex. Strong enhancement with contrast is common, especially with the more posteriorly localized lesions (Figure 101-2). Calcifications and cystic components can also be seen.

Isolated unilateral optic nerve tumors comprise 10% of visual pathway tumors and have a high degree of association with NF1. These tumors can result in optic atrophy and proptosis, which can sometimes be disfiguring. If progressive disfiguring proptosis and significant visual loss occur, surgical resection is warranted. Otherwise, expectant observation is the current management strategy until symptomatic or radiographic progression occurs at which time resection is again considered. Complete surgical resection results in greater than 90% survival at 15 years.

Involvement of both optic nerves and chiasm represent 33% of visual pathway tumors, while another 33% involve the chiasm itself and 25% predominantly the hypothalamus. Chiasmal involvement results in visual loss, manifested as poor visual tracking in infants, and sometimes see-saw nystagmus; chiasmatic tumors that extend into the third ventricle result in increased ICP and symptoms thereof; and tumors extending into the hypothalamic region result in growth and endocrine disturbances. In the youngest age group, diencephalic syndrome can be the presenting symptom of deeper-seated and more extensive optic tract gliomas.

Visual pathway tumors can take a variable course with some reports of spontaneous tumor regression, most often seen in children with NF1. Thus careful, expectant observation is considered if there is little visual compromise and the child is clinically stable. Surgical management is considered for exophytic chiasmatic tumors causing mass effect or hydrocephalus but is relatively contraindicated for diffuse or broadly infiltrative disease. Few patients are helped by extensive surgical resection, and resection of hypothalamic tumors can result in neuroendocrine and intellectual difficulties. Therefore, children less than 10 years of age and patients with NF1 who have progressive disease receive chemotherapy as their primary treatment. Regimens using vincristine and carboplatin afford 2- and 3-year-survival rates of 75% and 68%, respectively. Moreover, children less than 5 years of age seem to have the most favorable response.

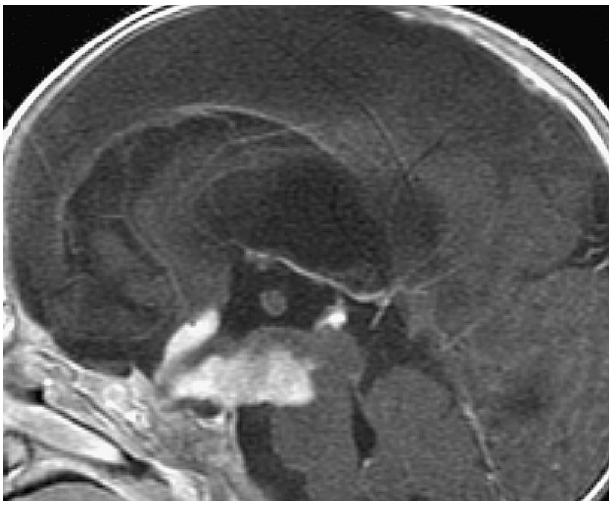

FIGURE 101-2. Postgadolinium, sagittal T1-weighted magnetic resonance imaging reveals an optic pathway glioma and resultant obstructive hydrocephalus.

Radiation therapy to the bed of the tumor can also effect tumor stabilization and is considered first-line treatment for persons 10 years and older who do not have NF1. Due to long-term cognitive, neuroendocrine, neurovascular, and visual sequelae, radiotherapy is only considered in children less than 10 years if their tumors progress through chemotherapy. Children with NF1 appear to have the most profound late-effects from radiotherapy therefore they should receive radiation only for symptomatic disease progression despite treatment with chemotherapy. Proton beam radiotherapy, where available, may diminish the untoward effects seen with conventional and conformal techniques.

Brain Stem Gliomas

Brain stem gliomas account for 10 to 15% of pediatric CNS tumors. The peak incidence is between 5 and 10 years of age. The large majority (80%) are diffuse, high-grade (WHO grade III and IV), infiltrative lesions localizing to the pons. These are termed *diffuse pontine gliomas*, which are aggressive and carry a very poor prognosis. Symptomatically, pontine gliomas commonly present with multiple cranial nerve dysfunction. The long tracts can also be affected resulting in weakness of the limbs and imbalance. As pontine gliomas tend to grow aggressively, symptoms can progress rapidly. On MRI, pontine gliomas are hypointense on T1-weighted images and hyperintense on T2-weighted series. Enhancement is variable. Pontine gliomas are considered inoperable given their widely infiltrative nature. Therefore, radiation therapy is the main treatment modality. Invariably symptoms often improve dramatically during and immediately following the course of radiation, but problems usually recur at 6 to 9 months with rapid progression thereafter. Survival past 12 to 14 months is uncommon.

Low-grade brain stem gliomas are less common and typically take on an indolent course with symptoms developing over months, sometimes years. They can be grouped into focal tumors, dorsally exophytic tumors, and cervicomedullary tumors. Focal tumors frequently involve

the tectum but also occur in the tegmentum, cerebral peduncles, pons, and medulla. Tectal lesions result in aqueductal stenosis and hydrocephalus but notably little in the way of cranial nerve deficits. Other focal brain stem tumors can also result in CSF obstruction but more often cause cranial nerve dysfunction, usually unilateral with a contralateral hemiparesis. The majority of tectal gliomas can be managed with CSF diversion alone with close follow-up monitoring. However, progressive focal brain stem tumors require further treatment with chemotherapy followed by radiation if necessary.

Dorsally, exophytic tumors probably arise from the subependymal cells below the floor of the fourth ventricle. There is minimal penetration into the brain stem but rather extension into and often filling of the fourth ventricle. Obstructive hydrocephalus is common while cranial nerve deficits are rare. Proximity to the cerebellar peduncles can result in ataxia. These tumors are managed with surgical resection, especially the exophytic component of the tumor. Repeat surgery or chemotherapy followed by radiotherapy as needed is considered for tumor recurrence or progression.

Lesions involving the lower two-thirds of the medulla and the cervicomedullary region are usually dorsally exophytic pilocytic astrocytomas. They result in lower cranial nerve deficits, such as swallowing difficulties, in addition to long-tract signs. Surgical resection is the main treatment modality, however, surgical morbidity with extensive resection can be significant warranting alternative strategies, such as partial resection, followed by chemotherapy then radiation.

Oligodendrogliomas

Oligodendrogliomas are rare in the pediatric population with only 6% of oligodendroglial tumors occurring during childhood. Oligodendrogliomas have been associated with NF1 and tuberous sclerosis but the majority are sporadic. Most oligodendrogliomas are slow-growing indolent tumors but can present as or evolve into the more aggressive anaplastic oligodendroglioma. Seizures are the most common presenting symptom in the majority of patients as these tumors have a tendency to diffusely infiltrate the cerebral cortex, usually involving one of the frontal lobes.

MRI of these tumors show signal heterogeneity but relative hypointensity on T1-weighted sequences and hyperintensity on T2-weighted sequences. Peritumoral edema can be seen but less often with low-grade lesions. Small cystic-appearing regions and hemorrhage are commonly found as is calcification. Contrast enhancement can be seen and holds prognostic significance as a strong negative predictive factor. In general, low-grade lesions do not enhance while anaplastic lesions enhance.

Combined loss of 1p and 19q is a significant predictor of overall survival in anaplastic oligodendroglioma, associated with longer recurrence-free survival and responsiveness to chemotherapy. Phosphatase and tensin homologue deleted by chromosome 10 *(PTEN)* gene alterations are associated with a poor prognosis.

Treatment strategy requires biopsy to confirm the specific tumor type and genetic characteristics. For anaplastic oligodendrogliomas with combined 1p/19q chromosomal deletions, chemotherapy is the primary treatment of choice. Otherwise, complete resection is attempted, which affords a 5-year-survival rate of over 90%. If total resection is not possible, radiation therapy is considered although controversial as to benefit. Long-term follow-up and continued radiographic surveillance is important as late progression of disease is common. Recurrent tumors are treated with a second surgery, radiation therapy, or chemotherapy. Patients with epilepsy should be treated with anticonvulsant therapy. Ideally, epilepsy medications metabolized through pathways other than the liver should be used as they are less likely to interact with chemotherapeutic agents or add to their liver toxicity.

Ependymomas

Ependymomas account for 10% of childhood CNS tumors. There is a bimodal peak incidence at age 5 years and then again at age 34 years, but the majority of patients are diagnosed before the age of 5 years. These tumors resemble normal ependymal cells and can occur anywhere along the ependymal lining including the entire ventricular system and full length of the spinal canal and filum terminale. However, greater than 60% are localized to the infratentorium. These often occupy the fourth ventricle and commonly extend through the foramen of Lushka into the cerebellopontine angle cistern (Figure 101-3). Thus, presenting symptoms are usually the result of increased ICP, but cranial nerve deficits are also seen. Supratentorial ependymomas present with varied focal neurologic findings. Spinal ependymomas present with motor, sensory, and bowel/bladder dysfunction.

Ependymomas are classified as four types: subependymoma and myxopapillary (grade I), low-grade (grade II), and anaplastic (grade III). Ependymomas spread by direct invasion, but dissemination has been reported in up to 10% of low-grade cases and upwards of 30% of infratentorial high-grade tumors. Thus, staging is a critical aspect in dictating management.

MRI shows heterogeneous signal with solid portions hypointense on T1-weighting and hyperintense on T2-weighting. Almost all ependymomas have irregular and patchy contrast enhancement with intratumoral cysts common in supratentorial ependymomas (see Figure 101-3).

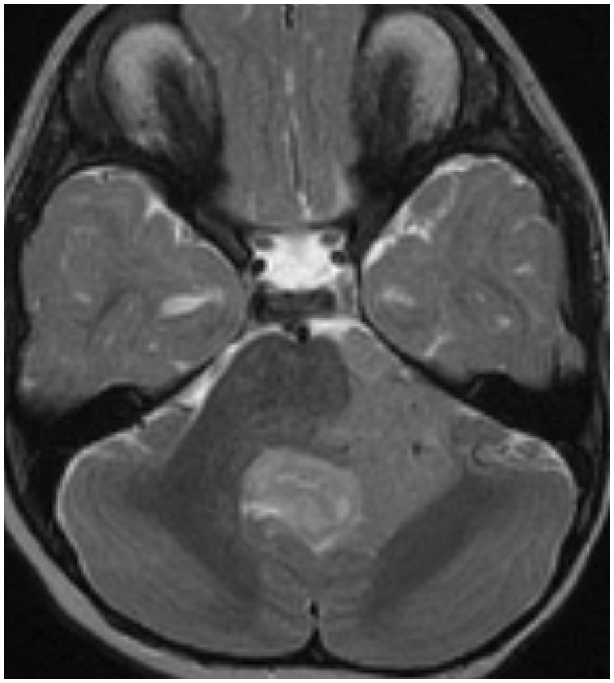

FIGURE 101-3. Axial T2-weighted magnetic resonance imaging reveals an ependymoma occupying the fourth ventricle, demonstrating classic extension through the Foramen of Luschka to the cerebellopontine angle cistern.

Surgery and radiation therapy are the major treatment modalities. Aggressive gross total surgical resection is strongly recommended as the amount of residual tumor after resection is one of the most important predictors for long-term outcome. However, extensive resection may not be possible for posterior fossa or spinal cord ependymomas. Resection is normally followed by radiotherapy with craniospinal radiation used only if there is evidence of dissemination by cytology or imaging. Chemotherapy has not been proven beneficial in several clinical studies, but radiosensitizing/preradiation chemotherapy can be considered in cases where only sub-total resection can be accomplished.

Significant independent predictors of outcome include age and extent of tumor resection. Patients < 3 years of age and children with subtotal resection have significantly worse outcomes. The overall 5-year-survival rates are reported at 25% for infants (< 1 year), 46% for children aged 1 to 4 years, and greater than 70% for children older than 5 years. Independent of age or tumor grade, complete tumor resection followed by local radiation affords survival rates of 60 to 80%, whereas partial resection followed by nonsurgical treatment only affords 30% survival.

Ependymoblastoma represents an embryonal form of ependymal tumor that occurs in infants and children younger than age 5 years of age and has historically been categorized as a form of PNET. This tumor is distinct from the other types of ependymomas, including anaplastic ependymoma, both biologically and pathologically. Ependymoblastomas as with other embryonal tumors tend to disseminate requiring craniospinal radiation when age allows. Children with this tumor rarely live more than 2 to 3 years and are treated with protocols similar to high-risk medulloblastoma.

Neuronal and Mixed Neuronal-Glial Tumors

Gangliogliomas

Gangliogliomas represent 4% of all pediatric brain tumors. They occur most commonly in the first 2 decades. These slow-growing tumors have both neuronal and glial components. The most common sites are the temporal lobes and third ventricle, but they also occur in the spine. Seizures are the most common presenting symptom and an association with disorders in cortical migration has been posited.

MRI shows a well-defined solid or mixed cystic/solid mass with minimal or no mass effect. Calcification is common. Enhancement pattern is variable, often peripheral. Lesions can be quite extensive at the time of diagnosis.

Complete surgical resection affords long-term survival near 100%. Radiation therapy can be necessary for subtotal resection with overall survival of 80 to 90%.

DNTs

DNTs were initially described as a curable tumor associated with intractable epilepsy. DNTs usually appear in the first 2 decades of life. They are hypothesized to arise from the external granular layer of the cortex. Two-thirds occur in the temporal lobe and one-third in the frontal lobe, thus the most common symptom is seizures, which are often refractory to multiple medications. Often DNTs are diagnosed years after the onset of seizures. MRI shows a nodular cortical lesion without edema or mass effect. A megagyric or multicystic appearance can be seen. Occasionally, DNTs enhance or contain calcifications. Calvarial remodeling is commonly seen.

Surgical resection is often curative of DNTs. Seizures usually improve as well but recurrence of seizures occurs in nearly 40% within 5 years. Presurgical invasive EEG monitoring is common when sensitive areas are involved. Patients rarely have tumor progression even when complete surgical resection is not possible, thus radiation and chemotherapy are typically not used to treat DNTs.

Choroid Plexus Tumors

Choroid plexus tumors represent 1 to 3% of all childhood brain tumors with choroid plexus carcinomas comprising about 10 to 15% of these. The majority (85%) occur before the age of 5 years but can present congenitally with

approximately half presenting within the first year of life. These tumors arise from the choroid plexus epithelium with papillomas considered low grade (WHO I) and choroid plexus carcinomas considered grade III-IV lesions. The lateral ventricles, especially the trigonal area, are the most common locations in the pediatric population (as opposed to the fourth ventricle in adults). Neuroimaging shows a well-demarcated strongly enhancing intraventricular mass with hydrocephalus.

Choroid plexus papillomas grow slowly and result in hydrocephalus due to CSF overproduction by the tumor. Gross total resection of a choroid plexus papilloma usually results in cure with long-term survival close to 100%. However, surgical complications can arise as this tumor is notably hemorrhagic. Additionally, hydrocephalus resolves in only half of the cases requiring VP shunting.

Choroid plexus carcinomas commonly invade nearby tissue and spread widely via the CSF, although dissemination can be seen with papillomas as well. Gross total resection of choroid plexus carcinomas remains the primary treatment and the most important predictor of outcome. However, tumor vascularity and friability is even more problematic than with the papillomas thus total resection carries a high perioperative complication rate. When gross total resection cannot be performed, multiagent chemotherapy can reduce both tumor volume and vascularity allowing for a second-stage resection and more complete removal. Otherwise, resection is often followed by chemotherapy and craniospinal irradiation resulting in overall survival of 65%.

Germ Cell Tumors

Germ cell tumors account for 1 to 3% of all childhood CNS tumors. They are most commonly diagnosed during adolescence with a peak incidence around puberty. These tumors are histologically classified as two fundamental subtypes, germinomatous and nongerminomatous, with each subtype having a different prognosis and treatment. The germinomatous germ cell tumor is simply termed a pure germinoma. The nongerminomatous germ cell tumors (NGGCT) include embryonal carcinoma, yolk sac tumor, choriocarcinoma, and immature teratoma. NGGCT typically occur earlier in life.

Germ cell tumors tend to localize to the pineal and suprasellar regions with the former being more common by 2:1. Nonetheless, 5 to 10% are found in both regions at the time of diagnosis. Pineal region tumors commonly present with Parinaud syndrome and/or signs of increased ICP, while suprasellar germinomas can present with visual field deficits and neuroendocrine axis dysfunction, most commonly DI. Delayed or precocious sexual development, hypopituitarism, and isolated growth failure are also commonly seen. Neuroimaging shows a solid midline mass with prominent enhancement. Teratomas also contain intratumoral cysts with calcifications and fat.

Serum and CSF levels of α-FP and β-hCG mimic the immunohistochemical patterns of the various germ cell tumors. These markers can aid in diagnosis and help monitor response to treatment. α-FP is highly positive in mixed germ cell tumors, endodermal sinus tumors, and to a lesser extent in embryonal carcinomas. β-hCG is highly positive in mixed germ cell tumors and choriocarcinomas, less so in endodermal sinus tumors and embryonal carcinomas, and weakly positive in pure germinomas. Teratomas express neither β-hCG nor α-FP.

Treatment and overall prognosis is dictated by histologic subtype. Germinomas are very sensitive to radiation therapy and over 85 to 95% of patients are cured with radiation therapy alone. Attempts to treat these tumors with chemotherapy alone have resulted in 60 to 70% overall survival. Some NGGCT subtypes also respond to radiation therapy, but cure rates are lower thus chemotherapy is used as an adjuvant. NGGCT have a reported collective 5-year-survival rate ranging from 40 to 70% after chemotherapy and full-dose craniospinal irradiation. The mixed germ cell tumor carries a slightly better prognosis. Teratomas are typically treated with surgical resection. Mature teratomas have a good overall prognosis while immature teratomas have an overall survival rate reported at 50 to 70%.

Craniopharyngiomas

Craniopharyngiomas represent 5 to 13% of childhood brain tumors with peak incidence between 5 and 10 years of age. Craniopharyngiomas are low-grade tumors derived from embryonic remnants of Rathke's pouch, the precursor of the adenohypophysis. Thus, craniopharyngiomas can develop anywhere from the sella turcica up the pituitary stalk to the hypothalamus and floor of the third ventricle. They tend to grow slowly and result in vague symptoms at first with insidious progression. Diagnosis usually occurs 1 to 2 years after symptom onset, which most commonly include headache, neuroendocrinopathy, and visual disturbances. Presenting endocrinopathies include hypothyroidism (~40%), adrenal failure (25%), and DI (20%). Young patients usually present with growth failure and delayed puberty. Visual deficits are noted in 40 to 70% of patients at the time of diagnosis, and vision rarely improves following tumor therapy. Damage to the surrounding thalamus and frontal lobes results in further endocrine and autonomic dysregulations and notable sequelae including morbid obesity, deficits of memory, affective disorders, and apathy.

The radiographic hallmark is a calcified cyst in the sellar/suprasellar region. Calcifications are found in 90% of childhood craniopharyngiomas, either in the rim of the tumor or in the solid regions of the tumor. Most lesions

(70–75%) are cystic and often multilobulated. Frequent recurrent expansion of these cystic structures can be a chronic problem after therapy requiring intermittent aspiration by stereotactic puncture or through Ommaya reservoir placement.

The current treatment algorithm is gross total resection of the craniopharyngioma without hypothalamic injury or subtotal resection with no hypothalamic injury followed by postoperative radiotherapy. Intracystic brachytherapy and intracystic chemotherapy have been used for large cysts associated with craniopharyngiomas, but systemic chemotherapy has not been shown to provide any benefit to date.

After complete resection, the 10-year-overall survival rates are reported from 86 to 100%. Sub-total resection or recurrence treated with surgery and radiation affords survival rates of 57 to 86%. However, successful outcome as determined by the ability to maintain independent social functioning and recurrence of tumor yields a far lower percentage. Obesity and sleep dysregulation are common and often overlooked morbidities. Specific deficits of memory and organization together with slow speed of information processing have a significant negative impact on school and vocational performance despite the fact that many of these children have normal intelligence quotient following therapy. As many endocrinopathies can be treated with replacement therapies, the neuropsychological and emotional deficits represent the major long-term limitations.

Spinal Cord Tumors

Primary spinal cord tumors comprise 1 to 2% of all childhood nervous system tumors. As is the case for primary brain tumors, such lesions are histologically heterogeneous. Low-grade astrocytomas and gangliogliomas comprise 70% of all intramedullary spinal cord tumors. Other intramedullary tumors include ependymomas, higher-grade glial tumors, and rarely embryonal tumors.

Because spinal cord tumors can grow slowly overtime, symptoms may develop over months. Symptoms commonly include chronic neck or back pain, decreased motor skills, weakness progressing to paralysis, sensory loss, loss of bowel or bladder control, and spinal deformity with scoliosis seen in up to one-third of children with spinal cord tumors. Prompt diagnosis and treatment are necessary to prevent permanent deficits.

Imaging characteristics depend on tumor type although appearance and location of lesions can sometimes hint at the diagnosis. Myxopapillary ependymomas have a tendency to develop in the conus and cauda equina regions. Both ependymomas and low-grade astrocytomas can be associated with large cysts that extend rostrally and caudally (Figure 101-4). These cysts can represent a syrinx or tumor as in the case of a "holocord" astrocytoma.

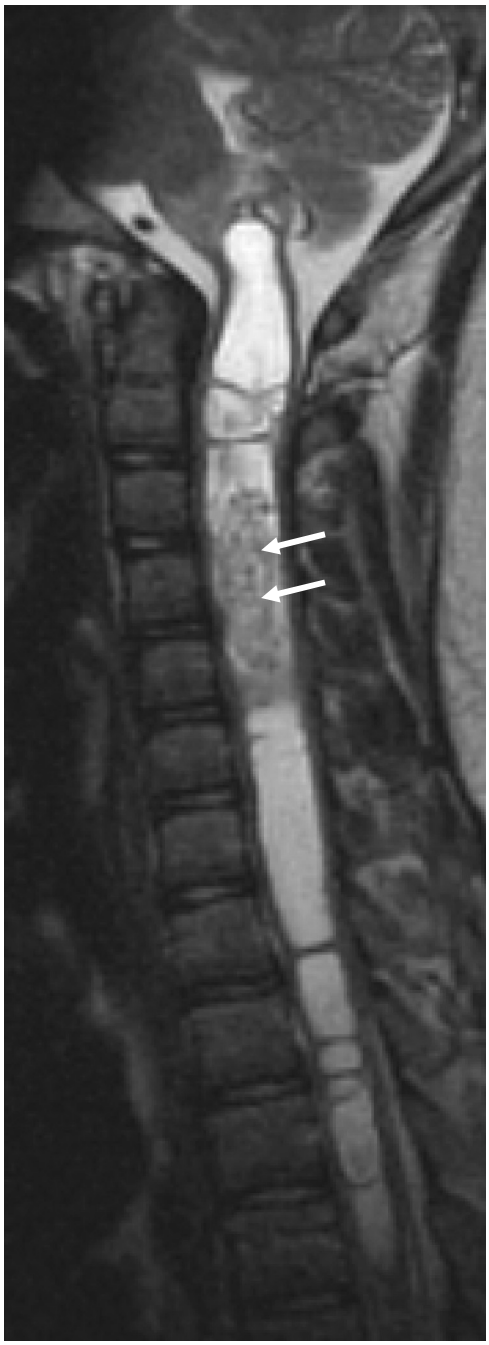

FIGURE 101-4. Sagittal T2-weighted magnetic resonance imaging reveals an ependymoma (arrows) and septated rostral and caudal syringes.

Treatment and prognosis of spinal tumors depend on histological type and location. Surgical resection is the treatment of choice for extramedullary tumors. Partially resected tumors, high-grade, and inoperable tumors are also treated with radiation and chemotherapy.

Summary

Children with primary brain and spinal cord tumors present major therapeutic challenges given the vast heterogeneity of tumor types. Moreover, treatment strategies continue to evolve, aiming for progression-free survival while limiting untoward side effects. As neurosurgical and radiotherapy techniques are pushed to their practical limits, it is becoming increasingly clear that chemotherapy and importantly molecularly targeted therapies will have an expanding role in the future management of pediatric CNS tumors. Optimal outcomes require the coordinated efforts of multiple pediatric specialists and therapists at the time of diagnosis, throughout treatment, and in long-term follow-up. This multidisciplinary team includes collaboration between neurosurgeons, radiation therapists, neuroradiologists, neuropathologists, neurologists, oncologists, endocrinologists, neuropsychologists, psychologists, physical and occupational therapists, social workers, and biostatisticians.

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Practitioner and Patient Resources

American Brain Tumor Association (ABTA)
2720 River Road
Des Plaines, IL 60018
Phone: (847) 827-9910 or 800-886-2282
Fax: (847) 827-9918
E-mail: abta@aol.com
<http:// www.hope.abta.org/site/PageServer>
ABTA is a nonprofit, independent, global organization that funds research and provides information to patients and regarding brain tumors, treatment options, clinical trials, and support. The Website provides a broad variety of social work resources and services.

Brain Tumor Society (BTS)
124 Watertown Street, Suite 3H
Watertown, MA 02472
Phone: (617) 924-9997 or 800-770-8287
Fax: (617) 924-9998
E-mail: info@tbts.org
<http://www.tbts.org>
BTS provides resources for patients, survivors, family, friends, and professionals. BTS exists to find a cure for brain tumors. It strives to improve the quality of life of brain tumor patients and their families. It disseminates educational information and provides access to psychosocial support. It raises funds to advance carefully selected scientific research projects, improve clinical care, and find a cure.

The Candlelighters Childhood Cancer Foundation (CCCF)
P.O. Box 498
Kensington, MD 20895-0498
Phone: (301) 962-3520 or 800-366-2223

Fax: (301) 962-3520
E-mail: info@candlelighters.org
<http://www.candlelighters.org>
CCCFs mission is to educate, support, serve, and advocate for families of children with cancer, survivors of childhood cancer, and the professionals who care for them. The Website provides information on how cancer affects children, how you can help, and where to find information and support.

The Childhood Brain Tumor Foundation (CBTF)
20312 Watkins Meadow Drive
Germantown, MD 20876
Phone: (301) 515-2900 or 877-217-4166
Fax: (301) 540-8367
E-mail: cbtf@childhoodbraintumor.org
<http://www.childhoodbraintumor.org>
The CBTF was founded by families, friends, and physicians of children with brain tumors. Their mission is to raise funds for scientific research, heighten public awareness of this most devastating disease, and improve the prognosis and quality of life for those who are affected.

Children's Brain Tumor Foundation
274 Madison Avenue, Suite 1301
New York, NY 10016
Phone: (212) 448-9494 or 800-228-HOPE
Fax: 212-448-1022
E-mail: info@cbtf.org
<http://www.cbtf.org>
The Children's Brain Tumor Foundation was founded by a group of parents, physicians, and friends to improve the treatment, quality of life, and long-term outlook for children with brain and spinal cord tumors through research, support, education, and advocacy to families and survivors. The Website provides an array of information and resources to assist you in accessing expert care to ensure quality of life for the child in your life with a brain or spinal cord tumor.

CureSearch
CureSearch/National Childhood Cancer Foundation
4600 East West Highway, Suite 600
Bethesda, MD 20814-3457
-or-
CureSearch/Children's Oncology Group
Research Operations Center
440 E. Huntington Drive, Suite 400
Arcadia, CA 91006-3776
Phone: (800) 458-6223
Fax: (828) 665-6894
E-mail: info@curesearch.org
<http://www.curesearch.org>
CureSearch represents the combined efforts of the National Childhood Cancer Foundation and the Children's Oncology Group to cure and prevent childhood and adolescent cancer through scientific discovery and compassionate care. The Website provides parents and families of children coping with cancer educational and support resources.

National Brain Tumor Foundation
414 Thirteenth Street, Suite 700
Oakland, CA 94612-2603
Phone: (510) 839-9777
Fax: (510) 839-9779
E-mail: nbtf@braintumor.org
<http://www.braintumor.org>
NBTF is a national nonprofit health organization dedicated to providing information and support for brain tumor patients, family members, and health care professionals, while supporting innovative research into better treatment options and a cure for brain tumors. The Website offers information about brain tumors and treatment, brain tumor medical centers, the latest brain tumor clinical trials, and connects patients to a network of brain tumor survivors.

Pediatric Brain Tumor Consortium (PBTC)
Operations and Biostatistics Center
St. Jude Children's Research Hospital
332 North Lauderdale Street
Memphis, TN 38105
Phone: (901)495-2714
Fax: (901)495-4585
E-mail: annemarie.fraga@stjude.org
<http://www.pbtc.org>
PBTC is a multidisciplinary cooperative research organization devoted to rapidly and effectively understanding and curing primary CNS tumors of childhood through the conduct of multicenter, multidisciplinary, innovative studies. The Website provides information for practitioners, patients, and their families regarding ongoing PBTC clinical trials.

Pediatric Brain Tumor Foundation of the United States (PBTF)
302 Ridgefield Court
Asheville, NC 28805
Phone: (828) 665-6891 or 800-253-6530
Fax: (828) 665-6894
E-mail: pbtfus@pbtfus.org
<http://www.pbtfus.org>
PBTF seeks to find the cause and cure of brain tumors in children by supporting medical research, increasing public awareness of the disease, and aiding in early detection and treatment of childhood brain tumors.

CHAPTER 102

PSEUDOTUMOR CEREBRI: IDIOPATHIC INTRACRANIAL HYPERTENSION

PAUL H. PHILLIPS, MD

Pseudotumor cerebri is a syndrome characterized by (1) increased intracranial pressure (ICP) (> 200 mm H_2O), (2) normal cerebrospinal fluid (CSF) composition, and (3) normal or small ventricles and no intracranial mass. The syndrome may be idiopathic or the result of a non–tumor-related etiology. When the syndrome is idiopathic, it is often referred to as idiopathic intracranial hypertension. In this chapter, the term pseudotumor cerebri will include idiopathic cases as well as cases in which the cause has been identified. Pseudotumor cerebri most frequently occurs in women of childbearing age. However, the syndrome is well documented in children and infants.

Pathophysiology

Pseudotumor cerebri syndrome often occurs from impaired cerebrospinal fluid (CSF) absorption by the arachnoid granulations. This results in elevated intracranial pressure (ICP) within the ventricles and around the cerebral convexities. The reason for the absence of ventricular enlargement is unknown. Increased brain water content may decrease brain compliance, resulting in normal-size ventricles, despite elevated CSF pressure. However, this explanation is speculative. Increased CSF production by the choroid plexus may be a component of the etiology of some cases of pseudotumor cerebri.

Conditions associated with pseudotumor cerebri are listed in Table 102-1. The association is well established, and the pathogenesis is well delineated for some of these conditions. For example, with vitamin A toxicity, unbound serum or CSF vitamin A damages the arachnoid granulations, resulting in decreased CSF drainage through the granulations. Dural sinus thrombosis and arteriovenous sinus shunts cause pseudotumor cerebri by elevating the intracranial venous pressure. Increased pressure within the venous sinuses reduces the pressure gradient across the arachnoid granulations, resulting in decreased CSF drainage through the granulations.

The role of some of the other associated conditions (see Table 102-1) in the pathogenesis of pseudotumor cerebri is speculative. Although corticosteroid withdrawal, nalidixic acid use, tetracycline use, head trauma, and renal failure are associated with pseudotumor cerebri, the mechanisms by which these associated conditions elevate ICP are unknown. Some conditions, such as oral contraceptive use, may be spurious associations and not a true cause of pseudotumor cerebri.

Epidemiology

Pseudotumor cerebri most frequently occurs in obese women of childbearing age. In adults, the syndrome is often idiopathic. The relationship of female gender and obesity to the pathophysiology of idiopathic cases is unknown. Vitamin A may contribute to the etiology of these cases. Obesity and female gender may be associated with elevated serum or CSF vitamin A levels, resulting in damage to the arachnoid granulations. Alternatively, female gender and obesity may be associated with

TABLE 102-1. Conditions Associated with Pseudotumor Cerebri

Idiopathic	
Secondary	
Neurologic associations	Dural venous sinus thrombosis
	Otitic hydrocephalus (dural sinus thrombosis from mastoiditis or ear infection)
	Arteriovenous sinus shunts
	Meningitis with damage to the granulations
Systemic associations	Malnutrition
	Renutrition after malnutrition
	Lupus erythematosus
	Polyangiitis
	Addison's disease
	Hypoparathyroidism
	Anemia
Toxic associations	Corticosteroid withdrawal
	Tetracycline
	Minocycline
	Vitamin A
	Isotretinoin
	Nalidixic acid
	Ciprofloxacin
	Thyroxine replacement
	Danazol
	Lithium
	Recombinant human growth hormone
Rare associations	Minor head trauma
	Corticosteroid use
	Oral contraceptive use
	Renal failure

TABLE 102-2. Presenting Symptoms of Pseudotumor Cerebri

Headaches
Retrobulbar pain
Nausea
Vomiting
Pulsatile tinnitus
Transient visual obscurations
Blurry vision
Diplopia
Photophobia
Strabismus noted by the parents
Fatigue
Neck pain and stiffness
Irritability
Somnolence
Nervousness
Apathy
Dizziness
Myalgias
Shoulder and back pain
Paresthesias
Decreased appetite
Ataxia
Papilledema noted on routine exam of asymptomatic patient

increased intracranial venous pressure, which causes a reduction of the pressure gradient across the arachnoid granulations, resulting in decreased CSF drainage, as described previously.

Among prepubescent children and infants, there is no gender predominance, and obesity occurs less frequently compared with adults. Associated causes (see Table 102-1) are common in children and are identified in approximately 50% of cases. After puberty, the clinical profile of children with pseudotumor cerebri is similar to that of adults.

Clinical Evaluation

Clinical Symptoms

The presenting clinical symptoms are from elevated ICP and are listed in Table 102-2. Headaches, sometimes associated with nausea and vomiting, are common. These headaches are often worse in the morning and may be exacerbated by coughing, sneezing, or lying flat. Pulsatile tinnitus is common in adults and older children. It may be unilateral or bilateral and is synchronous with the heartbeat. The tinnitus is attributed to intracranial vascular pulsations transmitted by CSF under high pressure to the walls of the venous sinuses. This creates pulsatile turbulent flow in the venous sinuses that is experienced by the patient as pulsatile tinnitus.

Decreased vision and diplopia are common presenting symptoms in children. Transient visual obscurations (TVOs) are common in older children and adults. TVOs are characterized by partial or complete visual loss in one or both eyes and are often associated with postural changes. They typically have a duration of < 30 seconds and may occur several hundred times in one day. Transient visual obscurations are a nonspecific symptom of disk edema and are probably related to transient optic nerve head ischemia.

Younger children and infants are often unable to verbalize the symptoms noted above. They frequently present with nonspecific symptoms such as irritability, fatigue, somnolence, dizziness, apathy, and decreased appetite. Strabismus observed by physicians or parents in an otherwise asymptomatic child may be the presenting complaint. Similarly, papilledema noted on a routine examination in an asymptomatic child may prompt referral.

Clinical Signs

The clinical signs of pseudotumor cerebri are attributable to elevated ICP. The most common signs are papilledema and oculomotor nerve palsies. Papilledema is less frequent in infants with pseudotumor cerebri and open cranial sutures.

Papilledema

Papilledema and disk edema are separate terms that are often used incorrectly. *Disk edema* is a sign of pathologic insult to the optic nerve head. Pathologic insults may be compressive, inflammatory, ischemic, or metabolic. These insults cause decreased axoplasmic flow and result in the intra-axonal accumulation of material at the optic nerve head. This is seen clinically as disk elevation, peripapillary opacification of the nerve fiber layer, and obscuration of the disk borders and disk vessels. Swollen axons at the optic nerve head secondarily compress the central retinal vein, resulting in loss of spontaneous venous pulsations, optic disk hyperemia, vessel tortuosity, flame hemorrhages, and cotton-wool spots.

Papilledema specifically refers to disk edema from elevated ICP. Elevated ICP is transmitted via the subarachnoid space to the optic nerve head. The elevated pressure at the optic nerve head causes local ischemia, resulting in disk edema and the clinical signs noted above. Papilledema cannot be distinguished from other causes of disk edema by the appearance of the optic nerve head. However, there are two clinical characteristics that suggest (but do not prove) elevated ICP as the cause of disk edema: bilaterality and intact visual acuity.

- *Bilaterality*: Elevated ICP is transmitted to both optic nerve heads and typically causes bilateral disk edema. However, bilateral asymmetric papilledema and unilateral papilledema occasionally occur.
- *Intact visual acuity*: Visual acuity is generally normal in acute papilledema. However, chronic papilledema may ultimately result in decreased visual acuity.

Thus, papilledema should be suspected in a patient with intact visual acuity and bilateral disk edema. However, elevated ICP must ultimately be confirmed by lumbar puncture before attributing disk edema to elevated ICP.

Chronic papilledema may result in gradual progressive axonal death. Clinically, the optic nerve head appearance changes from hyperemic papilledema to a pale swollen disk without hyperemia. As more axons die, disk swelling decreases, resulting in a pale, atrophic optic nerve head. These changes typically occur over several months. However, in severe cases, acute papilledema may progress to optic nerve pallor in several weeks.

Visual Function

Papilledema initially causes visual field loss in patients with pseudotumor cerebri. Although visual fields deficits are common, patients are often not aware of visual dysfunction during the early course of their disease. Enlargement of the blind spot is the most common visual field deficit. The physiologic blind spot is located about 12° to 15° temporal to fixation and is approximately 5° in size. With disk edema, the blind spot may be enlarged to 20° or more in size. The enlarged blind spot occurs from mechanical displacement of the peripapillary retina by a swollen optic disk and does not represent optic nerve dysfunction. Other common visual field deficits occur from optic nerve dysfunction. These include peripheral constriction, inferonasal steps, arcuate deficits, and depression of the nasal visual fields.

Visual acuity is typically spared until late in the disease course. Patients with chronic papilledema are at risk for progressive visual field deficits that may ultimately affect the central visual field, resulting in decreased visual acuity. Patients with decreased visual acuity typically have severe peripheral visual fields deficits and optic nerve pallor.

Color vision is also preserved until late in the disease course and is therefore an insensitive parameter for early visual loss. Relative afferent pupillary defects are sensitive signs of asymmetric optic nerve dysfunction. However, many patients with pseudotumor cerebri have bilateral optic nerve dysfunction and therefore do not have a relative afferent pupillary defect.

Oculomotor Nerve Palsies

Elevated ICP from any cause may shift the brainstem and stretch cranial nerve VI, resulting in a cranial nerve VI palsy. Cranial nerve VI palsies are common in children with pseudotumor cerebri. They may be unilateral or bilateral and are generally incomplete. Cranial nerve VI palsies due to pseudotumor cerebri generally resolve with normalization of ICP.

Children with pseudotumor cerebri may have other oculomotor abnormalities, including cranial nerve IV palsy, cranial nerve III palsy, cranial nerve VII palsy, skew deviation, and acute comitant esotropia (crossed eyes with no limitation of abduction to suggest a cranial nerve VI palsy). These other oculomotor deficits are uncommon and should be attributed to pseudotumor cerebri only if they resolve with normalization of the ICP and other causes are ruled out.

Diagnosis

Evaluation of a child with bilateral disk edema is a medical emergency. A thorough history should be obtained from the child and the parents. The symptoms noted in Table 102-2 should be addressed. Many patients will not volunteer a description of symptoms, such as pulsatile tinnitus or transient visual obscurations, unless the physician specifically inquires about these entities. The parents of infants should be questioned regarding the presence of irritability, somnolence, anorexia, and strabismus. The past medical history should identify medical conditions and medications that may be associated with pseudotumor

cerebri (see Table 102-1). Specific associations that should be addressed include recent ear infections, antibiotic treatment, and vitamin A consumption. Adolescents with acne may be treated with vitamin A or isotretinoin. Systemic and topical treatment of acne with vitamin A compounds has been associated with pseudotumor cerebri.

A detailed ophthalmologic examination is essential. The visual acuity of each eye should be documented, if possible. Visual acuities with picture symbols can be obtained in children as young as 3 years of age. Quantitative visual fields are essential to identify early signs of visual dysfunction and may be obtained in children as young as 5 years of age. Color vision deficits indicate severe visual dysfunction and should be documented. Ocular motility examination may reveal cranial nerve VI palsies and, less commonly, other oculomotor nerve palsies. A dilated fundus examination and stereoscopic disk photographs allow the detection and documentation of disk edema. Infants with open cranial sutures and bulging fontanelles may not have papilledema, despite the presence of elevated ICP.

Neuroimaging should be obtained emergently to rule out an intracranial mass and hydrocephalus. Magnetic resonance imaging (MRI) of the brain and orbits with gadolinium is the ideal imaging modality. MRI is superior to computed tomography for evaluation of the venous sinuses and will identify most cases of cerebral venous sinus thrombosis. Venous sinus thrombosis should be suspected in patients with a history of recent ear infections, multiple miscarriages, oral contraceptive use, and known coagulopathies, and in patients presenting in the postpartum period. Magnetic resonance venography should be considered for the evaluation of these patients.

MRI may reveal subtle signs suggestive of elevated ICP in patients with pseudotumor cerebri. These signs include flattening of the posterior sclera, empty sella, enhancement of the prelaminar optic nerve, distention of the perioptic subarachnoid space, vertical tortuosity of the orbital optic nerve, and intraocular protrusion of the prelaminar optic nerve.

If neuroimaging rules out an intracranial mass and hydrocephalus, a lumbar puncture should be obtained to rule out intracranial infections and malignancy and to confirm elevated ICP. The ICP should be measured with the patient in the lateral decubitus position with the legs relaxed. Sedation is often necessary in children. The ICP is considered elevated if it is above 200 mm H_2O for nonobese patients and above 250 mm H_2O for obese patients. CSF studies should include protein, glucose, cell count, bacterial cultures, fungal cultures, *Mycobacterium tuberculosis* cultures, and cytology. Older children may report that their symptoms of elevated ICP improve after the lumbar puncture. Improvement of symptoms such as headaches, nausea, vomiting, and pulsatile tinnitus after the lumbar puncture supports elevated ICP as the etiology for these symptoms.

Pseudotumor cerebri is diagnosed if neuroimaging shows normal or small ventricles, no intracranial mass, and if the lumbar puncture is normal except for elevated ICP. Blood tests may reveal conditions associated with pseudotumor cerebri, such as anemia, hypocalcemia, renal failure, and vitamin A toxicity. It is reasonable to obtain a complete blood count, electrolytes, serum calcium and phosphate levels, blood urea nitrogen, serum creatinine, antinuclear antibodies, serum vitamin A levels, and a urinalysis. Hypercoagulability testing should be obtained in patients with venous sinus thromboses of unknown cause.

Differential Diagnosis

Pseudopapilledema is a congenital disk anomaly that simulates papilledema. It is characterized by an elevated optic nerve head, which may contain optic nerve head drusen. Patients with pseudopapilledema may have TVOs and visual fields deficits similar to patients with true papilledema. Pseudopapilledema is differentiated from true disk edema by the absence of nerve fiber layer opacification, disk hyperemia, obscuration of the disk vessels, and cotton-wool spots. Patients with pseudopapilledema have normal ICP. However, the identification of pseudopapilledema on physical examination should obviate the need for neuroimaging and lumbar puncture.

Infiltrative central nervous system (CNS) malignancies may present with a pseudotumor cerebri syndrome. These "masquerade syndromes" include gliomatosis cerebri and primitive neuroectodermal tumors. Patients with these entities may initially have normal MRI and normal CSF studies, except for elevated ICP. They typically develop progressive cranial nerve deficits, and repeat MRI later in the disease course will reveal the tumor. Therefore, patients diagnosed with pseudotumor cerebri who develop progressive cranial nerve deficits should have repeat MRI.

Prognosis

Visual loss from papilledema is the major morbidity from pseudotumor cerebri. The disease course is chronic in adults, and permanent visual loss is common. The disease appears to be more self-limited in children, with frequent spontaneous remissions, although recurrent disease has been described. Children are also at risk for severe permanent visual loss. Therefore, visual function and optic nerve appearance should be monitored in children with pseudotumor cerebri until papilledema resolves. Quantitative perimetry is the most sensitive test for the detection of visual loss from papilledema and should be obtained when possible. Decreased visual acuity and color vision loss are signs of advanced disease.

The recommended frequency of examinations varies, depending on the visual function status, the level of ICP, and the current treatment. Examinations initially should be scheduled weekly in a patient with severe optic neuropathy. Bimonthly examinations are generally adequate for patients with normal visual function.

Unfortunately, visual function tests cannot be obtained in infants and young children. Visual evoked response testing remains normal until severe optic nerve damage has occurred. Therefore, this test has no role in monitoring children with pseudotumor cerebri.

Treatment

Asymptomatic patients with normal visual function may be monitored without specific treatment. Associated conditions should be identified and treated. Medications associated with pseudotumor cerebri should be discontinued, if possible. Obese patients should be encouraged to lose weight, and referral to a dietitian should be considered. Headaches may respond to tricyclic antidepressants or nonsteroidal anti-inflammatory drugs.

Medications that lower ICP are indicated for patients with headaches and/or mild visual field deficits. CSF production by the choroid plexus is dependent on carbonic anhydrase. Diamox® (acetazolamide) inhibits carbonic anhydrase and therefore lowers ICP by reducing the rate of CSF formation. A dose of 1 to 4 g/d in two or three divided doses is indicated for adults (5 mg/kg four times daily for children). Unfortunately, side effects are common and include paresthesias, unpleasant taste to carbonated beverages, altered taste of food, and a low serum bicarbonate level. Less common side effects include allergic reactions, renal stones, and aplastic anemia. Diamox® contains sulfa and should not be used in patients who are allergic to sulfa. Electrolytes and a complete blood count should be monitored every several months in patients treated with this drug.

Lasix® (furosemide), a weak carbonic anhydrase inhibitor and chloride reuptake blocker, also reduces CSF formation at the choroid plexus and may be used in patients who are unable to tolerate Diamox®. Alternatively, Lasix® may be combined with Diamox®, although increased effectiveness with this combination is not proven. Corticosteroids may rapidly lower ICP. However, chronic treatment with corticosteroids is associated with numerous side effects, and increased ICP may occur with cortico-steroid withdrawal. Therefore, treatment with cortico-steroids should generally be avoided.

Repeat lumbar punctures are not an effective treatment. A lumbar puncture lowers ICP for only several hours, as the entire CSF volume is renewed approximately four times a day.

Surgery is indicated for patients at risk for severe visual loss. Thus, indications for surgery include:

- Progressive visual loss despite maximum-tolerated medical treatment
- Severe visual loss at presentation
- Severe papilledema or chronic atrophic papilledema, especially in children who are too young to perform reliable visual field testing

Surgical options include optic nerve sheath fenestration (ONSF) and lumbar peritoneal (LP) shunt. These procedures rapidly reduce papilledema, although complete resolution may take several weeks.

ONSF involves making multiple slits in the perioptic meninges behind the globe. This allows the egress of CSF through the perioptic nerve sheath and reduces pressure at the optic nerve head. ONSF effectively treats papilledema, stabilizing or improving visual function in children with visual loss from pseudotumor cerebri. Unilateral ONSF will eliminate papilledema of both disks in approximately 50% of cases and reduce headache symptoms in some patients. Complications, including ischemic optic neuropathy, transient blindness, pupillary dilation, and retrobulbar hemorrhage, are infrequent. However, there is a high rate of failure with long-term follow-up.

LP shunting reduces ICP and therefore treats the headaches and relieves the pressure on both optic nerves. This procedure effectively resolves papilledema and stabilizes vision in children with visual loss from pseudotumor cerebri. However, low-pressure headaches associated with an acquired Arnold-Chiari malformation type I tonsillar herniation may occur. Shunt failures are frequent, and the procedure may need to be repeated many times over several years. Other complications include shunt infections, abdominal pain, CSF leak, and migration of the peritoneal catheter.

ONSF should be considered for patients with progressive visual loss after apparently successful LP shunting. Similarly, an LP shunt should be considered for patients with progressive visual loss after an ONSF.

Bariatric surgery effectively reduces ICP in severely obese patients with pseudotumor cerebri and has the added advantage of reducing comorbidity associated with excessive weight. Although bariatric surgery is most commonly performed on adults, it has been used to treat severely obese adolescents. The weight loss and reduction of ICP occurs gradually over several months. Therefore, this is not the treatment of choice for patients with acute visual deterioration.

Discussion

The diagnosis and treatment of children with pseudotumor cerebri requires collaboration among pediatricians,

neurologists, and ophthalmologists. Associated conditions must be recognized and treated. The integrity of the visual system should be evaluated by an ophthalmologist. Careful follow-up of visual function and aggressive treatment of progressive or severe visual loss should minimize morbidity.

Acknowledgment

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Suggested Readings

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Practitioner and Patient Resources

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CHAPTER 103

CENTRAL NERVOUS SYSTEM VASCULAR MALFORMATIONS

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Children can be afflicted with a variety of intracranial lesions, including arteriovenous malformations (AVMs), cavernous malformations (CMs), vein of Galen malformations, and "dural" arteriovenous fistulas (AVFs). Certain types of spinal cord AVMs also are known to occur in children and young adults, especially intradural spinal AVFs and juvenile AVMs. These lesions differ dramatically in their anatomy, pathophysiology, treatment, and prognosis. They are best managed in a multidisciplinary setting by neurosurgical, neuroendovascular, and neurocritical care teams.

Cerebral vascular malformations are divided into five types: (1) arteriovenous malformation (AVM), (2) "dural" arteriovenous fistulas (AVF), including dural AVF (DAVF), pial AVF (PAVF), and vein of Galen aneurysmal malformations (VGAM), (3) cavernous malformation (CM), (4) venous angioma, and (5) capillary telangiectasia. Typically, only AVMs, AVFs, and CMs become symptomatic and require neurosurgical care; venous angiomas and capillary telangiectasias often are found incidentally. AVMs, AVFs, and CMs, however, differ dramatically and will be discussed separately. The vein of Galen malformation is a special case of a dural AVF and will be discussed separately. Spinal AVMs and AVFs will also be discussed separately due to the different anatomic, pathologic, and clinical considerations associated with them.

Some of these lesions occur predominantly in adult populations. Often, less is known about the natural history and best management of these lesions in pediatric patients. When possible, we have focused our discussion on evidence from pediatric patients, but in many instances we will discuss the behavior and treatment of these lesions in adults in the hope that it sheds light on the same entities in pediatric patients.

Cerebral Arteriovenous Malformations

Cerebral AVMs are characterized by direct communication between one or more arterial feeders and one or more draining veins without an intervening capillary bed. Unlike the dural AVFs discussed below, cerebral AVMs reside inside the brain (although they often extend to the surface) and are intermingled with gliotic brain tissue. Cerebral AVMs appear grossly as a tangle of vessels but often have an identifiable center or "nidus." AVMs are high-flow lesions that cause multiple pathologic changes in the involved vessels and thus create tendency toward hemorrhage.

On the basis of a review of adult autopsy series and large clinical studies, Berman and colleagues at Columbia University (2000) estimated the annual incidence of cerebral AVMs to be roughly 1 per 100,000 and the prevalence to be 10 per 100,000. Owing to a smaller number of studies, prevalence rates specific to the pediatric population are more difficult to obtain. In a series of 4,122 pediatric autopsies reviewed by Pinar and colleagues at Brown University in 1998, however, 2% (82) of patients were found to harbor one of the five types of cerebral vascular

malformations, with AVMs accounting for 15% (12) of these 82 lesions. It is our current impression that the prevalence of AVMs in the population is about 0.2 to 0.4%.

Clinical Presentation

Cerebral AVMs most often present between the third and fifth decades of life with acute hemorrhage, seizure disorder, or nonhemorrhagic neurologic deficit. In 1996, Humphreys and colleagues at the Hospital for Sick Children reviewed their experience with 160 children harboring cerebral AVMs. Consistent with others, they found that a significant number of their patients (80%) presented with acute hemorrhage. Because children with AVMs seem to present more often with hemorrhage, the peak age for hemorrhage from an AVM is lower, possibly between 15 and 20 years old. Clinically, a child suffering from an AVM hemorrhage will complain of sudden, severe headache and may develop other signs or symptoms, including nausea, vomiting, seizures, or neurologic deficit. On the basis of Humphreys' series, hemorrhage from an AVM in the pediatric population may carry a higher mortality than in adults. The overall mortality in the group presenting with acute hemorrhage was 21% (27 of 126), whereas multiple adult series report roughly 10% overall mortality from hemorrhage. This is possibly secondary to the increased incidence of posterior fossa (brainstem and cerebellar) lesions in children. Humphreys and colleagues reported 23% (36 of 160) posterior fossa lesions in their pediatric series, while Jomin and colleagues (1985) found only 5% (8 of 150) in their adult series. According to another series by Humphreys that focused only on posterior fossa AVM, the reported mortality rate was 35% (1998).

Overall, AVMs represent the most common cause of intracranial hemorrhage in the pediatric population, but prospective data for the annual risk of hemorrhage are lacking. In adults, the annual risk of hemorrhage is roughly 2 to 4%, irrespective of a history of prior hemorrhage.

Evaluation and Diagnosis

Although cerebral AVMs are often first detected with computed tomography (CT) or magnetic resonance imaging (MRI), the "gold standard" for diagnosis and anatomic definition is cerebral angiography. Because many children present with acute intracranial hemorrhage, most will initially obtain a CT scan, which can demonstrate an acute thrombus or calcified vessels, if present. Addition of contrast is of little utility but, if done, can reveal dilated arterial or venous vessels. MRI can detect AVMs by the presence of multiple flow voids (areas of low signal) representing blood vessels in the malformation. Magnetic resonance angiography (MRA) may or may not demonstrate an AVM because it is gated to reveal arterial-type flow, but AVMs often have intermediate flow that is neither truly venous nor arterial.

Although AVMs are detectable with these other imaging modalities, all surgical, endovascular, and stereotactic radiotherapy management decisions are based on a four vessel (internal carotid and vertebral arteries) and often external carotid angiogram. Catheter angiography carries a very low risk of procedural complication in the pediatric population. It defines the vascular anatomy of the lesion and allows for possible endovascular embolization prior to either surgical resection or stereotactic radiotherapy (Figures 103-1 and 103-2).

Treatment

The ideal treatment for a cerebral AVM is total surgical resection. In selected cases, surgery is preceded by endovascular embolization of the AVM to aid surgical resection and limit intraoperative bleeding. Small AVMs in surgically difficult locations, however, are best treated with stereotactic radiotherapy. Although AVMs can be treated with stereotactic radiotherapy, this approach results in delayed obliteration of the AVM (over months) as the vessels respond to the radiation injury. As a result, the patient remains at risk for hemorrhage for a substantial amount of time after treatment. Furthermore, there may be risks associated with radiotherapy. Kaido and colleagues at the Nara Medical University in Japan described a 14-year-old patient who developed a glioblastoma multiforme (GBM) 6.5 years after radiotherapy for AVM. For these reasons, stereotactic radiotherapy is reserved for AVMs deemed surgically inaccessible due to depth or involvement of eloquent tissue.

Outcome

With better endovascular, radiotherapeutic, and surgical techniques, outcomes continue to improve for children with cerebral AVMs. Currently, overall mortality is roughly 10 to 15%, with 50 to 60% of children who undergo surgery regaining normal neurologic function. Although seizures are less often part of the clinical picture in children with AVMs (versus adults), 10 to 20% of children with AVMs will have a seizure disorder and require antiepileptic drugs.

Finally, pediatric patients appear to be at higher risk than adults for recurrence of their AVM, even after negative post treatment angiograms. Lindqvist and colleagues from the Karolinska Hospital in Stockholm reported in 2000 that pediatric patients are more likely than adults to experience recurrence of their AVM years after radiosurgical obliteration. Additionally, Kader and colleagues at the Albert Einstein College of Medicine reported five pediatric cases of recurrent AVMs years after negative postoperative angiography. These

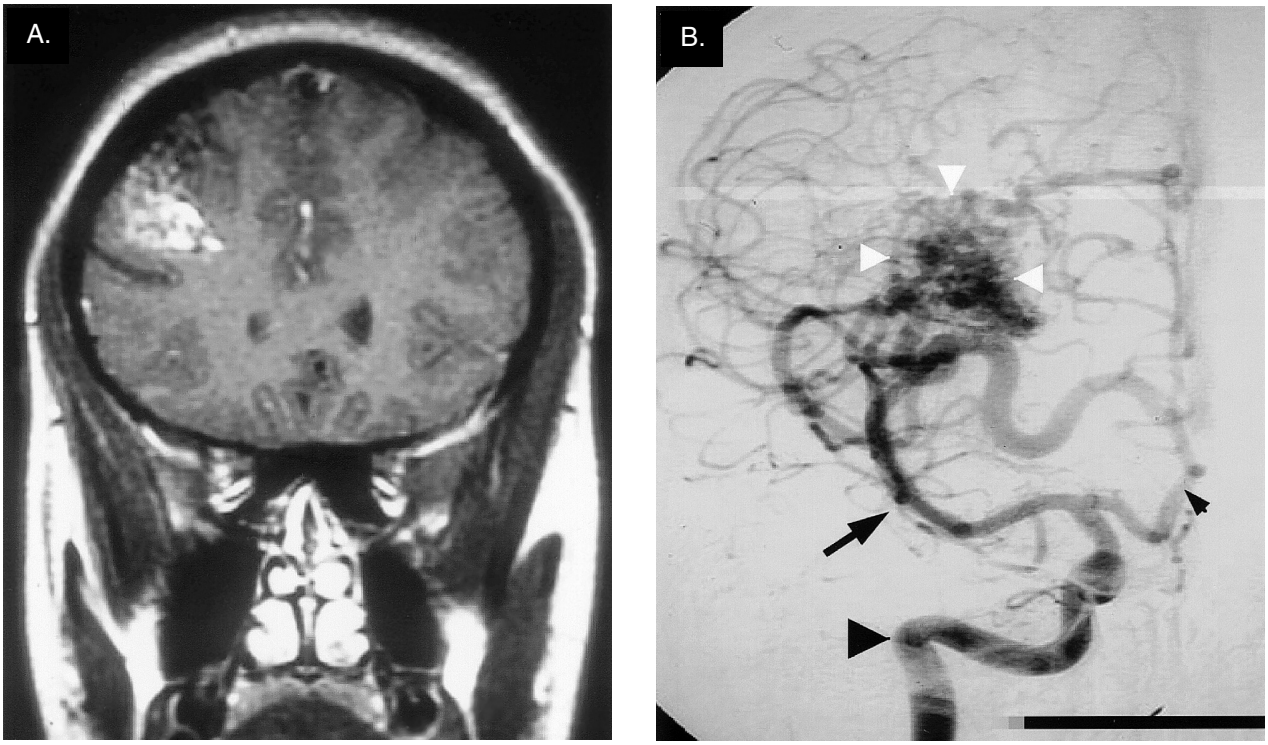

FIGURE 103-1. *A*, Coronal, gadolinium-enhanced magnetic resonance imaging demonstrates a right frontal arteriovenous malformation (AVM) extending to the cortical surface. *B*, Anterior view of right internal carotid angiogram in the same patient reveals the internal carotid artery (*large arrow head*), the anterior cerebral artery (*small arrow head*), and the middle cerebral artery (*black arrow*). The AVM nidus (*white arrows*) is fed largely by branches of the middle cerebral artery.

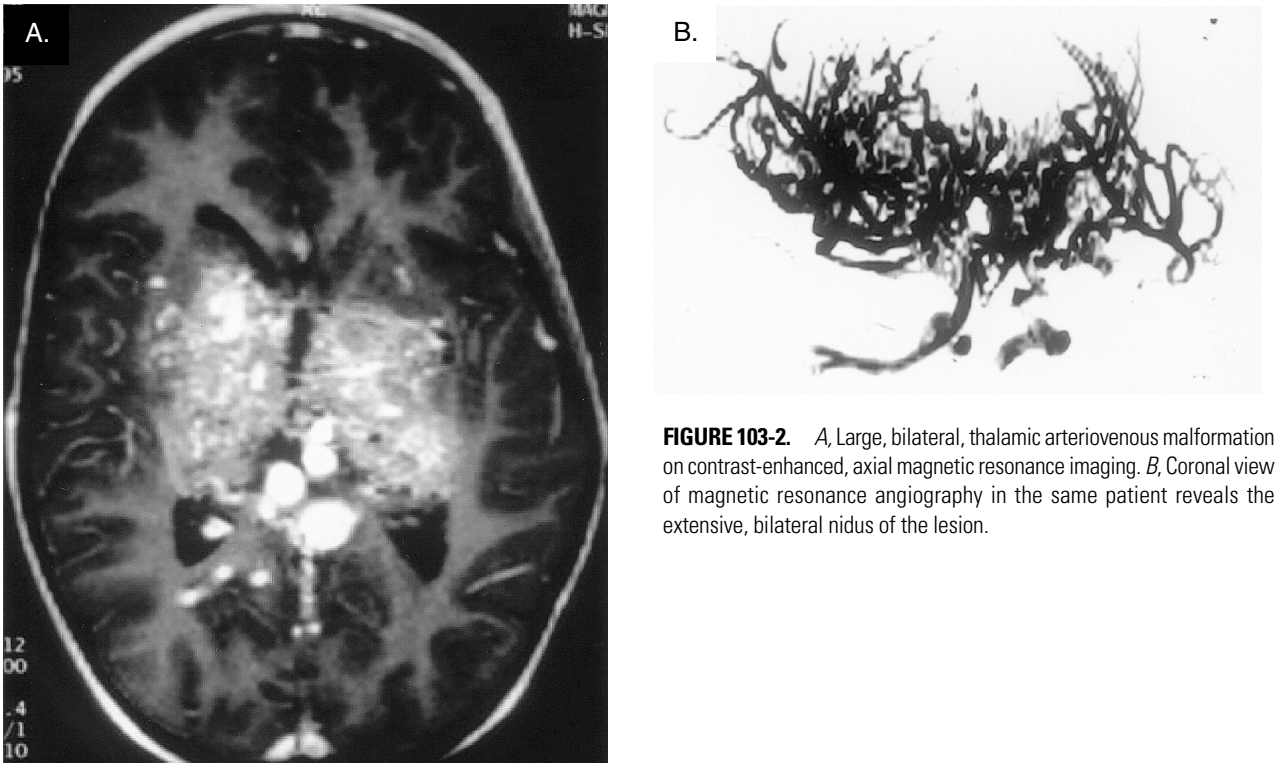

FIGURE 103-2. *A,* Large, bilateral, thalamic arteriovenous malformation on contrast-enhanced, axial magnetic resonance imaging. *B*, Coronal view of magnetic resonance angiography in the same patient reveals the extensive, bilateral nidus of the lesion.

results suggest delayed post-treatment imaging studies may be warranted in the pediatric population.

Intracranial AVFs

Intracranial dural AVFs are high-flow lesions consisting of arteriovenous shunting found outside the brain parenchyma, either in the subarachnoid space or dura. This is in contrast to cerebral AVMs, which reside in the brain and are intermingled with gliotic brain tissue. The arterial supply of AVFs is from dural arteries and the venous drainage is through either dural sinuses or leptomeningeal venous channels. A dural sinus is a venous channel located between the leaflets of the dura mater (eg, sagittal sinus, transverse sinus, sigmoid sinus). Even though the exact cause of AVFs is unknown, it is widely believed these lesions are acquired, occasionally secondary to sinus thrombosis and recanalization. The thrombosis allows fistulous connections to develop between meningeal and dural vessels, thus causing high-flow arteriovenous shunts to become established. The high-flow shunts and retrograde flow cause venous dysfunction and put the patient at risk for venous rupture and ischemia due to severe venous congestion.

In 1997, Lasjuanias described three types of pediatric AVFs on the basis of the patient's age at presentation and type of shunting: neonatal, juvenile, and adolescent. The neonatal AVF results from a congenital malformation of the dural sinuses. The juvenile type is associated with multifocal, high-flow shunts without sinus malformation and often is associated with secondary occlusion of the jugular bulb. The adolescent type is associated with slow flow and is located along the cavernous sinus or sigmoid sinus.

Sinus pericranii is an extracranial vascular malformation that should be distinguished from AVFs, because these are not fed by arterial feeders. Rather, they represent a group of vascular malformations involving the extracranial and intracranial venous systems, which usually involve the superior sagittal sinus and sometimes the transverse sinus. These lesions are thought to be congenital, presenting in young infants as a soft, reducible, fluctuant mass on the scalp. Because these venous malformations are directly connected to the intracranial sinuses, any changes in head position or activities that induce a Valsalva maneuver will change the size of the lesion. Diagnosis of a sinus pericranii depends on the physical exam and CT or skull radiograph showing a defect in the skull beneath the lesion. Angiograms will show the lesion only if digital subtraction and delayed images are taken. Treatment is recommended mostly for cosmetic reasons or, occasionally, because of risk of hemorrhage from trauma. In these cases, a craniotomy or craniectomy with cranioplasty is performed, followed by complete obliteration of the abnormal communications.

Clinical Presentation

The neonatal AVF occurs in neonates and infants and presents with symptoms of elevated intracranial pressure (ICP), such as emesis, limited up-gaze, bulging fontanelles, irritability, or neurologic deficits. The malformation of the dural sinus results in a giant dural lake that enlarges and communicates with other sinuses. Patients with a more midline sinus malformation tend to be more symptomatic. If the venous outlet undergoes thrombosis, the patient can present with a hemorrhage or a venous infarction.

The juvenile, or high-flow, AVF also can present in neonates or infants. Because these AV shunts are high-flow, neonates can present with congestive heart failure (CHF) similar to that seen in patients with vein of Galen malformations. Unlike the CHF seen in neonates with vein of Galen malformations, however, heart failure in juvenile AVF patients is often mild and more easily managed medically. This usually allows intervention to be delayed until the child grows, thereby reducing the morbidity and mortality that can accompany the treatment of neonates with vein of Galen malformations. The natural history of juvenile AVF is to produce progressive venous occlusive phenomena. This can interfere with the drainage of the high-flow shunts as well as the healthy brain. The patient's symptoms depend on the extent of venous congestion and the ability of the cavernous sinus to accommodate the venous outflow from the cortical venous system of the brain, thereby circumnavigating the dural shunt. Untreated, the patient may gradually develop neurologic deficits, seizures, and mental retardation. Intervention is recommended when the juvenile AVF causes macrocephaly, headaches, slowed development, or hemodynamic disorders.

Adolescent AVFs are similar in appearance and presentation to those seen in the adult population. The natural history of these lesions is highly variable. Many pursue a benign course, but some cause sudden and aggressive neurologic deficits. The clinical behavior of adolescent (and adult) AVFs is determined by lesion location, patterns of arterial supply, and venous drainage. The venous drainage is the most important factor determining symptoms. Venous dysfunction due to high pressure of direct and retrograde flow can cause increased ICP, significant neurologic deficits, and fatal hemorrhage. If various venous drainage systems can accommodate cortical outflow from normal brain, symptoms may be minor or absent. Symptoms other than hemorrhage or focal neurologic deficits rarely warrant radical treatment.

Evaluation and Diagnosis

In the acute setting of a new neurologic deficit, most patients will be evaluated with CT. Even though CT may allow proper diagnosis of a vascular anomaly, it is important to recognize that these lesions need to be further evaluated with MRI and MRA. Although MRI (and MRA and magnetic resonance venography [MRV]) shows the major vascular channels, as with AVMs, the gold standard for diagnosing and assessing the anatomy of dural AVFs is four vessel angiography that includes the external carotid circulation. The angiogram also provides important information about intracranial circulation and allows for preoperative planning by the surgeon and the neurointerventionalist.

Treatment

There are two treatment modalities for pediatric dural AVFs: (1) endovascular embolization and (2) surgical resection. Substantial improvements in both endovascular and surgical techniques have made treating dural AVFs safer and more effective. Currently, pediatric dural AVFs are managed using a multidisciplinary approach involving neurointerventionalists and neurosurgeons. The goal of surgical intervention is the interruption or excision of the pathologic dural leaflet or the obliteration of the arterialized venous connection. Despite improvements in surgical technique, risks are associated with surgical intervention. Therefore, the neurointerventionalist typically first attempts to embolize the arterial feeders. If the embolization is able to sufficiently treat the dural AVF, then surgery is avoided. If the embolization cannot sufficiently disconnect or reverse cortical venous reflux drainage by the dural AVF, then surgical intervention is considered.

Outcome

Outcome data on pediatric dural AVFs are limited because they are rare. The clinical progression of a neonatal type of dural AVF may be relentless, and the outcome poor because of venous infarction and hemorrhage. The patient with a juvenile dural AVF can have a good outcome if treated early and effectively. If the patient has multifocal AV shunts, treatment is difficult and the outcome can include seizures, neurologic deficits, and global retardation. The most important factor in the outcome of neonatal and juvenile AVFs, however, is the extent of the patient's heart failure. If the CHF can be managed effectively, the outcome can be quite good. Managing the child's CHF allows the patient to grow and gain weight, thus allowing the interventionalist to use more dye during the angiographic procedure and to more easily access the arterial feeders.

The adolescent dural AVF is similar to the adult type; therefore, adult numbers are reviewed here. In 1969, Newton and colleagues reviewed angiograms of patients with intracranial AVMs during a 6-year period and found that dural AVFs constitute 10 to 15% of all intracranial AVMs. The most important factor determining the outcome is the venous drainage. Untreated, the majority behave benignly, but some experience rapid neurologic deterioration with venous ischemia and hemorrhage. In 2000, Kawaguchi and colleagues reported results on 12 patients who had previously undergone embolization but then became symptomatic and underwent surgical removal of their dural AVF. They reported no surgical mortality or lasting morbidity and achieved symptomatic resolution in all patients. Substantial gains have been made in the outcomes of pediatric dural AVFs. As endovascular and surgical equipment and techniques continue to improve, so will outcomes.

Cavernous Malformations

CMs are angiographically occult vascular malformations that consist of sinusoidal vascular channels lined by a single layer of endothelial cells. They typically originate from dysmorphic capillaries that hemorrhage and create multiple thrombotic chambers. These vascular channels lack a full complement of normal vessel wall components and are embedded in loose connective tissue stroma. The lesion may be surrounded by gliotic tissue, but there is generally no neural tissue within the lesion. The channels are filled with blood in various degrees of thrombosis and degradation, leading to the characteristic "mulberry" appearance of these malformations grossly and their reticulated appearance on MRI.

CMs constitute roughly 10% of all cerebral vascular malformations and are present in about 5% of the population, according to a review of 24,535 autopsies conducted by Otten and colleagues in Geneva in 1989. As with AVMs, there are fewer studies focusing on the pediatric prevalence of CMs. If one looks at a number of large clinical series, however, pediatric patients (age < 18 years) comprise roughly 20% of the patient population. In our series of 68 patients at the Johns Hopkins Hospital, for example, 13 patients (19%) presented at or before 18 years of age.

CMs are found throughout the central nervous system and appear to be distributed in proportion to the amount of tissue in each region. Therefore, roughly 80% are found in the supratentorial compartment (hemispheres and deep nuclei), 20% are found in the infratentorial compartment (brainstem and cerebellum), and a very small number (< 1%) are found within the spinal cord.

CMs can occur in either a sporadic or familial form. Familial cases account for 20 to 50% of all cases, are transmitted in an autosomal dominant fashion, and have been linked to chromosome 7. Although clinically indistinguishable from sporadic cases, familial cases are more likely to harbor multiple lesions. In our series, 85% (11 of 13) of familial patients had multiple lesions, compared with 25% (14 of 55) of sporadic cases.

Clinical Presentation

Most patients with CMs present in their fourth decade, but the mode of presentation varies widely, and there are insufficient data to discern any difference between the clinical presentation in adults and children. Most series report headache, seizure, focal neurologic deficit, and hemorrhage as major symptoms. Seizures, occurring in 25 to 50% of patients, are often the primary complaint that prompts clinical evaluation. In our series at Johns Hopkins, 33 patients (49%) presented with seizures. In prospective follow-up of the patients without a seizure history, we found a 4.8% per patient-year risk of developing seizures. Prospective CM hemorrhage rates found in the literature are roughly 1 to 3% per patient-year. Similarly, analysis of our series yielded a prospective hemorrhage rate of 3.1% per patient-year.

Evaluation and Diagnosis

MRI is the imaging modality of choice for detecting CMs. In contrast, CT has poor sensitivity and specificity for these lesions, and their low flow and lack of large feeding or draining vessels render them largely undetectable by MRA. The relative merits of these different imaging modalities were best illustrated by Rigamonti and colleagues at the Barrow Neurological Institute (1987), who studied 10 patients with pathologically verified CMs. In these 10 patients, MRA was negative in four, revealed an avascular mass in three, and revealed subtle venous pooling or capillary blush in the remaining three. In the same 10 patients, three CT scans were negative, and a total of 14 lesions were detected in the remaining seven scans. This is in contrast to MRI, which demonstrated a CM in every patient and revealed 27 lesions overall.

The MRI appearance of CMs was divided into four types by Zabramski and colleagues at the Barrow Neurological Institute in 1994. The classic appearance (type II) is one of a mixed-signal, reticulated core (likened to popcorn) surrounded by a low-signal rim (Figure 103-3). Other possible appearances of CMs on MRI include a homogeneous, hyperintense core (type I), a markedly hypointense lesion (type III), and punctate, poorly visualized hypointense foci (type IV).

Treatment

Surgical resection is the mainstay of therapy for symptomatic CMs. Endovascular treatment cannot be used because of the lack of filling of these lesions on angiography. The efficacy of stereotactic radiotherapy is still questionable due to a lack of long-term follow-up in most series and a belief that the biology of these lesions differs from that of AVMs, making them inherently less amenable to radiation treatment.

Deciding to treat a CM surgically, however, requires comparing the natural history of the lesion with the risks of surgery. In general, CMs follow a more benign course than AVMs, and episodes of hemorrhage are (depending on location) not usually associated with a catastrophic neurologic deficit. Therefore, patients whose CMs have been identified incidentally can be monitored with serial MRIs, reserving surgical intervention for those developing a neurologic deficit, medically intractable seizures, or radiographic evidence of rapid growth or extralesional hemorrhage (blood extending beyond the rim of the lesion).

Cases of brainstem or spinal cord CMs present special treatment dilemmas. These lesions are in eloquent regions where even a small hemorrhage can be clinically devastating. For the same reason, however, surgical excision can be associated with significant postoperative morbidity. Currently, the high morbidity associated with hemorrhage in these regions leads many surgeons to recommend resection after multiple hemorrhagic events. Although large prospective studies have not addressed the issue, some retrospective analyses have indicated a benefit to early surgical resection of brainstem and (especially) spinal cord CMs.

Outcome

In general, patients with CMs fare better clinically than patients with AVMs. Unfortunately, most of our clinical data comes from mixed (adult and pediatric) series. In a series of 173 patients with CM, followed prospectively for a mean of 2.5 years per patient, Porter and colleagues at the University of Toronto (1997) recorded no fatal episodes of intracranial hemorrhage. Overall, 34% (59 of 173) of their patients presented with, or experienced during follow-up, an episode of neurologic deficit. Roughly one-third of these patients recovered completely, one-third recovered partially, and one-third experienced no significant improvement. In this study, lesions located in the basal ganglia, thalamus, brainstem, or spinal cord were associated with a higher rate of lasting neurologic deficit, a finding that mirrors our experience.

The risk of surgical intervention depends on the location of the lesion but is relatively low for most CMs. In a study of 94 patients who underwent 97 operations, Amin-Hanjani and colleagues at Massachusetts General Hospital

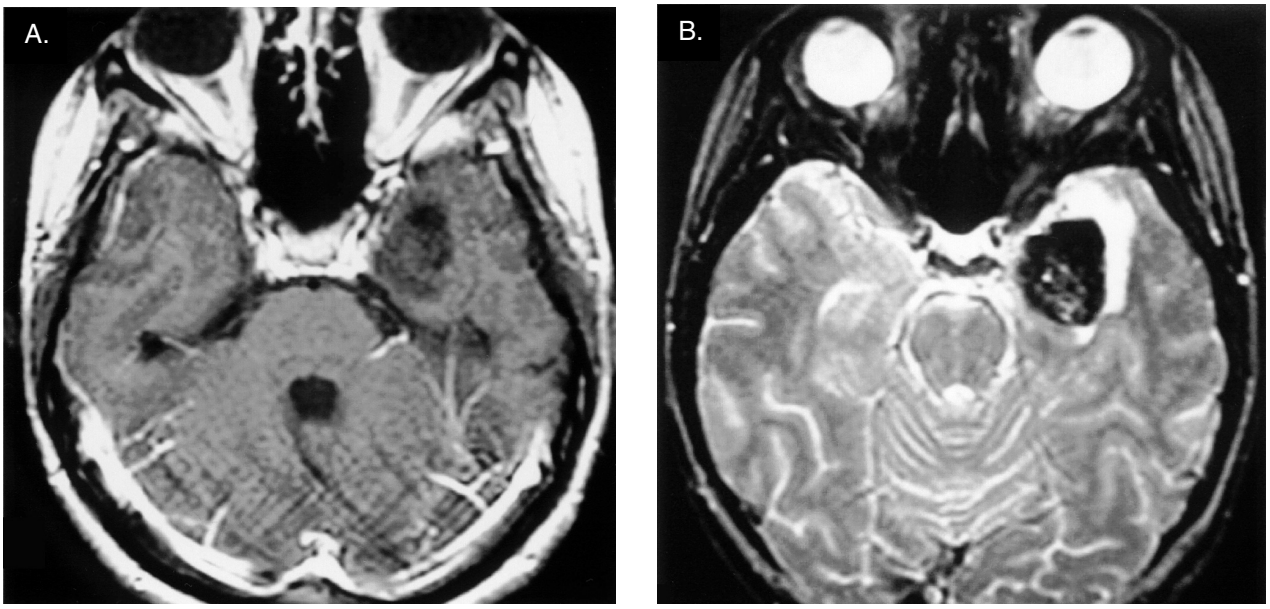

FIGURE 103-3. *A,* Enhanced, axial T_1-weighted, magnetic resonance reveals low signal lesion of left medial temporal lobe. As is typical for cavernous malformations, no enhancement with contrast is noted. *B,* Axial T_2-weighted image of same lesion reveals typical reticulated core and low signal (hemosiderin) ring surrounding lesion.

(1998) reported persistent, disabling neurologic complications in four cases and no mortality as a result of surgery. They also reported an overall neurologic outcome of excellent to good for 87 (90%) of the surgical procedures.

Surgery performed to treat medically intractable seizures secondary to a CM also carries a high success rate. Most series, including our own, indicate a complete cessation of seizures in more than 95% of patients.

Vein of Galen Malformation

The vein of Galen is a short (1 to 2 cm), large-diameter venous confluence that collects multiple tributaries from the deep venous system of the brain. It then drains directly into the straight sinus, which is superior and posterior to the pineal gland. Malformations of the vein of Galen often are referred to as vein of Galen "aneurysms," as they result in dilation of the vein of Galen. In the following discussion, however, we will refer to these lesions as vein of Galen "malformations." We do this for two reasons. First, intracranial aneurysms are arterial lesions with entirely different pathology and treatment. Second, vein of Galen malformations are vascular malformations that involve direct arteriovenous shunting.

Vein of Galen malformations were first comprehensively described by Jaeger, Forbes, and Dandy at Johns Hopkins in 1937. Since that time, this lesion has been subjected to multiple classification schemes. Each scheme differentiates between direct AVFs into the vein of Galen (considered the "true" vein of Galen malformation) and simple dilation of the vein of Galen secondary to another vascular malformation. Even for lesions representing true AVFs, however, the name "vein of Galen malformation" is likely a misnomer. A study of 23 cases by Raybaud and colleagues (1989) concluded that such lesions actually represent the persistence of the median prosencephalic vein of Markowski. Normally, this vessel exists only transiently during intrauterine development and then regresses as the paired internal cerebral veins replace all but its most caudal portion. The vein of Galen malformation, Raybaud and colleagues argue, represents the aberrant persistence of this vein of Markowski and its arterial tributaries, thus creating a high-flow AV communication.

Overall, vein of Galen malformations are rare vascular malformations, with only a few hundred cases having been reported in the literature since Jaeger's original description. If one considers only pediatric cerebrovascular malformations, however, vein of Galen malformations constitute a significant proportion of reported lesions. In a study by Long and colleagues at the University of Minnesota (1974), vein of Galen malformations made up 33% of all giant AVMs found in infancy or childhood.

Clinical Presentation

The clinical presentation of vein of Galen malformations depends on the patient's age. Neonates (0 to 1 month) usually present with high-output CHF requiring aggressive medical management. Infants (1 to 12 months) often present with hydrocephalus, compensated CHF, and occasional seizures or focal neurologic deficits. Patients who present between 1 and 5 years of age have even less severe CHF, whereas patients older than 6 years often present with parenchymal or subarachnoid hemorrhage as well as neurologic deficits and seizures.

Evaluation and Diagnosis

In addition to clinical signs of CHF—hydrocephalus, seizures, and possible auscultation of a cranial bruit—vein of Galen malformations can be detected using multiple imaging modalities. Ultrasound is a useful screening tool both in utero and during the neonatal period. The addition of Doppler ultrasonography allows better differentiation between vascular and nonvascular midline structures. Ultrasonography also allows one to follow the progress of occlusive surgical or endovascular therapy.

CT also is able to detect vein of Galen malformations. On CT, these lesions appear as rounded, low-density masses lying in the region of the quadrigeminal plate (the dorsum of the midbrain) and the pineal gland. If there is thrombus within the dilated vein of Galen, however, the lesion can appear radiodense on CT (Figure 103-4A). Calcification can be present, and if intravenous contrast is administered, the aneurysm as well as any large feeding arteries will appear enhanced.

Compared with ultrasound and CT, MRI affords much greater anatomic detail in evaluating a vein of Galen malformation. The malformation itself, its arterial feeders, and venous drainage will all appear as low signal "flow voids" on MRI (Figure 103-4B). MRA and MRV allow for some anatomic definition of arterial feeders, venous drainage, and the degree of thrombosis within the dilated vein. Despite the anatomic information yielded by MRI, conventional cerebral angiography remains the gold standard for anatomic definition and treatment planning in caring for patients with vein of Galen malformations (Figure 103-4C).

Treatment

Treatment of vein of Galen malformations depends in large part on the patient's age at diagnosis and medical condition. With improvement in ultrasonographic techniques, the diagnosis is often made during the prenatal period. In this instance, the fetus also must be assessed for evidence of other anomalies and distress. Once this information is obtained, the parents must be thoroughly counseled as to the nature of the disorder and the potential for significant morbidity or mortality.

In addition, it is important to stress to the parents that there are no known genetic factors involved in the disorder and that no predisposing environmental factors have been identified. In addition, prenatal diagnosis also allows for time to ensure the baby is delivered at a hospital with capable neurosurgical, neuroendovascular, and neonatal critical care teams. The prenatally diagnosed patient may be delivered vaginally, as there are not strict indications for cesarean section in cases in which both the baby and the mother are medically stable and no cephalopelvic disproportion exists. After delivery, the decision to intervene is based on clinical manifestations, including CHF, hydrocephalus, seizures, or developmental delay. If the patient remains asymptomatic, some would recommend close follow-up only, whereas others would recommend elective angiography and obliteration at about 6 months of age.

At whatever age a patient presents, multiple treatment techniques have been described for vein of Galen malformations. Although technically very different, all approaches share the common goal of obliterating the anomalous AV communication. This has been attempted surgically by careful exposure and clipping (occlusion) of all arterial feeders, thus initiating thrombosis of the aneurysm. Because of high surgical morbidity and improvements in endovascular technique, however, the endovascular approach has largely supplanted surgery in the treatment of vein of Galen aneurysms. Multiple endovascular routes have been described, but currently, transarterial access via femoral puncture is the most commonly used. This usually involves deposition of occlusive material (coils, balloons, acrylic glue) into the malformation to achieve complete obliteration. This is best achieved gradually with multiple endovascular procedures to avoid possible hemorrhage or cardiac decompensation that can accompany abrupt closure of vein of Galen malformations.

Outcome

In general, vein of Galen malformations carry a high morbidity and mortality depending on the flow characteristics of the lesion and the medical condition of the patient. Neonates presenting with severe CHF fall into the group with the worst outcome. In a review of 70 neonatal cases, Johnson and colleagues (1987) found an overall mortality of 91% (64 of 70) with little or no difference between medical, surgical, and endovascular management. More recent selected endovascular series, however, present a slightly more promising picture. Friedman and colleagues (1993) reported no mortality and 45% morbidity in 11 neonates; Lasjuanias and colleagues (1991) reported 8% mortality and 75% morbidity in 13 neonates; and Circillo and colleagues (1990) reported 25% mortality and 50% morbidity in eight neonates.

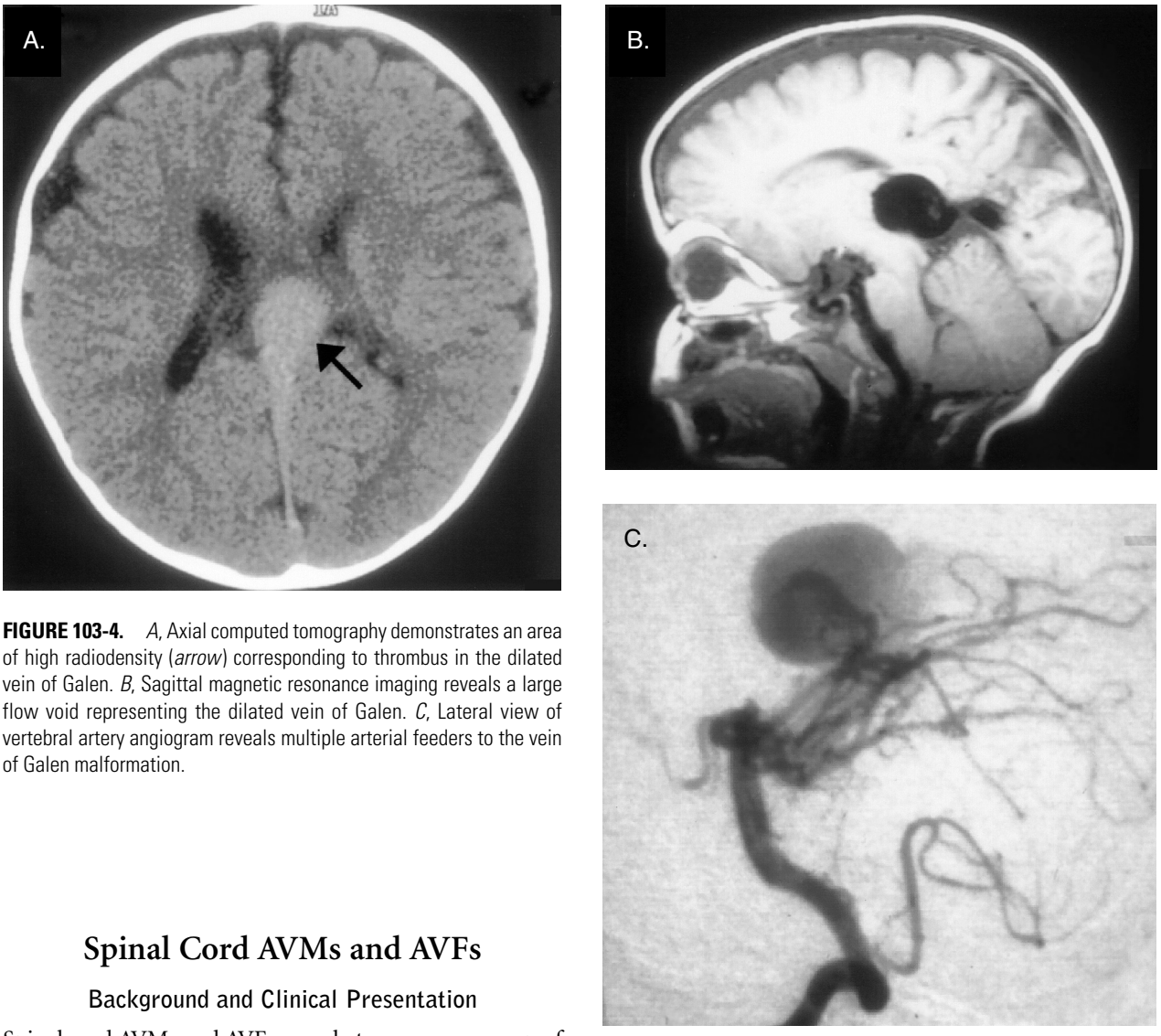

FIGURE 103-4. *A,* Axial computed tomography demonstrates an area of high radiodensity (*arrow*) corresponding to thrombus in the dilated vein of Galen. *B,* Sagittal magnetic resonance imaging reveals a large flow void representing the dilated vein of Galen. *C,* Lateral view of vertebral artery angiogram reveals multiple arterial feeders to the vein of Galen malformation.

Spinal Cord AVMs and AVFs

Background and Clinical Presentation

Spinal cord AVMs and AVFs are a heterogeneous group of lesions that are much rarer than intracranial AVMs. As with their intracranial counterparts, all spinal cord AVMs share the unifying trait of a direct AV connection in or around the spinal cord. The heterogeneity in this group has led to multiple classification attempts. In Table 103-1, we classify these lesions (as initially proposed by Rosenblum and colleagues at the National Institutes of Health [NIH] in 1987) into four types on the basis of the different anatomy, location, and extent of the anomalous AV connection. For the remainder of this section, we will expand upon the information summarized in Table 103-1.

Spinal AVFs are extradural spinal cord AVMs. These lesions represent a direct AVF between an extradural radicular artery (branch to the nerve root) and an intradural medullary vein. These lesions account for 60 to 80% of all spinal cord AVMs. Because they occur almost exclusively in older adults, however, they will not be discussed further.

Intradural spinal AVMs are further subdivided into intradural AVFs, glomus intramedullary malformations, and juvenile intramedullary AVMs. Intradural AVFs consist of an anomalous connection between the anterior spinal artery and vein. These lesions reside outside the pia mater and the spinal cord, frequently at the level of the conus medullaris. Intradural AVFs often present in adolescents or young adults with progressive myelopathy but also have been reported to cause spinal subarachnoid hemorrhage.

Glomus malformations are the spinal cord equivalent of the intraparenchymal, cerebral AVMs. These lesions reside within the spinal cord and involve a compact tangle of vessels (or "nidus") with multiple arterial feeders and draining veins. They most frequently occur in the cervical cord

TABLE 103-1. Spinal Cord Arteriovenous Malformations*

Type	Anatomy	Clinical Presentation	Pathophysiology	Age	Gender	Treatment	Comments
Dural AVF	Radicular artery-to-medullary vein fistula on superior aspect of dorsal nerve root sleeve	Progressive myeloradiculopathy	Venous hypertension in spinal cord	40–70	Male	Surgery	Most common spinal cord AVM
Intradural AVF	Fistula between anterior spinal artery and vein in subarachnoid space	Progressive myelopathy or subarachnoid hemorrhage	Compression, steal venous hypertension	5–40	Equal	Small = surgery Large = endovascular	Higher flow in larger lesions requires embolization
Glomus AVM	AVM without spinal cord. Usually has multiple feeders	Acute myelopathy or pain (progressive pattern much less common)	Hemorrhage, compression, steal	20–50	Equal	Surgery	Pathologically similar to intracranial AVM
Juvenile AVM	Large AVMs that can involve spinal cord, extramedullary space, and adjacent vertebral bodies	Pain or progressive myelopathy	Compression, steal, hemorrhage				Extremely rare and carry a poor prognosis

*Classified according to Rosenblum B, et al, NIH, 1987.

AVF = arteriovenous fistula; AVM = arteriovenous malformation.

of adults between 20 and 50 years of age and often present with hemorrhage, causing acute myelopathy.

Juvenile AVMs are extremely rare lesions that afflict a younger population than do the other three types of spinal cord AVMs. In general, patients present between 5 and 30 years of age with pain or progressive neurologic deficit. These lesions occupy entire segments of the spinal cord and canal and often extend into the adjacent vertebral body.

Evaluation and Diagnosis

As is the case with many vascular lesions, the "gold standard" for diagnosis and classification of spinal cord AVMs and AVFs is selective spinal angiography. Other imaging modalities, however, also can point to the diagnosis and are helpful in treatment planning. Chief among these is MRI. On MRI, spinal cord AVMs (depending on the type and size) often can be revealed by flow voids representing involved vessels, compression or expansion of the spinal cord, evidence of hemorrhage, or areas of spinal cord edema or infarction. MRI is also helpful in indicating the precise spinal level involved, allowing for planning of the surgical approach. A combination of MRA and MRI, however, are the central modalities used in the diagnosis of these lesions. Currently, both CT and conventional myelography are contraindicated in the presence of a spinal AVM or AVF because of the risk of puncturing a draining vein with the needle.

Treatment

The goal of treating any spinal cord AVM is to eradicate the anomalous AV connection. Depending on the type of AVM, this is currently best achieved by surgery, endovascular therapy (see Table 103-1), or a combination of the two. The best approach to intradural AVFs depends on the size of the lesion. In smaller lesions, surgery is preferred, as endovascular cannulation of the feeding vessels is difficult and risky. Larger lesions, however, are best treated via the endovascular route in many instances. In general, glomus AVMs are primarily treated surgically, with endovascular embolization playing an adjunctive role. In the case of juvenile AVMs, the extent of the lesion often makes surgical excision impossible or prohibitively morbid. Palliative endovascular therapy can be considered. The role of stereotacic radiotherapy with the Cyberknife in these lesions is unclear.

Outcome

Outcome after treatment of a spinal cord AVM depends largely on the type and extent of the lesion. The primary mode of therapy for intradural spinal AVF depends on the size of the lesion. Smaller lesions are best treated surgically, as the small feeding vessels are difficult to approach endovascularly. For larger lesions, the primary treatment modality is endovascular. These lesions are relatively rare and were only first described in 1977, so there are still too few patients treated to make strong statements about long-term outcome. In most series, however, the majority of lesions can be obliterated, and most patients either stabilize or improve clinically following treatment. In 1993, Mourier and colleagues in France reported on 35 patients with intradural spinal AVFs. Overall, 79% (27 of 34 treated patients) were completely obliterated and 91% (31 of 34 treated patients) were clinically improved or unchanged after treatment.

Glomus AVMs are primarily treated surgically but not without morbidity and mortality. Yasargil and colleagues

in Zurich (1984) reported a mortality of 5% and clinical deterioration in 20% of patients, and Rosenblum and colleagues at the NIH (1987) reported 2% mortality and neurologic deterioration in 14%.

Juvenile AVMs are difficult to treat by any means, and complete obliteration or removal is often impossible. Both the endovascular and surgical approaches have been attempted. Because of the extent of the lesion and its intimate involvement of the spinal cord, surgical excision carries a high morbidity. For these reasons, most favor endovascular palliation. As reported by Bao and colleagues at Beijing Hospital (1997), however, 74% (17 of 23) of their patients with juvenile AVMs required repeat endovascular treatment because the lesion recurred.

Suggested Readings

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terBrugge KG. Neurointerventional procedures in the pediatric age group. Childs Nerv Syst 1999;15:751–4.

Practitioner and Patient Resources

Neurosurgery 4 Kids
Primary Children's Medical Center
100 N. Medical Drive, Suite 2400
Salt Lake City, UT 84113
Phone: (801) 588-3400
http://www.neurosurgery4kids.com/vascular_malformations.htm
This site offers a comprehensive service in the management of all types of vascular malformations of the brain and spinal cord.

Chicago Institute of Neurosurgery and Neuroresearch
Phone: (800) 411-2466
http://www.cinn.org/ibsc/pediatric/vascular.html
This page describes a program that provides a multidisciplinary team approach needed to successfully treat these complex and complicated disorders.

The Johns Hopkins Pediatric Neurovascular Center
Phone: (410) 955 8525
A comprehensive multidisciplinary team with experience in neurosurgical, endovascular and radiotherapeutic management of pediatric neurovascular conditions.

CHAPTER 104

PEDIATRIC INTRACRANIAL ANEURYSMS

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Intracranial aneurysms are rare in the pediatric population. Because most physicians have little experience with these cases, the treatment of children with subarachnoid hemorrhage due to a ruptured cerebral aneurysm is not as well standardized as for adults. Consequently, the management of these complex and potentially lethal lesions can pose substantial problems for patients and their physicians.

Although the etiology of most pediatric intracranial aneurysms remains controversial and some systemic diseases have been associated with an increased risk for aneurysm formation, most patients with a cerebral aneurysm do not harbor any underlying disorders. Indeed, the presentation of any previously healthy child with stroke or stroke-like symptoms should prompt the physician to consider a ruptured cerebral aneurysm.

Because aneurysms in children are most likely to be fully formed congenital malformations, it follows that any child, no matter how young or healthy, can harbor one or more of these lesions. In the setting of stroke, early investigation and aggressive treatment are therefore imperative to prevent further neurologic deterioration and to fully optimize medical and surgical care.

Incidence

Pediatric intracranial aneurysms (birth to 18 years of age) represent, in most series, 0.5 to 4.6% of all diagnosed aneurysms, according to our meta-analysis of the pediatric aneurysm literature over the past 64 years, in which a total number of 703 cases were analyzed. In the 1966 Cooperative Aneurysm Study, which evaluated 6,368 patients, Locksley and colleagues found that only 41 children (0.6%) presented with aneurysmal subarachnoid hemorrhage (SAH). Patel and Richardson analyzed 3,000 cases involving ruptured aneurysms and found that 58 (2%) occurred in patients under the age of 19. In four other large series of spontaneous SAH involving nearly 8,000 cases, only 321 patients (4%) were under the age of 20 years. Most recently, Proust and colleagues described 22 patients treated at three hospitals in northwestern France between 1986 and 1999, with an incidence of pediatric aneurysm of 1.02%. Our series, comprised of 1377 aneurysm cases treated between 1991 and 2004, included 19 patients 18 years or younger (1.4%). In most of these series, aneurysmal rupture was rare in neonates and infants (< 1%). The incidence of aneurysmal SAH, however, clearly increases throughout childhood, and peaks in late adolescence. Although there is some discrepancy among the different pediatric series, most suggest a male predominance (male-to-female ratio 1.75:1).

Aneurysm Location and Size

The most common aneurysm site in the pediatric population is the internal carotid bifurcation. In our meta-analysis, 26% *adults.* of the 703 aneurysms occurred in this location. The second most common site is the anterior communicating complex (19% of cases), and the third is the MCA bifurcation (17% of cases). Aneurysms were

identified in the posterior circulation in 17% of the cases, in contrast with the adult population, where posterior circulation aneurysms are found in approximately 10% of the cases.

Most pediatric series report that large (> 12 mm) and giant (> 24 mm) aneurysms are common. For example, of the 29 pediatric aneurysm patients treated at the Hospital for Sick Children in Toronto, in which Storrs and colleagues reported that 10 (35%) had aneurysms in the posterior circulation, 9 (31%) had aneurysms at the carotid bifurcation, and 9 (31%) patients presented with giant aneurysms. In a 1998 study involving 21 patients at the University of Arkansas, Allison and colleagues found that 40% of aneurysms were judged to be large. These findings correlate well with Ferrante's 1988 review of 71 saccular aneurysms in children younger than 5 years of age, where the prevalence of large and giant aneurysms was reported at 50 and 27%, respectively.

Multiple aneurysms in children are relatively infrequent and represent less than 5% of all pediatric cases. However, when they do occur, as many as 20% appear to be associated with aneurysms that are infectious in origin.

Pathology

The pathogenesis of aneurysm formation in children is controversial but is likely to be due to a combination of congenital and degenerative factors. In a 1950 study, Carmichael demonstrated that the transition zone from a normal vessel wall into the aneurysmal sac is characterized by the absence of tunica media and increasing fragmentation of internal elastic lamina. Carmichael then went on to propose that the pathogenesis of aneurysm formation at these sites involves additional degenerative changes acquired throughout life. This concept of an underlying congenital defect accompanied by additional degenerative forces is known as the "combination hypothesis." This hypothesis not only explains why aneurysms are rare in children but also why they become increasingly common into late adulthood.

Although most aneurysms are sporadic in nature, several heritable diseases have been associated with intracranial aneurysms. Of these, only patients with polycystic kidney disease, aortic coarctation, sickle cell anemia, Ehlers-Danlos syndrome type IV, collagenopathy, and pseudoxanthoma elasticum are at increased risk of aneurysm formation. Furthermore, although a familial tendency for aneurysm formation may exist in some cases, the hereditary nature of infantile aneurysms remains an open question. As reported by Kuchelmeister in 1993, only one sibling of 45 patients with infantile aneurysms also suffered from an intracranial aneurysm. In all the remaining cases, there has been no evidence of hereditary nature of aneurysm formation. Fusiform aneurysms may occur in dysplastic vascular segments in the absence of systemic disease or in association with other disorders, such as an infectious or traumatic process.

Infectious aneurysms secondary to septicemia or endocarditis account for up to 2% of all pediatric aneurysms. The most common mechanisms of infectious aneurysm formation include (1) local invasion of a vessel, (2) infectious emboli to lumen of a vessel, such as from bacterial endocarditis, and (3) a cryptic infectious aneurysm with no obvious source of infection. The most commonly isolated organisms are *Staphylococcus aureus* and *Streptococcus*. Infectious aneurysms due to fungal infections, including *Aspergillus*, *Candida*, and *Phycomycetes*, are increasingly predominant in immunocompromised patients, such as those who have undergone organ and bone marrow transplantation.

Recently, there have been increasing reports of infectious aneurysms secondary to human immunodeficiency virus (HIV) infection. Mononuclear cells expressing HIV antigen have been demonstrated in the intima of the affected vessels. The notable pathologic changes in those patients include intimal fibroplasia, medial thinning, and elastic lamina destruction. The higher frequency of mycotic aneurysms in childhood may partly account for the greater percentage of peripheral aneurysms in the pediatric population.

Traumatic aneurysms account for 14 to 39% of all pediatric aneurysms in different series, and arise from both penetrating and nonpenetrating trauma. These aneurysms tend to differ from berry aneurysms in two ways: location and histology. Unlike berry aneurysms, traumatic aneurysms tend to be peripheral, irregular, and without necks. They also lack an endothelial lining, making them effectively pseudoaneurysms. In terms of penetrating injuries, stabbing injuries are much more likely to result in pseudoaneurysm formation than missile injuries. On the other hand, nonpenetrating injuries are usually secondary to acute shearing forces, as in rapid deceleration injury, or due to a skull fracture with underlying dural and cortical contusions. In this context, clinical deterioration in a patient with prior history of trauma should raise suspicions concerning the possibility of a traumatic intracranial aneurysm.

Clinical Presentation

Acute rupture with subarachnoid hemorrhage (SAH) accounts for up to 80% of all presentations in children. In neonates or infants, the signs and symptoms of SAH may be nonspecific, including irritability, drowsiness, poor oral

intake, or vomiting. Older children present with symptoms similar to those occurring in adults, such as acute headache, loss of consciousness, nausea, vomiting, photophobia, neck stiffness, and neurologic deficits. In our series, a complaint of headache prompted diagnostic inquiry in 3 of the 16 patients, who were found to have unruptured giant aneurysms. Seizures are especially common in both infants and older children. The relatively higher percentage of peripheral aneurysms in the pediatric population also has been associated with a greater frequency of parenchymal hematomas. Importantly, children tend to present in better clinical condition than do adults.

In cases of unruptured aneurysms, neurologic symptoms are most often related to mass effect. Given the higher percentages of large and giant intracranial aneurysms in the pediatric population, a higher frequency of neurologic abnormalities due to mass effect from the aneurysm is seen in children (18%) compared with adults (2.5%). Symptoms include partial complex seizures, cranial nerve palsies, or hemiplegia. In fact, up to 33% of giant aneurysms produce cranial nerve palsies or symptoms related to direct brainstem compression. In this context, new neurologic findings in a healthy child should prompt a search for vascular as well as intraparenchymal intracranial lesions.

Diagnosis

Timely diagnosis of a cerebral aneurysm depends upon a high index of suspicion. If the patient's history and neurologic examination reveal the possibility of any intracranial vascular pathology, that patient should be suspected of having an aneurysmal SAH until proved otherwise. Urgent computed tomography (CT) scan should be performed to confirm the clinical impression. A negative CT scan, however, may inadvertently reassure the physician. The sensitivity of CT scan in detecting intracranial blood is 92% on the day of SAH and subsequently decreases about 7% per day, so by day 5 only 58% of CT scans will be positive. In cases where the history and physical exam are compelling, a lumbar puncture is necessary to rule out aneurysmal SAH and may help to rule out other processes, such as an infection.

The presence of SAH on a cerebral CT scan or lumbar puncture requires four-vessel cerebral angiography. Cerebral angiography remains a useful and safe diagnostic modality in infants and children when used for appropriate indications by individuals with pediatric neuroangiographic training and experience. Recently, in a prospective study of 241 consecutive diagnostic pediatric cerebral angiograms, we found that the rates of intra-procedural and post-procedural complications were 0.0% and 0.4%, respectively. Angiography is essential not only to confirm the presence of the aneurysm but to further plan the surgical approach. By means of angiography, the neurosurgeon can (1) define the exact location and anatomic relationships of the lesion, (2) search for additional aneurysms, and (3) determine the lesion most likely to have hemorrhaged in the setting of multiple aneurysms. In most pediatric patients, the use of general anesthesia is recommended to safely conduct the procedure and make the patient as comfortable and pain free as possible.

The use of CT angiography or magnetic resonance angiography (MRA) is not advised at this point as replacement for standard angiography. Although the noninvasive nature of these tests makes them particularly appealing in the pediatric population, both suffer from serious limitations. These include the inability to visualize an aneurysm secondary to adjacent spasm or a blood clot, small aneurysm size, and presumed slow flow within the aneurysm. In addition, both tests have to be performed under heavy sedation or anesthesia because motion artifacts can severely affect the quality of the study. Consequently, although CT angiography or MRA may have a future role in the noninvasive screening of patients at risk for aneurysm rupture, conventional angiography remains the gold standard for preoperative imaging.

In active children, the diagnosis of aneurysmal SAH may sometimes be obscured by a history of a head injury. This is because trauma remains the most common cause of nonaneurysmal SAH in children. However, in a 1973 study by Sedzimer, aneurysmal rupture was identified in 40% and arteriovenous malformation hemorrhage in 27% of all pediatric SAH cases. In light of these findings, any delayed neurologic decline or failure to improve as expected after a blunt or penetrating head injury suggests that a traumatic aneurysm or an undiagnosed vascular injury may be present, regardless of previously negative imaging studies. In this clinical situation, cerebral angiography to further investigate or exclude a traumatic aneurysm is mandatory.

Management

Pediatric aneurysms are best managed by a multidisciplinary team familiar with all aspects of this rare disease. In this setting, appropriate decisions can be reached regarding the treatment of unruptured, ruptured, traumatic, and infectious aneurysms.

Unruptured aneurysms should be treated to exclude the aneurysm from the intracranial circulation. In adults, a recent analysis of unruptured aneurysms has shown an annual rupture risk of 1.3%. In children, who generally present with large and giant aneurysms, this number may be even higher. Given these numbers, the

cumulative annual risk of aneurysm rupture is much higher in younger patients and places them at a substantial lifetime risk of rupture. The case for considering treatment of asymptomatic lesions in children is, therefore, compelling.

The high mortality associated with rupture, together with a risk of rebleeding, further necessitates early and definitive intervention. This may take the form of either surgical clipping or endovascular coiling, depending on the lesion's anatomy. Children who present with evidence of hydrocephalus, intracerebral hematoma, or subdural hematoma warrant aggressive treatment, including cerebrospinal fluid (CSF) drainage, evacuation of hematoma, and, if possible, simultaneous exclusion of the lesion from circulation. In neonates and infants, care should be exercised to avoid intraoperative rupture and excessive blood loss, given the relatively small total blood volume of the child.

The surgical management of vertebrobasilar aneurysms is frequently complex and challenging. Of the 26 posterior circulation aneurysms in children treated by Amacher in 1981, 10 required procedures other than direct clip obliteration. Likewise, in a 1989 study, Meyer and colleagues reported that 10 of 24 children with vertebrobasilar aneurysms required specialized treatment, including trapping of the parent vessel, microanastomosis, and bypass procedures. Indeed, low-flow deep hypothermic circulatory bypass (DHCB) and pharmacologic cerebral protection have emerged as useful adjuncts in the treatment of complex intracranial vascular lesions. A combined therapy of hypothermia at 18 to 20°C and barbiturates provides a safe circulatory bypass time of up 45 to 60 minutes. When used under appropriate circumstances, these interventions can allow successful obliteration of these complex lesions, resulting in optimal neurologic outcome.

Intracranial traumatic aneurysms, or pseudoaneurysms, are usually managed by operative intervention. Optimal surgical approach and technique must be tailored to fit each individual situation but remain constant for each regional aneurysm site. Traumatic aneurysms arising from the main arterial trunk may be treated by direct clipping or trapping or, in some circumstances, may prove more amenable to arterial reconstruction or bypass. Aneurysms arising more distally may not always be treated by a direct surgical attack and may require sacrifice of the parent vessel with or without bypass or anastomosis. In either case, survival and outcome depend on the severity and extent of the primary and secondary central nervous system injuries generated by the initial trauma. A review of 22 series has demonstrated better clinical outcomes and lower death rates of death in those that had higher proportions of surgically treated patients.

The optimal treatment of infectious aneurysms has sparked a debate in recent years. Although some advocate a conservative approach using antibiotics, others contend that surgical results appear to be associated with better outcome. At the heart of this debate are reports that up to 50% of patients improve with long-term antibiotics alone, as documented by a decreasing size of the aneurysm. At the same time, the mortality in patients treated with antibiotics alone approaches 40% versus 7 to 10% with surgery. The high mortality associated with conservative treatment is inherent to the variable and unpredictable course of these aneurysms; however, the risk of surgical intervention, especially with proximal, friable aneurysms and inaccessible, distal aneurysms, is high and likely related to the significant selection bias in the surgical group. Consequently, while a course of antibiotic therapy may be appropriate during initial therapy, the persistence of an infectious aneurysm should warrant surgery.

During the past 10 years, endovascular procedures have been increasingly used to treat patients with intracranial aneurysms. This form of therapy is most suitable for small aneurysms and will probably continue to play an important role in the management of children in the future. Endovascular coils are not recommended for large or giant aneurysms, lesions with large necks, pseudoaneurysms, or fusiform aneurysms. Sanai and colleagues found that 15% of endovascularly treated aneurysms recurred, compared to no recurrences in the microsurgically treated aneurysms. Recently, liquid thrombotic material, such as cellulose acetate polymer, which attaches to irregular vessel walls, has been used to successfully embolize a pseudoaneurysm. Long-term follow-up of these alternatives, however, is not yet available to establish their durability. Furthermore, recurrences with endovascular treatment are especially relevant in young patients with extended life expectancies. Combined approaches will probably be required in the management of most of these complex and challenging cases.

Finally, medical management of pediatric patients with aneurysmal SAH is as important as the surgical or endovascular intervention in ensuring a favorable outcome. For instance, of the 1,368 patients treated by Ostergaard and Voldby between 1943 and 1980, 53% showed radiologic evidence of vasospasm, as documented by angiograms obtained 4 to 16 days after the SAH. To date, ischemic events related to vasospasm are infrequently reported in the pediatric literature, and the prognostic significance of vasospasm has yet to be determined in children. Nevertheless, the avoidance of factors such as hypotension and hypovolemia can prevent the development of cerebral vasospasm. Other standard treatments that have been used in adults, such as nimodipine,

hypervolemia, hemodilution, angioplasty, or intra-arterial papaverine, are recommended for use in children in the prevention and treatment of vasospasm.

Outcomes

The outcome of aneurysm surgery for children is better than that for adults. The data are especially compelling in cases of elective surgery, where up to 98% of children with unruptured aneurysms have an uneventful perioperative course and go on to lead normal lives.

For children who present with aneurysmal SAH, early diagnosis and treatment also can lead to good results. In general, children tend to present in better clinical grades and appear to have a lower incidence of ischemic complications related to vasospasm that account for much of the morbidity and mortality associated with aneurysm rupture. The surgical management of pediatric aneurysms serves well to illustrate this point: of the 43 patients treated in the 1988 French Cooperative Study, 27 (63%) were cured without any sequelae, 9 (21%) lost one school year but were able to lead a normal life, and 2 (5%) remained severely handicapped. The overall postoperative mortality was 12%. In our series, favorable outcomes were achieved in 94% of the cases.

Conclusion

Pediatric aneurysms are rare, and children with these lesions benefit most from a multidisciplinary team at an experienced tertiary care center. An awareness of the disease and a high level of suspicion establish the grounds for successful intervention. The basic tests, including CT of the brain and, when appropriate, a lumbar puncture, can usually be performed in the emergency department. Any suspicion of SAH should be subsequently evaluated with four-vessel cerebral angiography, the gold standard for diagnosing intracranial vascular lesions. The choice of surgery or endovascular coiling depends on the lesion, with most complex aneurysms requiring combination therapy. The results with surgical clipping or endovascular coiling are excellent and have greatly improved the outcome in children with ruptured and unruptured aneurysms.

Case Illustration

A 14-week-old male infant was brought to the emergency department because of a single generalized tonic-clonic seizure after a 5-day history of fevers and irritability. His past medical history was notable only for sickle cell trait. Upon examination, he was noted to be febrile and to have meningismus. He otherwise had a normal neurologic exam. A lumbar puncture revealed bloody cerebrospinal fluid. The diagnosis of a hemorrhagic viral meningoencephalitis was therefore entertained, and the patient was started on acyclovir. An atypical course, however, prompted a repeat lumbar puncture the following day, which was equally bloody. Computed tomography (CT) and magnetic resonance imaging scans were obtained and revealed a large vascular lesion in the region of the left sylvian fissure (Figure 104-1A and B). The diagnosis of aneurysmal subarachnoid hemorrhage was then made, and the patient was started on nimodipine and diphenylhydantoin. Maintenance intravenous fluids were continued. A cerebral angiogram was then obtained and confirmed the presence of a giant left middle cerebral artery (MCA) fusiform aneurysm (Figure 104-1C and D). The following day, while preparations were being made for surgery, the patient developed a right hemiparesis. A CT scan did not reveal any changes but a transcranial Doppler evaluation showed elevated velocities in the left MCA distribution. Given the onset of clinical vasospasm, surgery was postponed and hypervolemic therapy was initiated with rapid improvement in the hemiparesis.

The following day, the patient became acutely unresponsive after a bowel movement. A CT scan revealed a large repeat intraparenchymal hemorrhage in the left frontal region associated with the aneurysm. The patient was stabilized and subsequently again became alert and interactive again. Nevertheless, he displayed worsening of the right hemiparesis and a new slightly dilated left pupil. The decision was then made to proceed with emergent surgery for clipping of the aneurysm and evacuation of the hematoma under deep hypothermic cardiopulmonary bypass.

The patient tolerated the surgery well and awoke with mild accentuation of the right hemiparesis, which returned to the preoperative baseline within two days. The major postoperative therapeutic manipulation was a continuous infusion of 3% sodium chloride solution (reaching a serum sodium of 150–156 mEq/L) to simultaneously treat cerebral edema and maintain a high intravascular volume for the treatment of vasospasm.

The patient was discharged 15 days after surgery. His subsequent course has been characterized by steady recovery and significant improvement of the right hemiparesis. At 1 year after surgery, the patient displayed ageappropriate language function and proximal functional movement of the right upper and lower extremities but limited movements of the right-hand fingers and slight delay in ambulatory function. The only complication since surgery has been a brief recurrence of seizures when an attempt was made to withdraw antiepileptic drugs. He has remained seizure-free on carbamazepine and primidone.

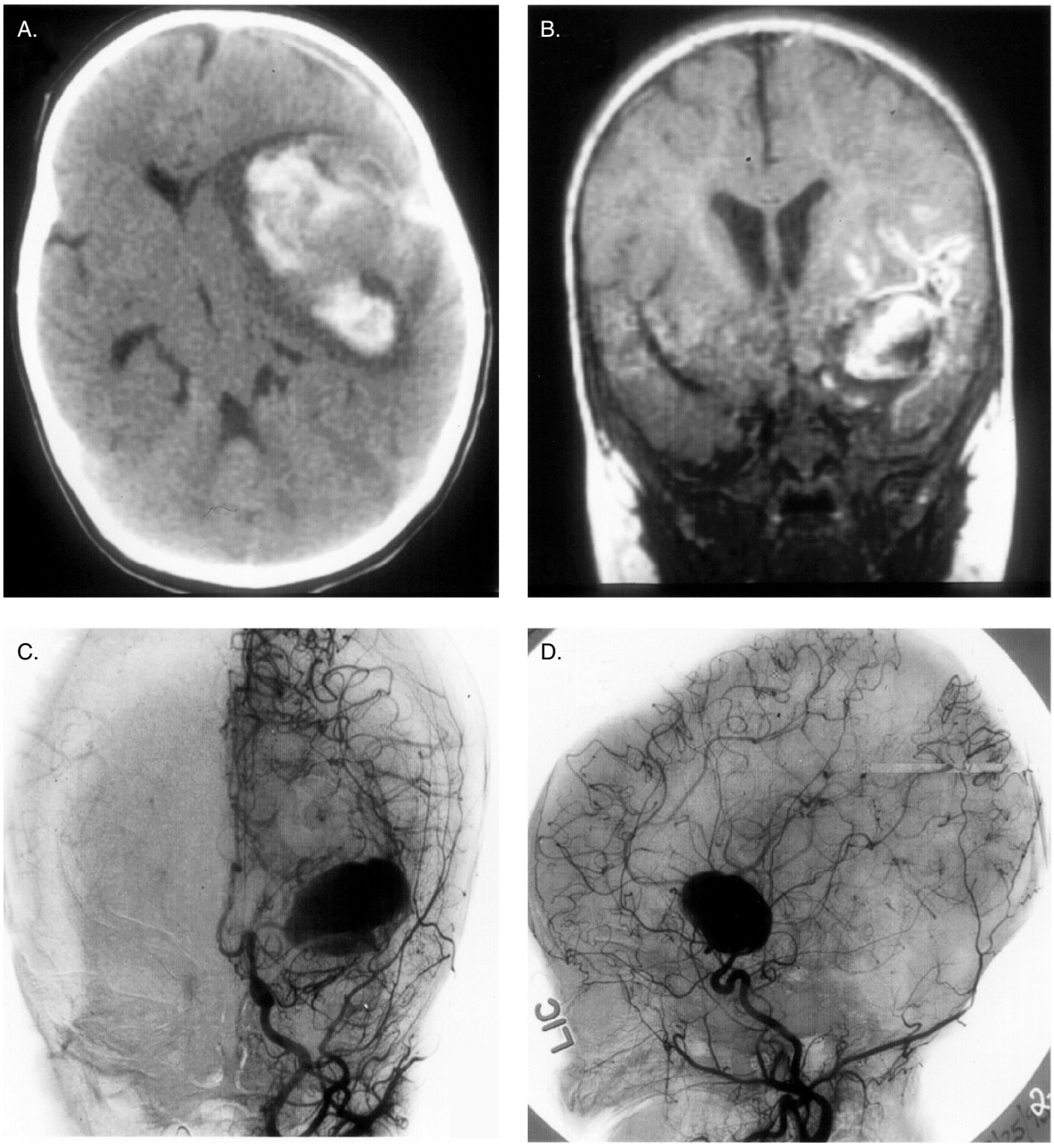

FIGURE 104-1. *A,* Computed tomographic scan and *B,* magnetic resonance image of an acute left intraparenchymal hemorrhage with mass effect and midline shift. A cerebral angiogram (*C* and *D*) subsequently confirmed the presence of a giant left middle cerebral artery fusiform aneurysm.

Suggested Readings

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Ventureyra EC, Higgins MJ. Traumatic intracranial aneurysms in childhood and adolescence. Case reports and review of the literature. Childs Nerv Syst 1994;10:361–79.

Practitioner and Patient Resources

Brain Injury Resource Center
212 Pioneer Bldg.
Seattle, nWA 98104-2221
Phone: (206) 621-8558
E-mail: brain@headinjury.com
http://www.headinjury.com

A service of Head Injury Hotline providing difficult to find information about head injury since 1985. This site offers educational and supportive links and resources aimed at teaching families how to cope with brain injury and aneurysm.

Skull Base Institute
8635 West 3rd Street
Los Angeles, CA 90048
Phone: (310) 691-8888
Toll-free: (866) 266-9627
staff@skullbaseinstitute.com
The Skull Base Institute is devoted exclusively to the treatment of patients with brain and skull base disorders including aneurysms and arteriovenous malformations. The site offers a toll-free hotline, information about treatments and procedures, and links to newsletters, articles and peer-reviewed journals.

CHAPTER 105

STROKE AND CEREBROVASCULAR DISEASE

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GABRIELLE DEVEBER, MD, FRCP(C)

Stroke and cerebrovascular disease cause pediatricians considerable anxiety, in part because these conditions are relatively rare and protocols for investigation and treatment are not well established. As a result of controlled trials of patients with thrombolysis, there is increased awareness of the need for rapid assessment and appropriate management of adults with acute stroke, and the concept of a "brain attack" has been widely publicized in the United States. There is little doubt that stroke units save adult lives and improve outcome in survivors. In contrast, services for children are relatively poorly organized, and it has not yet proved possible to conduct large randomized trials of treatment in groups of children with similar pathologies.

Several units around the world have acquired expertise in the treatment of stroke and cerebrovascular disease, and in this chapter we attempt to summarize the current position. The evidence to date has come largely from studies in adults or from case series in children and must be evaluated in that light when attempting to design a management strategy for an individual child that can be justified to the parents. There is, however, no longer an excuse for doing nothing, as cerebrovascular disease is an important cause of progressive childhood disability.

Background

A number of congenital and acquired cerebrovascular disorders in childhood may lead to substantial disability. Vascular pathologies seen in children include the following:

- Cerebral sinovenous thrombosis (CSVT)
- Stenosis and occlusion of the intracranial internal carotid or middle cerebral or anterior cerebral arteries, sometimes with "moyamoya" collaterals
- Dissection of the extracranial and intracranial carotid and vertebrobasilar circulations
- Embolus from the placenta in neonates, from a structurally abnormal heart, or from proximal cerebrovascular disease (eg, carotid or vertebral dissection)
- Small-vessel "vasculitis" (see Chapter 106, "Vasculitis")
- Aneurysm (see Chapter 104, "Pediatric Intracranial Aneurysms")
- Arteriovenous malformation (see Chapter 103, "Central Nervous System Vascular Malformations")
- Vein of Galen malformation (see Chapter 103, "Central Nervous System Vascular Malformations")
- Sturge-Weber syndrome (see Chapter 83, "Sturge-Weber Syndrome")

This chapter focuses on ischemic stroke, including arterial ischemic stroke (AIS) and CSVT, and discusses important differential diagnoses, such as hemorrhagic stroke and reversible posterior leukencephalopathy, in passing. Children may present with clinical stroke (ie, a focal neurologic deficit with neuroimaging evidence of abnormality in an established vascular territory) or transient ischemic attack (as for stroke, but deficit lasts < 24 hours and is not associated with new neuroimaging abnormality). Seizures and coma may be secondary to vascular pathology, however, and less common presentations include cardiac failure secondary to vein of Galen malformation. Conventionally, these children have not been extensively investigated, on the basis that the risks (eg, of conventional arteriography) were not justified when there was no effective treatment. With the advent of noninvasive ultrasonographic and magnetic resonance imaging

TABLE 105-1. Neuroimaging of Brain and Vessels

1. MRI (including diffusion and perfusion), MRA, and MRV
   - Exclude hemorrhage
   - Define extent and territory of infarct
   - MRA to define vascular anatomy of circle of Willis and neck vessels
   - T_1-weighted spin echo of the neck with fat saturation sequence to exclude dissection
   - MRV to exclude sagittal sinus thrombosis
   - Diffusion imaging to differentiate acute from chronic infarction
   - Perfusion imaging to demonstrate areas of abnormal cerebral blood flow, blood volume, and mean transit time
2. CT scan to exclude hemorrhage if MRI not available acutely
3. Conventional angiography if
   - Hemorrhage without coagulopathy
   - Ischemic stroke, MRA normal, and MRI of the neck does not demonstrate dissection or vasculitis suspected

CT = computed tomography; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; MRV = magnetic resonance venography.

TABLE 105-2. Diagnostic Protocol after Neuroimaging

For those with hemorrhage
- Basic coagulation studies
- Platelets
- Conventional angiography if no bleeding diathesis

For those with no infarct
- Electroencephalogram (unihemispheric slowing in hemiplegic migraine)

For those with an infarct in a vascular distribution or cerebrovascular disease
- Precordial echocardiography
- Electrocardiography
- Consider transesophageal echocardiography if normal precordial echocardiography (possible same general anesthetic as conventional arteriogram)
- Consider transcranial Doppler with bubble contrast
- Blood tests (4 mL ethylenediaminetetraacetic acid [EDTA], 6–8 mL citrated, 2 mL heparinized, 5 mL clotted). Those marked with an asterisk should be repeated after 3 to 6 months, if abnormal acutely; both parents should be investigated before a persistent inherited abnormality is diagnosed.
  - Full blood count and differential white cell count
  - Iron, folate, and red cell folate
  - Erythrocyte sedimentation rate
  - Hemoglobin electrophoresis if patient is in an appropriate ethnic group
  - Protein S (total and free),* protein C,* antithrombin,* and plasminogen*
  - von Willebrand factor antigen, factor VIII,* and factor XII*
  - Lupus anticoagulant
  - Anticardiolipin antibodies*
  - Factor V Leiden and activated protein C resistance
  - Prothrombin G20210A gene
  - Thermolabile methylenetetrahydrofolate reductase (*tMTHFR*) gene
  - Total homocysteine*
  - Fasting cholesterol and triglycerides and lipoprotein (a)
  - Infection screen, including *Mycoplasma, Chlamydia, Helicobacter,* and *Borrelia* titers, antistreptolysin O test
- Serum and cerebrospinal fluid to look for intrathecal production of antibodies to varicella zoster virus
- Sleep study to look for obstructive sleep apnea or nocturnal hypoxemia

For those with infarction in the territory supplied by the vertebrobasilar system
- Radiography of cervical spine in flexion and extension

For those with infarction not in a typical vascular distribution
- Cerebrospinal fluid lactate
- Plasma ammonia
- Plasma amino acids
- Urine organic acids

(MRI), it is now much easier to investigate these patients safely. In parallel, management strategies have developed, although few are evidence based (Tables 105-1 and 105-2).

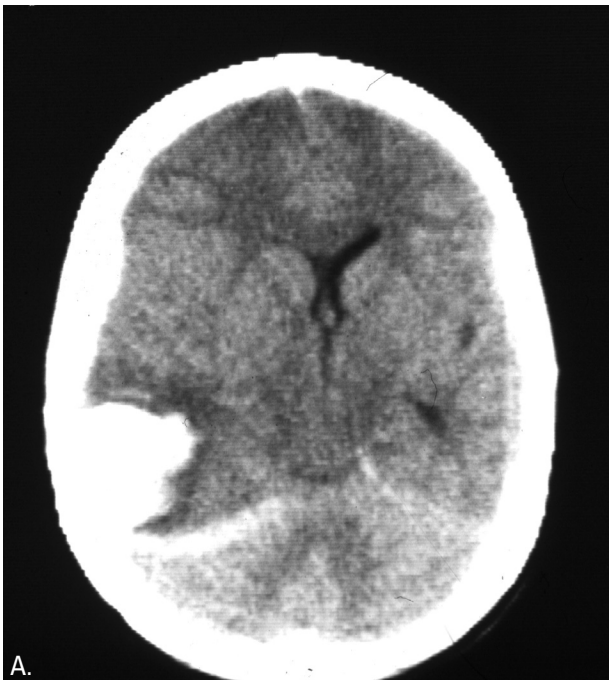
Stroke is relatively rare in childhood, with an incidence of between 2.5 and 13 per 100,000 (1.2 to 9 per 100,000 for AIS), but when it occurs it usually has a profound long-term effect on the child and family. Around one-quarter of childhood strokes occur in neonates (40 per 100,000), and the pathology in this age group suggests an embolic etiology, presumably from the placenta, with an otherwise normal arterial tree and a low risk of recurrence. Most older children with AIS are found to have cerebrovascular disease, which may be progressive and is associated with a significant risk of recurrence. CSVT occurs at all ages and is particularly common in neonates. There is increasing evidence infection plays an important role in triggering stroke in the young, but there are many other predisposing factors, which are illunderstood at present.

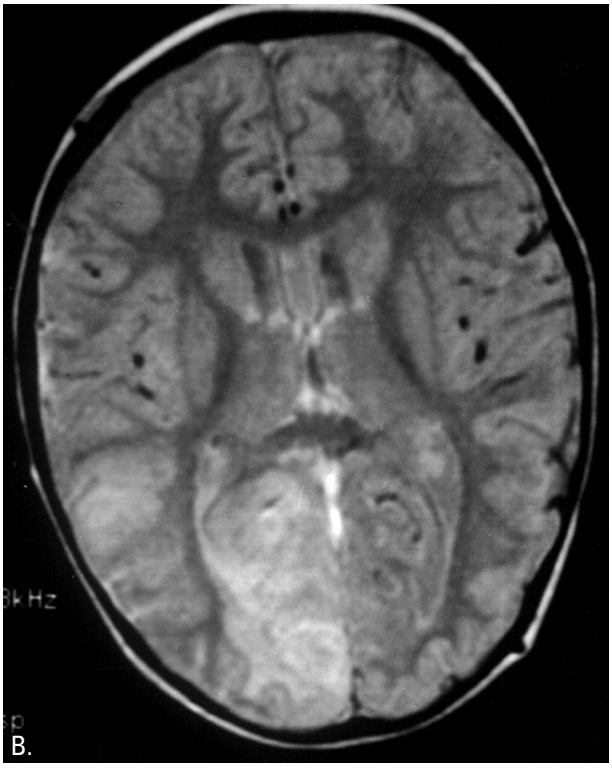
Hemorrhagic Stroke

One-half of all childhood strokes are hemorrhagic, often presenting with headache, vomiting, and irritability and occasionally with a depressed level of consciousness; these patients require immediate transfer to a neurosurgical unit in case decompression is required. Structural lesions, such as arteriovenous malformations, and hematologic disorders, including coagulopathies such as hemophilia, are the most common pathologies. Mortality may be up to 10%, but around one-half the survivors have no residual deficit, although if they have an underlying arteriovenous malformation, the risk of recurrence is 2 to 3% per year for life if untreated. Ideally, a vascular team with considerable experience should evaluate these children so that an individual management strategy, targeted at preventing recurrence, can be implemented.

Arterial Ischemic Stroke

Approximately one-half the children presenting with AIS have a known predisposing condition, particularly sickle cell disease, cardiac disease, bacterial meningitis, or immunodeficiency. Some of these children are candidates for emergency management of the stroke (eg, transfusion for patients with sickle cell disease). It has been argued that these children do not require full evaluation when a recognized cause has been identified, but they may also have unexpected pathologies (eg, primary cerebrovascular disease associated with congenital heart anomalies) or may have modifiable risk factors (eg, hypertension





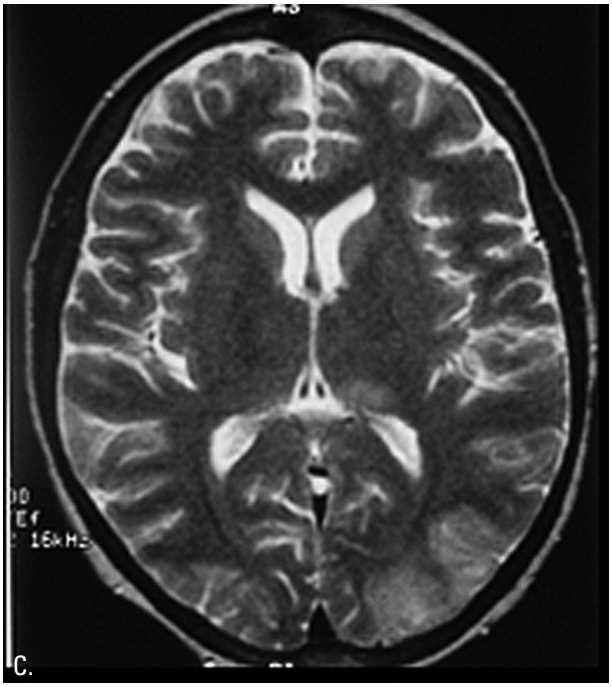


FIGURE 105.1. Brain imaging in acute stroke A) hemorrhage (CT) B) 'reversible posterior leukoencephalopathy' (MRI) C) occipital infarction in sinovenous thrombosis (MRI) D) basal ganglia infarction associated with 'transient cerebral arteriopathy' stenosis (MRI) E) widespread infarction after recurrent stroke (MRI) F) bilateral frontal infarction in moyamoya.

associated with sickle cell disease). Primary prevention is possible in this group, including early operation for congenital heart disease and prophylactic transfusion for children with sickle cell disease and internal carotid and middle cerebral arterial velocities > 200 cm/sec on transcranial Doppler ultrasonography.

The literature on the remaining children presenting with initially unexplained (cryptogenic) stroke suggests that there is a daunting list of possible etiologies, but because the series have mainly been small, it has been difficult to evaluate the relative importance of the reported associations. About 80% of children with an infarct in an arterial territory have large-vessel disease demonstrable on magnetic resonance angiography (MRA) (eg, stenosis, occlusion, or dissection). The proportion of patients with cerebrovascular disease may be even higher if patients with a normal MRA

are assessed acutely for evidence of sinovenous thrombosis with computed tomography (CT) or magnetic resonance venography (MRV) or dissection with fat-saturated T_1-MRI of the neck or conventional angiography. The latter is usually required for the diagnosis of small vessel vasculitis and sometimes for the diagnosis of dissection, particularly in the posterior circulation.

Currently, most patients have irreversible infarction by the time they arrive at a hospital, and therapeutic efforts have traditionally concentrated on rehabilitation and the prevention of recurrence. However, acute management to minimize factors that increase infarct volume has become increasingly emphasized. This includes maintenance of normoglycemia and normoxia and appropriate treatment for fever, seizures, and hypotension. Although there are no epidemiologically based data, children with nonsickle stroke referred to teaching centers have an early recurrence risk for stroke of 10 to 25% and an even higher risk of further transient ischemic attacks. Unfortunately, there is no evidence-based strategy for secondary prevention. However, approximately 50% of children who do not receive aspirin or anticoagulants have recurrent transient ischemic attack (TIA) or stroke. Treatment with aspirin or anticoagulants appears to be safe. Therefore aspirin, given as soon as possible after diagnosis in a dose of 3–5 mg/kg, is now standard therapy in pediatric AIS except in situations where anticoagulation seems reasonable (eg, dissection and cardiogenic embolus). Around two-thirds of children with sickle cell disease presenting with their first stroke will have a further episode if untreated. Emergency simple transfusion in patients with hemoglobin < 10 g/dL may reduce infarct size and prevent early recurrence. Regular simple, manual, or automated (erythrocytapheresis) transfusion to a hemoglobin S of < 30% reduces the recurrence rate over the long term to around 10%.

Three-quarters of children who have had an ischemic stroke from any cause have a residual motor deficit and additional subtle cognitive deficits and behavioral difficulties that may significantly affect functioning and future employment prospects. Recurrent stroke usually causes a significant increase in disability; it is, therefore, important to look carefully for risk factors in order to attempt secondary prevention.

Traditionally, once a putative "cause" was identified, no further tests were undertaken; the patient and family were reassured and were discharged from follow-up. The approach to etiology in adults has been very different, as it has long been recognized there are multiple risk factors for vascular disease and stroke, which may interact over long periods of time. Many are modifiable, and there has been considerable interest recently in using knowledge about risk factors to prevent stroke in adults. There is a good case for taking a similar approach in children and investigating for vascular disease and any modifiable risk factors. Prophylaxis (eg, vitamin B supplementation for hyperhomocysteinemia revascularization for moyamoya disease) may then be recommended on a logical basis. Although controlled trials of low-dose aspirin therapy have not been conducted in children, long-term use of 1 to 3 mg/kg/d is a reasonable prophylactic measure and, at this dose, carries a negligible risk of Reye's syndrome.

Cerebral Sinovenous Thrombosis

CSVT may present as stroke but commonly causes headaches, symptomatic of intracranial hypertension in older children, or seizures, particularly in neonates. Dehydration and fever are common associations. A low threshold for contrast CT with CT venography or MRI with MRV is required if the diagnosis is suspected. There is more evidence for an association with prothrombotic coagulopathies for venous, as opposed to arterial, stroke, and a full prothrombotic work-up is justified, in addition to the exclusion of iron deficiency. Data from adult studies suggest a benefit for anticoagulation, although the approach is still controversial, and there have been no controlled trials in children. The authors' current approach is to anticoagulate with low molecular weight heparin or warfarin, in older children in the absence of hemorrhage for 6 weeks to 3 months.

Evaluation

Previously recognized conditions predisposing to AIS include the following:

- Sickle cell disease
- Cardiac disease
- Bacterial meningitis
- Immunodeficiency
- Homocystinuria
- Neurofibromatosis
- Down syndrome
- Inflammatory bowel disease

Previously recognized conditions predisposing to CSVT include the following:

- Head and neck infection, including otitis media, meningitis, and tonsillitis
- Chronic anemias, including sickle cell disease, thalassemia, and warm autoimmune hemolytic anemia
- Cardiac disease
- Dehydration (eg, in gastroenteritis)
- Nephrotic syndrome
- Inflammatory bowel disease
- Systemic lupus erythematosus
- Homocystinuria
- Procoagulant drugs (eg, L-asparaginase)
- Malignancy (eg, brain tumors and leukemia)

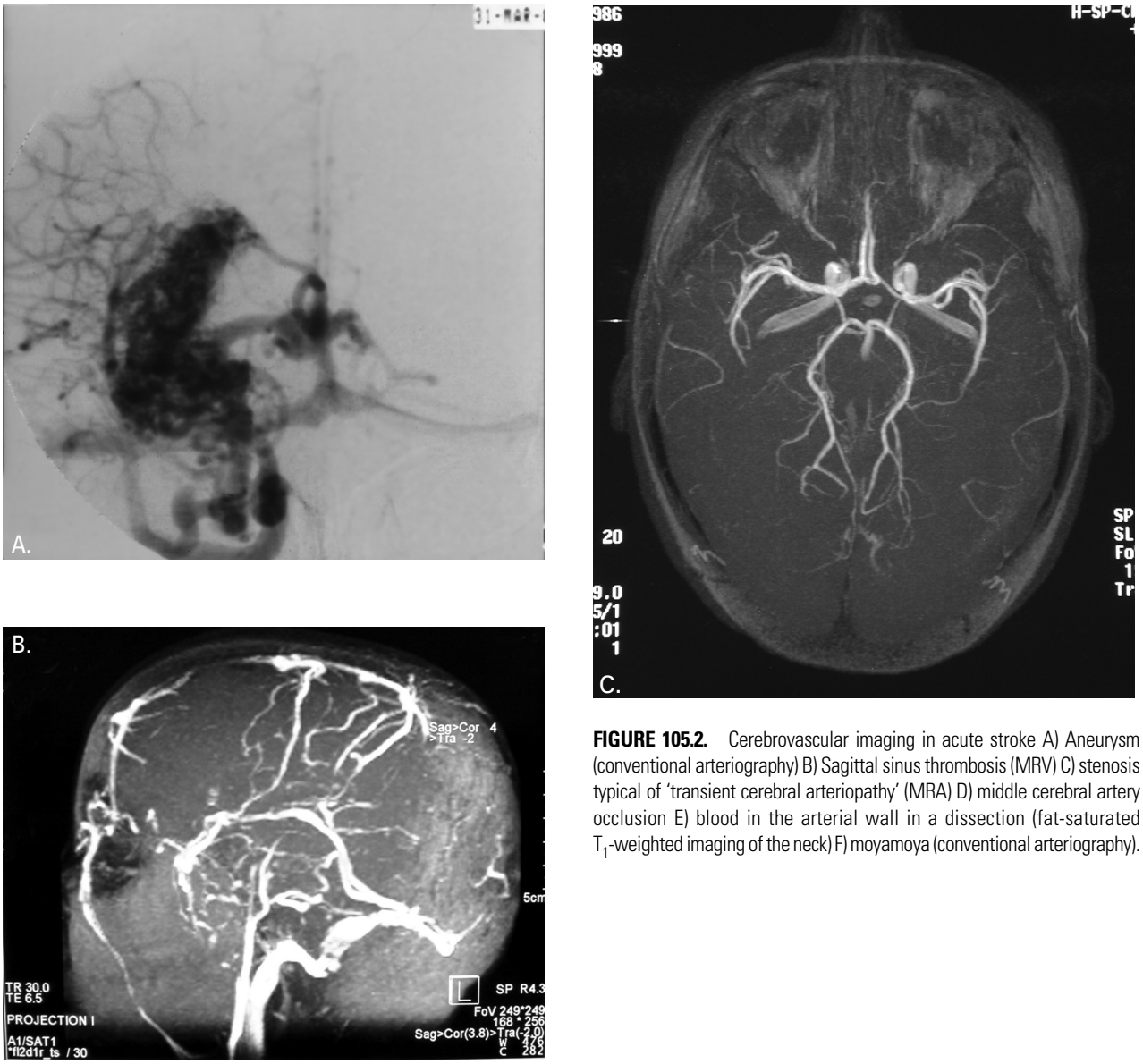


FIGURE 105.2. Cerebrovascular imaging in acute stroke A) Aneurysm (conventional arteriography) B) Sagittal sinus thrombosis (MRV) C) stenosis typical of 'transient cerebral arteriopathy' (MRA) D) middle cerebral artery occlusion E) blood in the arterial wall in a dissection (fat-saturated T_1-weighted imaging of the neck) F) moyamoya (conventional arteriography).

- Head injury
- Diabetic ketoacidosis
- Cerebral malaria

Approximately one-third to one-half of children with AIS or CSVT have no previously diagnosed underlying condition, but full evaluation may reveal etiologic risk factors.

Additional risk factors that may have an etiologic role in ischemic stroke in childhood include the following:

- Infection (chickenpox and tonsillitis)
- Head or neck trauma (arterial dissection)
- Anemia or iron deficiency
- Hypertension
- Hyperhomocysteinemia
- Prothrombotic disorders (eg, protein C deficiency, factor V Leiden, prothrombin gene, and antiphospholipid syndrome [more evidence for role in venous thrombosis])
- Hyperlipidemia (cholesterol or lipoprotein [a])
- Hypoxemia and reactive polycythemia in sickle cell disease and cyanotic congenital heart disease
- Immunodeficiency (eg, human immunodeficiency virus infection [HIV])

History

History should include the following:

1. Rapidity of onset
   - Sudden onset, suggesting embolus
   - Stuttering, which suggests thrombotic occlusion of underlying cerebrovascular disease

2. Known medical conditions
3. Recent illnesses
   - Chickenpox in the previous 12 months
   - Recent head trauma, major or minor (predisposes to arterial dissection)
4. Family history of thrombosis in the young (< 55 years)

Examination

The patient should be examined for the following:
1. Level of consciousness
2. Presence of aphasia
3. Distribution and severity of weakness, facial involvement, associated features
4. Cardiovascular examination

Diagnosis

Hemorrhage must be excluded by CT or MRI. MRI is more likely to show abnormalities in the first few hours after stroke, particularly if diffusion imaging is used. It also detects smaller ischemic lesions in symptomatic and asymptomatic high-risk patients and is particularly useful for separating ischemic stroke from alternative pathologies (eg, hemiplegic migraine, mitochondrial cytopathy). Carotid and vertebral dissection is often diagnosed on T_1-weighted MRI with axial fat-saturated images of the neck. MRA allows diagnosis of some of the possible underlying cerebrovascular abnormalities (eg, demonstrating turbulence or occlusion in the distal internal carotid or proximal middle cerebral arteries). MRV may demonstrate occlusion of the large venous sinuses (eg, in sagittal sinus thrombosis).

Conventional arteriography may be required to diagnose arteriovenous malformations or aneurysms in patients with hemorrhage or to delineate the cause of stroke in ischemic cases if MRA is normal or not diagnostic (eg, in arterial dissection or vasculitis) (Table 105-3). Relatively few children with stroke have previously unrecognized cardiac abnormalities, such as patent foramen ovale with significant shunting.

Electrocardiography and precordial echocardiography are essential, and bubble contrast may be given during precordial or transesophageal echocardiography or transcranial Doppler if there is a high index of suspicion of a significant shunt.

The remainder of the work-up concentrates on looking for modifiable risk factors for progressive cerebrovascular disease and recurrent stroke, such as prothrombotic abnormalities, iron deficiency, hyperhomocysteinemia, and hypoxemia. However, many tests that are abnormal acutely are normal a few months later. There is considerable controversy about the etiologic role of the various putative risk factors and an absence of evidence-based strategies for prevention of further episodes at present.

TABLE 105-3. Differential Diagnosis in a Child Presenting with Acute Focal Neurologic Signs

Postictal (Todd's paresis)
Short duration so neuroimaging essential if persistent
Children with prolonged seizures may develop permanent hemiparesis with seizures (hemiseizure, hemiplegia, and epilepsy)
Hemiplegic migraine (but diagnosis of exclusion-migrainous symptoms also seen in cerebrovascular disease [eg, dissection])
Acute disseminated encephalomyelitis
Brain tumor
Nonaccidental injury
Subdural hematoma
Strangulation with compression of internal carotid artery
Encephalitis (eg, secondary to Herpes simplex [usually have seizures])
Rasmussen's encephalitis (usually have seizures [eg, epilepsia partialis continua])
Posterior leukencephalopathy (eg, secondary to hypertension, with or without reduction in blood pressure)
Unilateral hemispheric cerebral edema (eg, secondary to diabetes or hyperammonemia [ornithine carbamoyltransferase deficiency])
Mitochondrial encephalopathy with stroke-like episodes
Alternating hemiplegia of childhood

Treatment

Acute Management

In adults, recent studies have focused on using thrombolysis or neuroprotection to possibly minimize the effect of the initial stroke. One randomized controlled study of intravenous tissue plasminogen activator (t-PA), conducted in adults who could be treated within 3 hours, showed significant benefit on outcome at 3 months despite the presence of hemorrhage in 10%. However, treatment beyond the 3-hour window is associated with considerable rates of hemorrhage and mortality, and only about 5% of patients fulfill the criteria for treatment. Although children who suffer a stroke often present to a physician within 3 hours, the diagnosis is rarely made with any degree of certainty at this stage because of the rarity of stroke, the low sensitivity of CT for acute infarction, and the wide differential in this age group. In addition, mortality is lower, and most children presenting with stroke can probably expect to lead independent lives as adults. It is, therefore, difficult to see a major role for t-PA in this age group at the present time, although it may occasionally be justified in children known to be at risk (eg, because of congenital heart disease) who suffer a stroke while hospitalized or who are seen less than 3 hours from documented onset or time "last seen well." As in adults, t-PA is contraindicated immediately after surgery. There are no neuroprotective medications available at the present time that could be recommended for use in children or adults.

There are, nevertheless, a number of management strategies (in addition to the need for clot removal in hemorrhage) for individual patient groups that may make a difference. Infarct volume and clinical outcome appear to be related to body temperature during the first few days after stroke; a direct causative effect remains unproven, but maintaining body temperature just below 37°C is unlikely to do harm. Seizures in the acute phase should be managed appropriately, although there is no evidence they have a detrimental effect on outcome in adults. Hypotension should be managed appropriately with fluids and catecholamines; if blood pressure is high, intracranial hypertension should be excluded before expert consideration of extremely slow reduction (eg, in reversible posterior leukencephalopathy). Oxygen saturation should be maintained within normal limits; patients should be monitored continuously with pulse oximetry (which should be maintained between 96 and 99%, as hyperoxia may be as harmful as hypoxia). Prophylactic stockings should be used to prevent deep vein thrombosis in patients with weak or paralyzed legs. There is a case for surgical decompression in children presenting in coma with large ischemic middle cerebral infarcts, which are almost always fatal if managed conservatively. In children with sickle cell disease, simple or exchange transfusion is recommended acutely to reduce hemoglobin S to < 30%, although this must be conducted with caution in view of the association with neurologic deterioration.

The acute management of the remaining patients remains controversial, and many physicians give no specific treatment (Table 105-4). The question of anticoagulation remains a difficult one. One large trial in adults suggested benefit, whereas others have demonstrated no benefit over antiplatelet agents. Despite the risk of hemorrhage, there are patient groups (eg, those with vessel dissection, venous sinus thrombosis, and known prothrombotic abnormalities) who should probably receive anticoagulants acutely to prevent early recurrence. In two very large controlled trials in adults, aspirin appeared to be associated with a modest improvement in outcome, probably because of a reduction in early recurrence and perhaps via its antipyretic effect. The risk of hemorrhage appears to be lower with aspirin than with anticoagulants, and although there is no evidence of benefit in children, it is a reasonable option.

Increased Intracranial Pressure after CSVT

Prolonged increased intracranial pressure is treated with repeated lumbar punctures removing cerebrospinal fluid, acetazolamide (Diamox®) and, in resistant cases, lumboperitoneal shunting. Optic nerve fenestration may be helpful in patients with increasing visual loss.

TABLE 105-4. Acute Management Protocol

Keep temperature between 36.5° and 37°C
Keep oxygen saturation between 96 and 99%
Use prophylactic stockings to reduce the risk of deep venous thrombosis in the legs
Treat acute seizures

1. Hemorrhagic stroke
   Immediate referral to a center with neurosurgical facilities (possibly for drainage of hemorrhage)

2. Ischemic stroke
   For cerebellar stroke presenting in coma: referral to a center with neuro surgical facilities (possibly for drainage of hydrocephalus or posterior fossa decompression)
   For large MCA territory lesions with progressive lethargy or stupor (eg, Glasgow Coma Score < 14): referral to a center with neurosurgical facilities (possibly for hemispheric decompression)
   For stroke in sickle cell disease: dilution of % hemoglobin S by exchange transfusion (if exchange transfusion is problematic, then simple transfusion initially)
   For ischemic stroke arriving in hospital with radiographic confirmation of stroke and treated < 3 hours from documented onset: consider intravenous t-PA if no contraindications (eg, recent procedure)
   For venous sinus thrombosis, extracranial arterial dissection, known prothrombotic disorders:
      Heparin acutely (intravenous or low molecular weight with careful monitoring)
      Warfarin (Coumadin®) for 6 months with regular INR
   For strokes secondary to other mechanisms:
      Early prophylaxis with low-dose aspirin (1–3 mg/kg)
      Consider warfarin (Coumadin®) if recurrence despite ASA
   For vasculitis (biopsy proven or recurrent strokes with progressive abnormalities on angiography) (see Chapter 106, "Vasculitis"):
      Steroids
      Cyclophosphamide

3. All patients
      Early rehabilitation by team comprising nursing staff, physiotherapist, occupational therapist, speech therapist, and psychologist

ASA = acetylsalicylic acid; INR = international normalized ratio; MCA = middle cerebral artery; t-PA = tissue plasminogen activator.

Rehabilitation Therapy

Early referral will maximize the benefits of rehabilitation therapy, which should be conducted by a multidisciplinary team. Infants and young children with stroke have unique rehabilitation considerations, including hemiatrophy of affected limbs and associated orthopedic problems, longer duration of recovery than in adults with stroke, and modification in their rehabilitation needs over time as they grow and develop age-related skills. For those with a significant hemiparesis, a hinged ankle-foot orthosis should be used to facilitate normal gait patterns. Botulinum toxin may have a role in improving motor patterns if there is spasticity, but dystonia is a common problem that may be very difficult to treat; Ldopa and tetrabenazine may be tried. The use of constraint-induced therapy should be

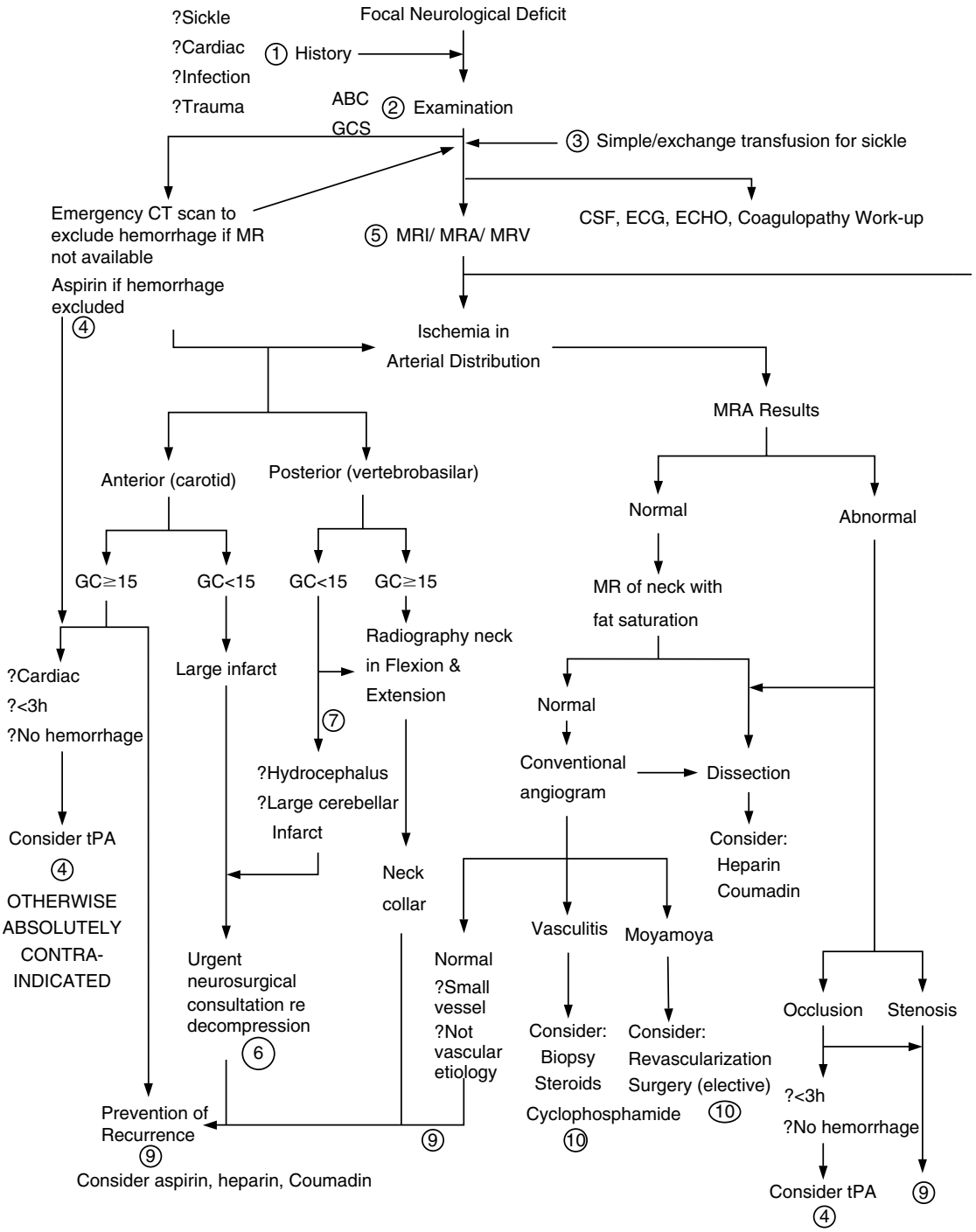
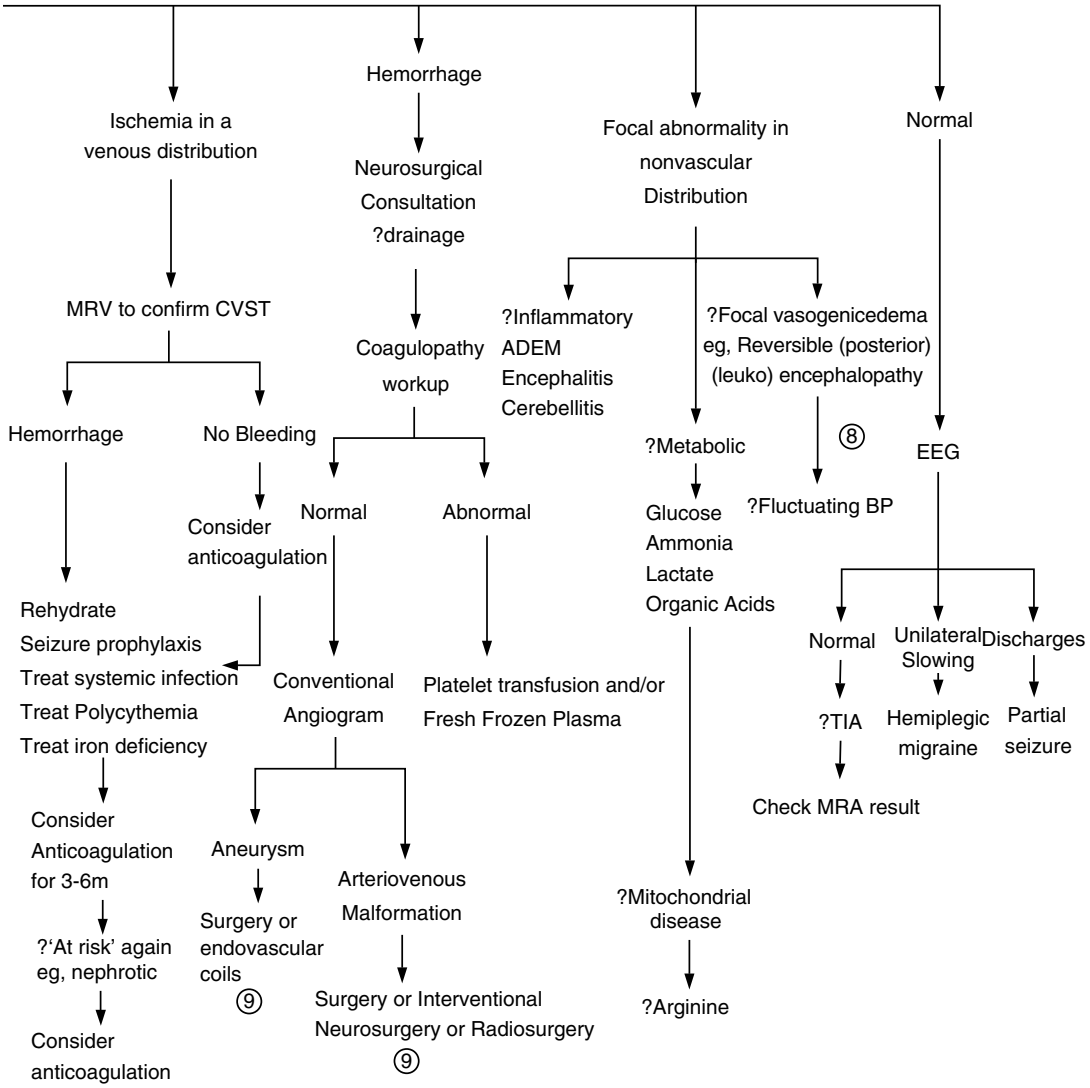


FIGURE 105-3. History of an underlying cause such as sickle cell disease, cardiac disease or meningitis may require urgent specific treatment.

1. Examination should include an assessment of vital signs (airway, breathing, and circulation) and Glasgow Coma Scale. Complete neurological examination includes visual fields & acuity & retinal examination. General examination includes careful auscultation of the heart and neck, palpation of pulses and documentation of cutaneous abnormalities and dilated scalp veins.
2. In sickle cell stroke, simple/exchange transfusion should be performed urgently.
3. In the exceptional circumstance that a patient > 10 years has known cardiac disease (but no recent procedure) and no hemorrhage on CT, thrombolysis (eg, tPA) may be considered within three hours of the onset of the focal deficit ("time last seen well"); otherwise it is absolutely contraindicated.
4. Magnetic Resonance imaging (MRI), Magnetic Resonance Angiography (MRA), and Magnetic Resonance Venography (MRV) should be obtained as soon as possible in all patients with suspected new onset cerebrovascular disease. FLAIR, Diffusion and Perfusion-weighted MRI improve diagnostic accuracy.



5. In a large anterior infarct, surgical decompression may prevent cerebral herniation and death. Non-communicating hydrocephalus may require CSF drainage via a ventricular drain.
6. Vertebral body instability may be associated with vertebral dissection. If this is likely, the patient should wear a neck collar in the acute phase.
7. Focal vasogenic edema has been reported in hypertensive encephalopathy and with drugs eg, cyclosporin. Blood pressure must be reduced very slowly & may need raising first with volume expanders if it has fallen below previous baseline.
8. Secondary prevention strategies should include advice on diet (including adequate vitamin intake eg, folate) and exercise, and the exclusion of obstructive sleep apnea. Aspirin may be prescribed for non-neonates (or anticoagulation if studies indicate vascular dissection, venous sinus thrombosis or a prothrombotic state) but there are no controlled data evaluating safety or efficacy in preventing stroke recurrence in children.
9. The decision about choice of treatment for aneurysms or arteriovenous malformations should be made by an experienced team with access to all options. Referral should also be considered for patients with rare conditions with specific treatments eg, moyamoya or vasculitis.

TABLE 105-5. Protocol for Prevention of Recurrence

1. Hemorrhagic stroke
   - For arteriovenous malformation (see Chapter 103, "Central Nervous System Vascular Malformations")
     - Refer to team with access to surgery, interventional neuroradiology, and stereotactic radiotherapy for optimal treatment for individual patient
   - For aneurysm (see Chapter 104, "Pediatric Intracranial Aneurysms")
     - Refer to neurosurgeon with an interest in vascular pathology for consideration of operative treatment
   - For coagulopathy
     - Replace deficiency (eg, factor VIII)
     - Consider fresh frozen plasma or cryoprecipitate
     - Replace platelets as needed
2. Ischemic stroke
   - For sickle cell disease
     - Regular transfusion (3 to 5 weekly) to keep hemoglobin S < 30%
     - Exclude nocturnal hypoxemia/obstructive sleep apnea
     - Consider revascularization if moyamoya disease
   - For moyamoya disease
     - Consider revascularization, particularly if transient ischemic attacks or cognitive decline
     - Exclude nocturnal hypoxemia or obstructive apnea
   - For homozygotes for the *tMTHFR* gene or patients with hyperhomocysteinemia (plasma level > 13.5 mmol/L):
     - B-complex vitamin (especially folic acid) supplementation
   - For those with persistent multiple prothrombotic disorders:
     - Consider warfarin with regular monitoring of INR (discuss with hematologist in individual case)
   - For those with hypercholesterolemia (> 5.5 mmol/L)
     - Low-cholesterol diet
     - Consider cholesterol-lowering agents (eg, statins)
   - For large atrial defects with a significant right-to-left shunt or additional prothrombotic disorders:
     - Consider transcatheter or operative closure
   - For others with stroke in a vascular distribution and/or cerebrovascular disease:
     - Low-dose aspirin (1–3 mg/kg)
3. All patients
   - General advice about
     - Improving diet (eg, increasing intake of fruit and vegetables to 5 portions/d); decreasing consumption of fat in "junk" food
     - Increased exercise (eg, walking to school)
     - Seeking immediate medical attention in hospital if further symptoms

Follow-up by telephone contact with liaison nurse who can feed back information about risk factors and can discuss anxieties with families.

INR = international normalized ratio.

considered as an option for improving upper limb and hand skills in children with upper limb motor dysfunction. The method and period of constraint used should be decided in conjunction with the child and family. There is no evidence to support routine use of functional electrical stimulation in children affected by stroke, but aspects of hand and wrist function may be improved in selected patients. If parents, professionals, or the child's educational assessment raise concerns regarding language or communication, the child should be referred to a speech and language therapist and specific rehabilitation may be indicated. A detailed neuropsychological assessment of the child's cognitive and functional abilities should be carried out in collaboration with the child, parents or caregivers, and teachers to identify any special educational needs.

Prevention of Recurrence

There is a significant risk of recurrence of hemorrhagic stroke if arteriovenous malformations and aneurysms are left untreated. For untreated aneurysms, around 50% rebleed over the first month, whereas for arteriovenous malformations, there is a 2 to 3% per year lifelong risk of rebleeding. Aneurysms are rare in childhood, and a surgical opinion should be sought urgently. The options for arteriovenous malformations include surgery, stereotactic radiotherapy, and interventional neuroradiology (Table 105-5). Some lesions may not be treatable by all three methods, but there are no controlled data available yet to guide management for those that are. The best approach is probably to seek advice from an experienced team with access to the alternatives. Hematologic advice should be sought for those with coagulopathies.

For AIS, long-term prevention of recurrence is controversial. Neonates with AIS have a negligible risk of recurrence and only rarely require secondary preventative treatment. In older infants and children, B-complex vitamin supplementation is probably reasonable in those with hyperhomocysteinemia, although more research is required. The lifelong risk of recurrence has not been defined for children. However, within 3 years of initial stroke, the recurrence rate in children not receiving acetylsalicylic acid (ASA) or anticoagulants is up to 51% (Lanthier et al, 2004). As cerebrovascular disease is commonly found on follow-up MRA, a low-dose aspirin regimen (1 to 3 mg/kg) is justified. The relative risk of further stroke and life-threatening hemorrhage on long-term warfarin has not been assessed for patients with inherited thrombophilias, such as factor V Leiden, but there is occasionally a case for cautious anticoagulation in some patients, particularly if there are ongoing symptoms. Few children have hypercholesterolemia, but those who do, or who have a high lipoprotein (a), should reduce cholesterol intake and may be considered for treatment with statins. Although patent foramen ovale may be closed at catheterization, the long-term risk-benefit ratio is impossible to determine at present. Patients with moyamoya disease often benefit from direct and indirect revascularization, in terms of cognitive and motor improvement. This may also apply to some patients with sickle cell disease, for whom the present recommendation of long-term transfusion remains unsatisfactory because of the inevitable iron overload and the difficulties in ensuring adequate chelation. Nevertheless, until further evidence is available, children with sickle cell disease who have had a

TABLE 105-6. Specific Treatment Schedules

1. Unfractionated ("standard") heparin
   When used in pediatric patients with AIS or CSVT, between 5 and 10 days of therapy are usually given depending on the clinically assessed risk of clot extension or recurrence. One role for standard heparin over low molecular weight heparin is in situations in which there is a particularly increased risk of hemorrhage or imminent need for surgery since the former can be more rapidly reversed with protamine and fresh frozen plasma. Adverse effects of heparin include the risk of hemorrhage, the risk of osteoporosis after long-term courses of therapy, and thrombocytopenia.

   No loading dose is usually given.
   Initial maintenance dose: age ≤ 1 yr: 28 units/kg/h IV
   age > 1 yr: 20 units/kg/h

   Monitoring: APTT every 4 hours and adjust heparin to APTT of 60 to 85 s.

2. Low molecular weight heparin (LMWH)
   LMWHs are becoming increasingly used as the first choice for acute anticoagulant therapy in childhood. LMWH is more stable pharmacokinetically, safer, easier to administer, and easier to monitor than regular heparin; LMWH can usually be given in two daily subcutaneous injections, avoiding the need for intravenous access, and monitored with weekly or monthly antifactor Xa levels.

   For enoxaparin (Lovenox) (110 anti-Xa units/mg):
   Loading dose: not required
   Maintenance treatment dose: age ≤ 2 mo: 1.5 mg/kg subcutaneous every 12 h
   age > 2 mo: 1.0 mg/kg subcutaneous every 12 h

   Monitoring: antifactor Xa level (4 hours postdose) every few days and adjust dosage to achieve target antifactor Xa level of 0.5–1.0.

3. Warfarin (Coumadin®)
   Target INR is 2.0–3.0. The INR is preferred over the prothrombin time for monitoring of warfarin effect, because it allows standardization for various machines and reagents. After acute anticoagulation, children with AIS or CSVT can be treated as is the practice in adults, with 3 to 6 months of warfarin.
   Loading dose: 0.2 mg/kg orally

   Maintenance dose and monitoring:
   If INR < 1.5, repeat initial dose
   If INR between 1.5 and 3.0, give 50% of loading dose
   If INR > 3.0 give 25% of loading dose
   If INR > 3.5 hold and restart at 50% of previous dose

4. Aspirin
   The recommended dosage is 3–5 mg/kg/d in the acute phase and 1–3 mg/kg/d for secondary prophylaxis. Dosage should not be decreased during acute febrile illness, but additional doses for antipyresis should not be given by parents. Annual influenza immunization should be considered.

5. Transfusion therapy
   For acute stroke or other CNS complications of sickle cell disease, if hemoglobin < 10 g/dL and if receiving exchange transfusion continually: simple transfusion as soon as possible to raise hemoglobin to 10 g/dL
   For all patients with acute stroke or other CNS complications of sickle cell disease: manual or automated (erythrocytapheresis) exchange as soon as possible to reduce hemoglobin S to < 30%
   For primary prevention of stroke in patients with sickle cell disease and maximum ICA or MCA velocity > 200 cm/s or secondary prevention in patients with previous stroke: regular simple, manual or automated (erythrocytapheresis) exchange to maintain hemoglobin S < 30% for at least 2.5 years.

AIS = arterial ischemic stroke; APTT = activated partial thromboplastin time; CNS = central nervous system; CSVT = cerebral sinovenous thrombosis; ICA = internal carotid artery; LMWH = low molecular weight heparin; MCA = middle cerebral artery.

stroke should receive transfusions long-term to achieve a hemoglobin S below 30% for 3 years and below 50% subsequently, as there is considerable, albeit anecdotal, evidence that this effectively reduces recurrence. Those with moyamoya disease have a high recurrence risk despite transfusion and may be considered for revascularization (Table 105-6).

Discussion

Currently the lack of randomized controlled trials in childhood stroke creates major management challenges. Although suggested treatment strategies such as those outlined in this chapter can be considered, a case-by-case management approach is needed as well as access to stroke expertise. We are at an exciting phase of research in childhood stroke and in the next 10 years it is likely clinical trials will provide evidence upon which to base therapies. There are currently ongoing trials of primary prevention of stroke in at-risk patients with sickle cell disease in the United States (STOP2, randomly assigning those previously transfused for transcranial Doppler velocities > 200 cm/sec to stopping transfusion; SITT, randomly assigning children with silent infarction in the context of sickle cell disease to transfusion) and the United Kingdom (a randomized trial of overnight oxygen supplementation in patients with nocturnal hypoxemia). A trial of aspirin versus anticoagulation to prevent

recurrence in the first 6 months after nonsickle stroke is in the early planning stages. It is hoped that strategies for the management of pediatric cerebrovascular disease and stroke will be evidence based by the time the next edition of this book is published.

Acknowledgments

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Practitioner and Patient Resources

50 King St. East
Andrew M. Blood clots and strokes: a guide for parents and little folks. Hamilton (ON): BC Decker; 1998.
Available from: BC Decker Inc.
20 Hughson St S, 10th Floor
P.O. Box 620, LCD1
Hamilton, ON L8N 3K7
Phone: (905) 522-7017 or 800-568-7281
http://www.bcdecker.com/productDetails.aspx?BJID=147

Children's Hemiplegia and Stroke Association (CHASA)
Suite 305, PMB 149
4101 West Green Oaks
Arlington, TX 76016
Phone: 817-492-4325
E-mail: info5@chasa.org
http://www.hemikids.org

The CHASA is a non-profit organization offering support and information to families of infants, children, and young adults who have hemiplegic cerebral palsy, hemiplegia, hemiparesis, prenatal stroke, childhood stroke, infant stroke, perinatal stroke, neonatal stroke, in utero stroke, and stroke in neonates.

HemiHelp
2nd floor, Bedford House
215 Balham High Road
London SW17 7BQ
Phone: 020 8672 3179
Fax: 020 8767 0319
E-mail: support@hemihelp.org.uk
http://www.hemihelp.org.uk
The aims of HemiHelp are to offer information and support to families where there is a child with childhood-acquired hemiplegia and to raise awareness about the condition both among the professionals who care for our children and the public.

The Stroke Association
Stroke Information Service
240 City Road
London EC1V 2PR
Phone: 0845 3033 100
E-mail: informationservice@stroke.org.uk
http://www.stroke.org.uk
The Stroke Association is a national charity that is solely concerned with stroke. It provides support for people who have had strokes, their families, and careers. The Association campaigns, educates, and informs to increase knowledge of stroke at all levels of society.

CHAPTER 106

VASCULITIS

ELKE H. ROLAND, MD

Vasculitis is a descriptive term that implies inflammation of the blood vessel wall that may affect arteries and veins of all sizes in any organ and may result in ischemic damage, hemorrhage, or aneurysm formation. The vasculitides are relatively rare, acquired diseases in childhood with highly variable and overlapping clinical presentations.

"Vasculitis," which implies inflammation of the blood vessel wall, may be a manifestation of a diverse number of conditions (eg, systemic vasculitides, collagen vascular diseases, infection, malignancy, or toxic drug exposure). Traditionally, the term *perivasculitis* has been used to describe inflammation surrounding blood vessels without involvement of the vessel wall itself and *vasculopathy* is a broader term that implies blood vessel abnormality with either an inflammatory or degenerative etiology. However, from recent advances in cell and molecular biology and immunology, it is becoming increasingly clear that the traditional separation between inflammatory and noninflammatory vascular pathology is no longer strictly valid. For example, in atherosclerotic vascular disease, it appears that inflammatory and immune processes are crucial components in atherogenesis, plaque rupture, and ischemia, processes that would be considered more consistent with the classic vasculitides.

Because the vasculitides comprise a heterogeneous group of diseases, the underlying pathogenesis may vary. Immune complex disease, antibody-dependent cellular cytotoxicity, endothelial activation, and coagulopathy have all been invoked in models of vascular inflammation. Although clinical classification systems have been proposed for vasculitic disorders in children and adults, most patients will not fit into such a classification and may present with overlapping clinical syndromes or nonspecific constitutional signs only. Diagnosis is often an evolving process and later organ damage may indicate a need for revision of the initial diagnosis.

Numerous other diseases that may mimic vasculitis (eg, infectious, inflammatory, and thromboembolic disorders) must be ruled out. Thus, although childhood vasculitis is uncommon, it demands a disproportionately large amount of a clinician's time because diagnosis may be difficult, monitoring disease activity may be problematic, and the outcome may be serious.

This chapter reviews the neurologic features of childhood vasculitis, emphasizing conditions that have significant neurologic morbidity.

Evaluation

The investigation of suspected vasculitis requires a multidisciplinary approach by a team that should include a physician knowledgeable in the diagnosis and treatment of vasculitis, including the use of long-term immunosuppressants, as well as pediatric subspecialists depending on the specific organ involvement (ie, a neurologist, a radiologist or neuroradiologist, surgeons or neurosurgeons, and a knowledgeable neuropathologist).

Clinical Features

Vasculitis may affect either the central or the peripheral nervous system, and this process should be considered in any child who presents with unexplained, acquired multifocal or diffuse neurologic symptoms. The most common clinical presenting features are headaches and focal neurologic deficits. In addition, because underlying systemic vasculitis or collagen vascular disease is most common, patients often have unexplained acquired multiorgan involvement, often in conjunction with recurrent fever, weight loss, and mucocutaneous and musculoskeletal manifestations. The onset may be acute (eg, Kawasaki disease or Schönlein-Henoch purpura), but more frequently

the presentation is subacute or chronic, with varying signs and symptoms that fluctuate over weeks to months. The most common clinical features associated with vasculitic disease in children are summarized in Table 106-1. Definitive diagnosis may be difficult and requires a high index of suspicion and persistence leading to thorough investigation of symptomatic and asymptomatic (but potentially affected) organs such as the heart, lungs, liver, and kidney. Thus, a careful review of systems during the history-taking is crucial in the evaluation of suspected vasculitis. In addition, because genetic predisposition may play a role, the family history should be reviewed specifically for vasculitis, arthritis, and autoimmune or collagen vascular disease.

In addition to primary vasculitic processes, it may occur secondary to collagen vascular disease, infection, malignancy, or toxic drug exposure (eg, cocaine or amphetamine abuse in adolescents).

Central nervous system (CNS) manifestations of vasculitis are protean and include headache, impaired cognitive function, fluctuating level of consciousness, psychosis or confusion, seizures, transient ischemic attacks, cerebral infarction, cranial neuropathies, and ataxia. Primary angiitis of the CNS (PACNS) is extremely rare in childhood and should be considered as a diagnosis of exclusion after thorough investigation of all other possibilities.

Involvement of the peripheral nervous system may manifest with symptoms of mononeuritis multiplex, peripheral neuropathy, myalgia, or myositis.

Laboratory Investigations

Laboratory abnormalities include nonspecific markers of inflammation, such as leukocytosis, thrombocytosis, anemia, and elevated erythrocyte sedimentation rate (ESR) or C-reactive protein. In systemic lupus erythematosus (SLE), cytopenia may occur instead of leukocytosis or thrombocytosis. Factor VIII antigen, a marker of endothelial cell activation, may be elevated and hypocomplementemia is common. Underlying systemic disease may result in abnormalities of routine tests of liver and renal function as well as elevation of muscle enzymes (eg, creatine kinase and aldolase). Initial screening for autoantibodies in suspected vasculitis or collagen vascular disease should include cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA; antiproteinase 3), perinuclear antineutrophil cytoplasmic antibodies (p-ANCA; antimyeloperoxidase), antinuclear antibodies (ANA), and rheumatoid factor. If the ANA is strongly positive or the clinical features are suggestive of a specific collagen vascular disease, an extended panel of specific autoantibodies should be requested. The common laboratory investigations that may support a diagnosis of vasculitis are summarized in Table 106-2.

Unfortunately, in CNS vasculitis, the markers sensitive in other conditions, such as the presence of elevated acute-phase reactants in systemic vasculitis, are frequently normal. Thus, it is not possible to rule out CNS vasculitis through laboratory tests.

Suspected infectious etiology of vasculitis may be confirmed by blood cultures, serologic investigations, or polymerase chain reaction (PCR). In specific circumstances (eg, tuberculosis), skin testing may be helpful.

Investigation for suspected cerebral vasculitis should include examination and culture of the cerebrospinal fluid (CSF). There may be pleocytosis (predominantly mononuclear cells) and elevated protein in CSF. Lumbar puncture is of value primarily to help rule out infectious diseases and malignancies that may mimic vasculitis. Thus, any tissue biopsy should also be submitted for culture, and acid-fast and fungal staining, as well as for routine histologic studies.

Electrophysiologic Studies

Nerve conduction studies may confirm peripheral neuropathy or mononeuritis multiplex, characteristic of several systemic vasculitides, including Wegener's granulomatosis, Churg-Strauss syndrome, and polyarteritis nodosa, and may be seen occasionally in other connective tissue disorders and SLE. Electromyography is not diagnostic but may support a diagnosis of childhood dermatomyositis.

Radiologic Investigations

Chest radiographs may demonstrate nodular pulmonary infiltrates or cavitations in Wegener's granulomatosis as well

TABLE 106-1. Common Clinical Features of Vasculitis

Fever, weight loss, fatigue
Skin lesions (palpable purpura, nodules, ulcers, livedo reticularis, urticaria)
Joint problems (arthritis, arthralgia, serositis)
Hypertension, renal dysfunction
Pulmonary infiltrates or hemorrhage
Neurological dysfunction (headache, cognitive dysfunction, focal central nervous system lesions, mononeuritis multiplex, myalgia or myositis)

TABLE 106-2. Laboratory Investigations Suggestive of Vasculitis

Anemia, leukocytosis
Eosinophilia
Increased erythrocyte sedimentation rate or C-reactive protein
Antinuclear antibody (ANA), Smith, double-stranded DNA
Antineutrophil cytoplasmic antibodies (ANCA): cytoplasmic or perinuclear
Elevated factor VIII-related antigen (Von Willebrand factor)
Cryoglobulinemia
Circulating immune complexes
Hematuria
Other specific autoantibodies, eg,: SS-A/Ro, SS-B/La (Sjögren's syndrome), SCL-70 (scleroderma), RNP (mixed connective tissue disease)

as cardiomegaly and loss of normal pulmonary vascular markings indicating pulmonary hypertension or cor pulmonale in allergic granulomatosis. In Wegener's granulomatosis, sinus radiographs may show thickening of sinus linings or opacification of maxillary or frontal sinuses.

Abdominal ultrasonography may be useful for confirming bowel involvement (eg, dilated bowel loops, abnormally thickened walls of small intestine, decreased bowel motility and intussusception that may occur in Schönlein-Henoch purpura, as well as hydrops of the gallbladder, which may be a useful diagnostic sign in Kawasaki disease). Plain abdominal films may detect pneumoperitoneum in cases of bowel perforation. Doppler ultrasonography may demonstrate turbulence of flow in abnormal vessels.

For confirmation of suspected CNS ischemia, magnetic resonance imaging (MRI) is generally most sensitive, except in cases of suspected intracerebral hemorrhage. Both gray and white matter may be affected, often in a multifocal pattern in both supratentorial and infratentorial distributions. Modifications of MRI technique (eg, diffusion-weighted and fluid-attenuated inversion recovery sequences), and possibly single photon emission computed tomography and positron emission tomography scanning, may further improve sensitivity. In patients with the granulomatous variant of CNS vasculitis, enhancement of the leptomeninges may be seen, which may improve the sensitivity of tissue biopsy. Approximately 15% of adults with CNS vasculitis present with mass lesions on MRI or CT, which may lead to erroneous diagnosis of tumor or infection.

Angiography is the most powerful diagnostic modality and is often used as the gold standard for diagnosis of CNS vasculitis. Angiography or magnetic resonance angiography may show irregular contour of vessels along their course with alternating ectasia (ie, beading and stenosis of affected vessels, and possibly nonvisualization of one or more vessels, presumably from thrombosis and occlusion). Ideally, changes should be confirmed in multiple vessels in multiple vascular distributions. Unfortunately, in adults with CNS vasculitis, cerebral angiography has been reported to be normal in up to 40% of biopsy-proven cases, and its specificity has been shown to be only approximately 26%. The highest level of diagnostic specificity is associated with visualization of beading in multiple vessels in multiple vascular distributions. The sensitivity and specificity of cerebral angiography in children is not known, although this technique is sometimes used erroneously as the gold standard for diagnosis of CNS vasculitis in childhood. A recent report describes no significant difference in the ability of MRA to detect and characterize CNS lesions in children compared with conventional angiography. Angiography-negative, biopsy-confirmed small—vessel CNS vasculitis has been described recently as a newly recognized inflammatory CNS disease in children which responds well to treatment with immunosuppressive therapy plus aspirin. Recently there has been interest in the use of monoclonal antibodies (eg, inflixamab which is a chimeric monoclonal antibody directed against TNF—alpha) as immunomodulatory treatment in vasculitides that are refractory to conventional therapy. However, aside from the associated high cost of such therapy there is concern that this novel approach to treatment may actually cause the development of autoantibodies and autoimmune syndromes.

Biopsy and Tissue Histology

A proposed classification of childhood vasculitis, as outlined in Table 106-3, is based on a combination of the dominant size of affected vessels (small, medium, or large) and the presence or absence of granulomata. Confirmatory biopsy is usually obtained from systemic organs (eg, skin, kidney, liver, muscle, lung, or peripheral nerve). Unfortunately, problems may arise from sampling error, which may necessitate repeat biopsy. Furthermore, with the exception of hereditary spastic paraparesis (HSP) and Kawasaki disease, which have consistent pathology, histopathologic findings are often of limited consistency within any clinical diagnostic category of vasculitis, and the histologic picture is often mixed, with variable lesions occurring in individual patients or in patients with similar clinical syndromes. In fact, the term *polyangiitis overlap syndrome* has been suggested to describe the high frequency (approximately 40%) of patients who exhibit features of several distinct vasculitis syndromes. Thus, to date, the classification and nomenclature of childhood vasculitis remains somewhat arbitrary.

TABLE 106-3. Classification of Primary Systemic Vasculitis in Childhood by Vessel Size and Presence of Granulomata

Vessel Size	Granulomatous	Nongranulomatous
Large (aorta and larger branches)	Takayasu's arteritis, Temporal arteritis	Kawasaki disease
Medium (renal, hepatic, coronary, mesenteric arteries)	Primary CNS angiitis (PACNS)	Polyarteritis nodosa, Kawasaki disease
Small (venules, arterioles, capillaries)	Wegener's granulomatosis*, Churg-Strauss syndrome (allergic granulomatosis), Hypersensitivity angiitis	Henoch-Schönlein purpura, Microscopic polyangiitis*, Drug-induced vasculitis, SLE, Infection-associated vasculitis, Paraneoplastic vasculitis, Serum sickness, Behçet's syndrome

*Strongly associated with ANCA antibodies.

Biopsy of CNS tissues would be logically considered the gold standard for diagnosis of CNS vasculitis, and the procedure, although invasive, may be done with minimal morbidity by an experienced neurosurgeon. Although selection of the biopsy may be individualized, in most patients the procedure of choice is open-wedge biopsy of the tip of the nondominant temporal lobe, with sampling of the overlying leptomeninges. Alternatively, biopsy of an area of leptomeningeal enhancement may be considered. Unfortunately, it must be recognized that CNS vasculitis is a patchy disease and it has been reported in adults that approximately 25% of biopsies will show false negative results. The incidence of false-negative biopsies in children is not known.

Primary Vasculitic Disorders in Childhood Systemic Vasculitis

The relative frequencies of vasculitis in the pediatric population differ from those seen in adults and may vary also according to geographic location. In North America and Europe, Kawasaki disease and HSP are most common, whereas in Asia, Takayasu's arteritis is also common, especially in adolescent and young adult women. Polyarteritis nodosa and Behçet syndrome are more common in Turkey and Japan.

Diagnosis of Kawasaki disease requires high fever for more than 5 days, together with four of the following five features: polymorphous rash, cervical lymphadenopathy, mucocutaneous involvement, conjunctivitis, and changes in peripheral extremities (eg, erythema, edema, or desquamation). Additional features include hydrops of the gallbladder, myocarditis, and coronary artery aneurysms. Affected children almost invariably have extreme irritability, most probably related to aseptic meningitis and inappropriate antidiuretic hormone production with hyponatremia. Rarely, the associated CNS vasculitis may result in focal neurologic lesions (eg, hemiplegia, seizures, ataxia, and coma). The cause of the persistent sensorineural hearing loss in some children with Kawasaki disease is not known.

Clinical diagnosis of HSP is based on a triad of palpable purpura, abdominal pain, and periarticular swelling or arthritis in individuals younger than 20 years of age. Glomerulonephritis may be a late finding. Approximately 50% of patients report a preceding upper respiratory infection or pharyngitis. Possible neurologic symptoms include seizures, coma, subarachnoid hemorrhage, and Guillain-Barré syndrome. Tissue biopsy shows granulocytes in the walls of arterioles and venules.

Clinical features of Takayasu's arteritis include fever, weight loss, abdominal pain, claudication in extremities, diminished peripheral pulses, blood pressure differences of more than 30 mm Hg in arms, and abnormalities of the aorta and major branches on arteriography.

Two rare vasculitidies in childhood, polyarteritis nodosa and Churg-Strauss syndrome, may have peripheral nerve involvement.

Childhood Dermatomyositis

Childhood dermatomyositis is distinguished from other inflammatory myopathies by its widespread necrotizing small-vessel vasculitis, which may be life-threatening. Cutaneous vasculitis is the most frequent vasculitic manifestation, with telangiectatic involvement of upper eyelids, often with edema and ulceration, lesions of nailbeds and digits, and other skinfolds. In addition, children often complain of abdominal pain, hematemesis, or melena from gastrointestinal vasculitis involving the esophagus, stomach, and small and large intestines. Complications of hemorrhage, ulceration, perforation, infarction, or peritonitis may require surgical intervention. Less commonly, there may be pancreatitis, myocarditis, retinal vasculitis, or even CNS vasculitis. The latter complication is often fatal. Patients have fever, altered mental status, and seizures. Laboratory investigations are of limited value: nonspecific inflammatory indicators are present but there are no consistent serological autoantibodies.

Primary Angiitis of the CNs

PACNS remains the least well-defined disorder among the vasculitides, and it is recognized increasingly that the term encompasses a highly heterogeneous group of conditions. Two clinical subsets of PACNS have been defined in adults: *granulomatous angiitis of the CNS* (GACNS), which has a chronic, progressive course unless treated with high-intensity immunosuppressive therapy, and *benign angiitis of the CNS* (BACNS), which may resolve spontaneously or require less aggressive intervention. The latter disorder has been documented by angiography alone and pathology is lacking. The essential diagnostic criteria for GACNS and BACNS are outlined in Table 106-4. Unfortunately, most cases of PACNS fail to fit into either of these clinical subsets. Approximately 15% of PACNS patients present with single or multiple mass lesions. The underlying pathology in these cases may be granulomatous or nongranulomatous. Cure by surgical resection or corticosteroid therapy alone has been reported. PACNS may be limited to spinal cord involvement that presents as acute or progressive paraparesis or spinal subdural hemorrhage.

Reports of PACNS in children are extremely rare. Reported cases were diagnosed by angiography alone and appear atypical, with a preponderance of large vessel involvement, unilateral disease on angiography, and relatively greater morbidity. In the absence of histology, it is impossible to confirm whether these pediatric cases represent the same disease that has been described in adults.

TABLE 106-4. Essential Features of Major Categories of PACNS

Granulomatous Angiitis of the CNS (GACNS)
Clinical
Prodrome of 3 months or longer
Focal and nonfocal neurologic signs
Abnormal CSF analysis in 90% (aseptic meningitis picture)
Neuroimaging
Signs of multifocal ischemia of varying ages
Variable leptomeningeal enhancement
Angiography normal in approximately 40%
Pathology
Vasculitis of small and medium-sized vessels of leptomeninges and cortex
Granulomata
Benign angiitis of the CNS (BACNS)
Clinical
Acute onset (hours to days)
Severe headache or focal neurologic event
Normal or essentially normal CSF
Neuroimaging
Angiogram highly suggestive of vasculitis (eg, segmental narrowing, ectasia, or beading in multiple vascular territories)

CNS = central nervous system; CSF = cerebrospinal fluid; PACNS = primary angiitis of the central nervous system.

Secondary Vasculitic Disorders

Collagen Vascular Diseases

SLE, Sjögren's syndrome, scleroderma, and mixed connective tissue disease may all have features of CNS vasculitis as well as involvement of the peripheral nervous system, usually in more severe cases. Detailed description of the systemic clinical features of these disorders is beyond the scope of this discussion.

SLE is extremely diverse clinically, and vascular injury may affect almost any organ. It is characterized by the presence of ANA, most commonly with diffuse or homogeneous nuclear staining. Antibodies to native double stranded DNA (anti-dsDNA) are also frequently present.

Although CNS dysfunction (eg, cognitive problems, psychosis, seizures, or ischemia) is common, true CNS vasculitis is relatively rare. It may result in subarachnoid hemorrhage and is frequently associated with retinal vasculitis. Large-vessel cerebral vasculitis is a serious problem associated with a high mortality rate. The MRI in SLE may show periventricular white matter lesions of uncertain etiology that do not necessarily correspond to clinical problems and may be seen in asymptomatic patients. Transverse myelitis is a rare complication that often responds rapidly to intravenous cyclophosphamide. Peripheral neuropathy or mononeuritis multiplex may also occur. Numerous drugs have been implicated as possibly exacerbating vasculitis in SLE. The presence of antiphospholipid antibodies in SLE may result in a prothrombotic state resulting in stroke.

Sjögren's syndrome is a systemic autoimmune disease characterized clinically by severe dry eyes and dry mouth. The spectrum of CNS involvement is similar to that seen in SLE.

Infectious Diseases

Numerous bacterial, viral, and fungal infections may result in vasculitis, either by direct extension of a localized focus of infection or hematogenous seeding of normal or abnormal blood vessels, by septic embolization or direct microbial invasion of vessel walls. When they occur in medium to large vessels, these lesions may be termed *mycotic aneurysms*, which is somewhat of a misnomer because true aneurysm may not develop. Classically mycotic aneurysms occur in the setting of infective endocarditis. Many of the nonspecific manifestations of bacterial endocarditis (eg, fever, cutaneous lesions, anemia, elevated ESR) may mimic polyarteritis or other systemic vasculitic syndromes. Mycotic aneurysms carry a risk of rupture and hemorrhage.

There is no uniform approach to treatment of mycotic aneurysms. Approximately 50% resolve with appropriate antimicrobial therapy. It is generally recommended that serial angiography be performed approximately every 2 weeks and surgery should be considered for aneurysms that increase in size or fail to resolve after 4 to 6 weeks of appropriate antibiotic treatment.

A wide variety of viruses have been associated with vasculitis, most notably the hepatitis viruses (hepatitis A, B, C), the retroviruses (eg, human immunodeficiency virus [HIV], human T-lymphotropic virus 1 [HTLV-1]), the herpes viruses (eg, cytomegalovirus [CMV]), Epstein-Barr virus (EBV), varicella zoster virus (VZV), herpes simplex virus (HSV), enteroviruses, human parvovirus B19, rubella virus, and influenza virus. Serology and PCR-based diagnostic tests may assist in identifying a viral etiology. As new techniques for viral isolation are developed and new viruses are discovered, additional new associations between viruses and vasculitic syndromes may become apparent. Early and accurate diagnosis may facilitate appropriate treatment and avoidance of immunosuppressive therapy in certain cases.

In addition to bacterial and viral causes, vasculitis may occur in the context of mycobacterial infection (eg, tuberculosis; spirochetal infections, such as Lyme disease; syphilis; and rickettsial infection, such as Rocky Mountain spotted fever). Recent infection may be suspected on the basis of evidence including a history of recent travel to endemic locations and exposure to animals or infected individuals and can be confirmed by serology.

Drug-Induced Vasculitis

A great number of drugs from almost every pharmaceutical class and category may cause vasculitis. Among the most commonly used drugs in children are most classes of

antimicrobials, antiviral agents and antifungal agents, immunizations (most commonly hepatitis B and influenza vaccines), diuretics, antineoplastic drugs, antirheumatic agents, antiepileptic drugs (eg, phenytoin, carbamazepine, and valproic acid), and miscellaneous drugs (eg, heroin and cocaine). Clinical involvement may range from isolated skin or CNS disease to multiorgan involvement. Although most cases occur within several weeks after initial drug exposure, the onset of clinical symptoms may range from several days to many years. There are no specific diagnostic tests for drug-induced vasculitis. Treatment includes drug withdrawal (which may be sufficient in mild cases) and selective use of glucocorticoids and cytotoxic agents (eg, cyclophosphamide), in ANCA-positive, severe, or refractory cases.

Malignancy

The association between vasculitis and malignancy is extremely rare but has been reported with hematologic malignancies, lymphomas, and solid tumors. Moreover, vasculitides may present as mass lesions or "pseudotumor," resulting in false diagnosis of neoplasia. Conversely, malignancies may be misdiagnosed initially as vasculitis (eg, leukemia, lymphoma, or cardiac myxoma). Finally, malignancy may arise as a complication of the long-term treatment of vasculitis with cytotoxic agents (eg, cyclophosphamide, azathioprine, or chemotherapy).

Treatment

Treatment of systemic vasculitis usually involves administration of high-dose corticosteroids, often together with cyclophosphamide, azathioprine, methotrexate, and, possibly, high-dose intravenous immunoglobulins.

Vasculitis associated with infection, thromboembolism, and malignancy must begin with treatment of the underlying condition. Drug-induced vasculitis requires discontinuation of the causative agent. Treatment of PACNS includes high-dose corticosteroid therapy, with the addition of cyclophosphamide in patients with progressive neurologic deterioration. Treatment should be continued for many months. No controlled studies have assessed the efficacy of various treatment protocols.

Suggested Readings

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Practitioner and Patient Resources

Lupus Foundation of America, Inc.
2000 L Street, N.W., Suite 710
Washington DC 20036
Phone: (202) 349-1156
http://www.lupus.org
This is a national organization of chapters and support groups which provides education and patient services for individuals and families affected by lupus as well as health professionals and provides research funding support.

Arthritis Foundation
P.O. Box 7669
Atlanta, GA 30357-0669
Phone: (404) 872-7100 or 800-283-7800
http://www.arthritis.org
This voluntary organization provides information, patient services and research updates as well as research funding support for various types of arthritis in humans (also in canines).

The Leukemia & Lymphoma Society of America
1311 Mamaroneck Avenue
White Plains, NY 10605
Phone: (914) 949-5213 or 800-955-4LSA (4572)
Fax: (914) 949-6691
http://www.leukemia.org
This large voluntary organization provides education and patient services as well as funding for research on blood cancers.

Cleveland Clinic Foundation,
Patient Education and Health Information
http://www.clevelandclinic.org/health/AboutSite/

CHAPTER 107

GUILLAIN-BARRÉ SYNDROME

LESLIE A. MORRISON, MD

As the most common cause of acute flaccid paralysis, Guillain-Barré syndrome is important to recognize and diagnose. Proper monitoring and appropriate management can be lifesaving.

Since the eradication of poliovirus in the developed world, Guillain-Barré syndrome (GBS) is the most common cause of acute flaccid paralysis in childhood, affecting approximately 1 in 100,000 children each year. The discovery of several forms of similar but distinct immune-mediated polyneuropathies has expanded the term GBS to include acute inflammatory demyelinating polyradiculoneuropathy (AIDP), Miller Fisher syndrome of ophthalmoparesis, areflexia and ataxia, acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), and acute sensory axonal neuropathy (ASAN). Nervous system involvement is peripheral, though cranial nerve involvement and myelopathy may coexist.

Fortunately, most children regain almost full motor function. Even so, rapid pulmonary decline and complications of intensive care result in mortality rates of 3 to 5%. Mechanical ventilation and prolonged hospitalization are noted in another 20 to 25%, and relapse and residual disability are seen in approximately 5 to 20%. Axonal forms, more frequently seen in Asian and Latin American children, tend to have more severe weakness and longer duration of illness. Beyond supportive care, treatment focused on modulation of the immune response can shorten the duration of disability, an important consideration in severely weak children. Deciding when and how to treat GBS depends on severity of illness, availability of resources, and age of the child. Various assessment scales have been used to determine severity and to monitor improvements. Practice parameters are established in adults, but little class I evidence is available for children.

Clinical Course

An antecedent respiratory or gastrointestinal infection is reported in more than one-half of children, followed by pain in the back or limbs, progressive symmetrical weakness, and areflexia. The degree of weakness varies widely, with some children showing only minor gait disturbance and others developing complete paralysis requiring intubation within hours of presentation. Maximum weakness is usually within 2 to 3 weeks of onset followed by a period of stabilization and gradual improvement over days to months in a proximal to distal fashion. Relapsing or chronic forms lasting more than 2 months are termed chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Pathogenesis

Evidence for an immune-mediated mechanism of injury to the peripheral nervous system is mounting. There are known antibodies to gangliosides and other proteins found in peripheral nerve axons and myelin associated with GBS. Immunoglobulin G antibodies to GQ1b are found in a high percentage of patients with Miller Fisher syndrome, and GD1a and GD1b in AMAN. In some regions, strong associations with *Campylobacter jejuni* infections are found in Miller Fisher syndrome and AMAN. *Campylobacter* has the ability to stimulate the formation of antibodies to gangliosides found in GBS. These findings support the concept of molecular mimicry after viral or bacterial infection and the subsequent development of an immune-mediated post-infectious disease. A large number of studies suggest that there may be genetic susceptibility to the development of antibodies that result in GBS, though familial cases of GBS are rare. An underlying metabolic or genetic disease may predispose to GBS as in the cases of Refsum's disease and hereditary demyelinating motor and sensory Neuropathies.

An immune attack is supported in pathological studies of nerve fibers in humans and animals with specific regions on axons or myelin involved that correspond with electrophysiologic findings. Increased relative risk of development of GBS after immunizations seems small, with the exception of the swine influenza vaccine given in 1976/1977. Since the introduction of the meningococcal vaccine Menactra®, 15 cases of GBS have been reported within 6 weeks of immunization, with one case recurrent in patients 11–19 years of age. However, the CDC has not changed the recommendation to give this immunization in patients 11–55 years of age.

Diagnosis

Diagnosis can be confirmed through history, physical examination, electrodiagnostic studies, and lumbar puncture. Abnormalities on electrodiagnostic studies evolve over the first 2 weeks and differ between AIDP and AMAN (Table 107-1). After the first days, cerebrospinal fluid (CSF) typically shows albuminocytologic dissociation with fewer than 10 to 50 leukocytes, along with an elevated protein. The 14-3-3 protein was found in 29 or 38 adult patients with GBS as early as 12–24 hours after disease onset but was also elevated in other neuropathies. Stool can be cultured for *Campylobacter*, with highest associations in Miller Fisher syndrome and AMAN. The clinical utility of specific antibody tests is not yet established, but they may have prognostic significance. Magnetic resonance imaging (MRI) of the spinal cord with gadolinium shows anterior nerve root enhancement but is of little diagnostic use unless other diagnostic studies are equivocal or when myelopathy is suspected.

Differential Diagnosis

West Nile virus infection can present with acute flaccid paralysis, a nonpoliovirus poliomyelitis. There is a well documented report of inflammatory demyelinating polyneuropathy in an adult patient with West Nile infection. *Enterovirus 71* can cause brainstem encephalitis that may resemble Miller Fisher syndrome or an acute flaccid paralysis in infants and young children. Children are likely to be febrile, and spinal fluid may show pleocytosis in both conditions. Rapid onset of weakness in spinal muscular atrophy (SMA) may mimic GBS even in the neonatal period, and vice versa. In most cases, SMA can be excluded by electrophysiologic studies and deoxyribonucleic acid (DNA) analysis. Treatable infections such as herpes-virus myelitis or mycoplasma-associated weakness should not be missed, and cases of human immunodeficiency virus (HIV)- and hepatitis-associated GBS have been reported. Botulism should be considered in infants, as botulism immunoglobulin can reduce duration of critical care. Myasthenia should be considered when ophthalmoplegia and bulbar signs are present. Acute transverse myelitis with acute areflexia and urinary retention mimics GBS, especially in young children where a sensory level may be difficult to discern. Toxic neuropathies should be excluded on the basis of history, with specific inquiry with regard to excessive intake of vitamins and food supplements. Metabolic diseases such as disorders of oxidative phosphorylation and porphyria can mimic post infectious polyneuropathy. Thorough examination, especially along the hairline, excludes tick paralysis. History and examination can help exclude other envenomations.

In the critical care setting, paralysis after lightening of sedation should raise the question of critical illness polyneuropathy or myopathy. Analysis of creatine kinase and electrophysiologic evaluation may be useful in cases with minimal or no improvement. Children with hereditary motor and sensory neuropathy are at increased risk of developing a secondary immune-mediated acute worsening.

TABLE 107-1. Electrophysiologic Findings in Guillain-Barré Syndrome

AIDP	AMAN
Reduced conduction velocities	Diminished CMAP amplitudes
Prolonged distal and F-wave latencies	Preserved motor nerve conduction velocities
Abnormal temporal dispersion	Denervation on EMG
	Normal sensory conduction studies

AIDP = acute inflammatory demyelinating polyradiculoneuropathy; AMAN = acute motor axonal neuropathy; CMAP = compound muscle action potential; EMG = electromyogram.

Treatment

Children should be hospitalized for observation with close monitoring of respiratory, autonomic, and motor function until they have stabilized. Declining respiratory function and autonomic instability warrant intensive care admission. Negative inspiratory force can be followed in older children, but infants and young children require a more creative approach, such as counting, blowing a pinwheel, or pretending to blow out a candle. Pulse oximetry is not always a reliable predictor of impending respiratory failure. Autonomic instability, manifested by rapid swings in blood pressure, pulse, cardiac arrhythmias, urinary retention, and pupillary abnormalities, must be closely monitored. Rapid treatment responses may be necessary to manage potential life-threatening fluctuations of blood pressure, pulse, and cardiac rhythms.

Specific treatment of GBS depends on respiratory and autonomic involvement and the degree of weakness. Most

clinicians would advise treatment in nonambulatory children and those with respiratory compromise and would defer specific treatment in cases where symptoms are mild and stable or improving (Table 107-2).

Corticosteroids are ineffective in GBS. Based on inference from class I studies in adults and small pediatric case series, the safety and efficacy of intravenous immunoglobulin (IVIg) and plasma exchange (PE) are established. The duration of disability is shortened by either of these two treatments in AIDP and AMAN but their effectiveness is less clear in AMSAN and often they are not necessary in ASAN. Differences in overall outcome in subtypes with and without treatment have not been established. The child's age and size are important factors, as PE requires a secure intravenous catheter of relatively large bore. Most authors recommend 5 to 7 treatments (measured in plasma volumes) given daily or every other day, depending on severity of weakness and tolerance of the procedure. In patients with renal failure, PE may be preferable to IVIg.

In most cases, treatment with IVIg is selected on the basis of equal efficacy, safety, and ease of administration. Early concerns over increased risk of relapse have largely abated. Empiric dosage is a total of 2 g/kg given over 1 to 5 days. No controlled studies prove superiority of a particular dosing schedule in GBS, but most authorities recommend that the infusion rate not exceed 0.08 mg/kg/min. Children appear to tolerate more rapid infusion rates than adults, and many centers infuse over 1 or 2 days. Decisions are often made on the basis of tolerance, monitoring requirements, and clinical severity and stability.

IVIg is manufactured from pooled human plasma from 3,000 to 10,000 donors that have been screened for HIV, human T-lymphotropic virus type I, and hepatitis A, B, and C. It is purified and mixed with stabilizer sugars or amino acids. CD4, CD8, human leukocyte antigens, cytokines, and coagulation factors may be present in the final product. IVIg has a half-life of 18 to 32 days, so repeated treatment courses seem unnecessary unless there is relapse. Side effects of IVIg treatment include infusion-related headache, fever, nausea, and rash. These are managed by slowing the infusion rate or by pretreatment with acetaminophen, antihistamines, or corticosteroids. Because the pooled product can contain up to 2.5% immunoglobulin A (IgA), there is risk of serious allergic reaction in IgA-deficient patients; therefore, an immunoglobulin panel is recommended before treatment. Renal failure may be averted through careful hydration and by avoiding high-sucrose–containing preparations. Concern over risk of hepatitis has diminished since the addition of detergents that inactivate this and most other infectious particles, with the exception of prions, about which there is insufficient information.

Combined treatment with both IVIg and PE does not improve outcome; however, when the first treatment fails to be effective in severe, refractory cases, the alternate treatment might be offered. In this scenario, controversy persists as to which treatment to give first. CSF filtration was compared with PE in a small study of 37 adult subjects, showing equal efficacy. This treatment is not available in most centers and is unlikely to become widely used because of potential serious infectious complications. A recent study of 19 patients treated with interferon IFNb-1a or placebo in addition to IVIg showed no significant difference in rate of improvement.

Pain management should be timed before physical maneuvers and therapy and may be severe enough to warrant narcotics. Dysesthesias are more likely to respond to gabapentin.

Finally, rehabilitation should begin very early. Prevention of deep venous thrombosis is aided by range of motion and intermittent compression devices. Heel cord contractures can develop within days of onset, requiring range of motion exercises, and splinting or casting. Supervised sitting and standing should begin once the child is able to do so. Respiratory therapy is provided to reduce atelectasis and mobilize secretions. The illness may have long-lasting psychological effects on children, and attention to mental health is essential for good outcome. The child and family will need ongoing education and emotional support, particularly when the treatment does not appear effective and the child is on a ventilator. A means of communication with simple measures, such as chalkboard or paper, or with more

TABLE 107-2. Treatment of Guillain-Barré Syndrome

Treatment	Administration	Mild Side Effects	Serious Side Effects
IVIg: 2 g/kg total dose	Single dose, slow IV infusion, or divided over 2–5 d; start within 2 wk of symptoms	Headache, myalgia, fever, chills, rash; may pretreat with acetaminophen, diphenhydramine, or corticosteroids; slow infusion rate	Congestive heart failure, thromboembolic events, renal failure, anaphylaxis, and aseptic meningitis; prescreen for IgA deficiency and clotting disorders
PE: approximately one plasma volume per treatment	5–7 separate exchanges over 1–2 wk; start within 4 wk of symptoms	Less likely to complete course but may be preferable in renal failure	Hypotension, cardiac arrhythmias, sepsis, thrombosis, hemorrhage, and increased risk of IV infections

IgA = immunoglobulin A; IV = intravenous; IVIg = intravenous immunoglobulin; PE = plasma exchange.

highly technical devices is important. Selection is made on the basis of duration of ventilation, degree of hand function, and age of the child.

Treatment of CIDP includes corticosteroids, PE, and IVIg, as well as continued supportive measures and rehabilitation. Immunosuppressive therapies may be required.

Outcome

Outcome is generally good in GBS. Most children with AIDP regain full function. Initially, children with AMAN were believed to have a worse prognosis, but new information supports good recovery in these children as well. Risk factors for residual weakness include rapidity of onset, severity of paralysis, respiratory or infectious complications, or diagnosis of AMSAN. Relapse occurs in a small percentage of children. There is a low risk of relapse or recurrence after immunizations, but one author has advised waiting one year before immunizations and avoiding any immunization given within 12 weeks of onset.

Suggested Readings

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Practitioner and Patient Resources

Guillain-Barré Syndrome International
http://www.guillain-barre.com
Patient support in English and Spanish.

Chapter 108

Neural Tube Defects and Spinal Dysraphism

Stephen L. Kinsman, MD

Myelomeningocele is the most common form of spinal dysraphism, a term this author prefers to spina bifida because it signifies the embryonic abnormalities underlying this condition. Areas of importance for the neurologist to assess include as follow: level of the lesion and its relationship to motor function, changes in sensory function, degree of neurogenic bladder and bowel, symptoms and signs of increased intracranial pressure from hydrocephalus, cognitive function, assessment of brainstem and cerebellar function in all age groups, assessment of lower motor neuron, and peripheral nerve changes over the life span and such general health problems as urinary tract infections, constipation, latex allergy, obesity, skin breakdown, and folic acid supplementation.

Myelomeningocele (MM) is the most common form of spinal dysraphism, a term this author prefers to spina bifida because it signifies the embryonic abnormalities underlying this condition. MM has the potential to affect every aspect of nervous system function, both central and peripheral, and poses many challenges for the neurologist. Neurologists will encounter other forms of spinal dysraphism, particularly the occult forms (Figure 108-1). The major difference is that the occult forms rarely have the other central nervous system (CNS) manifestations and present as pure spinal cord and nerve root malformations. MM is a condition that continues to have significant mortality from multiple causes, neurologic etiologies being an important contributor. Those who evaluate the person with MM must be prepared to assess problems that are multifactorial and cut across traditional boundaries of both medical and surgical specialties.

Most experts in spinal dysraphism advocate for assessments and treatments to be provided in a multidisciplinary setting because of the level of complexity involved. Whenever possible, those with MM should receive their health care services at multidisciplinary centers dedicated and organized toward what could be called spina bifida health care. However, changes in the delivery of health care often prevent this from occurring. The neurologist must therefore be prepared to assess these patients in isolation. Neurologists must be prepared to advocate for their patient in order to justify a referral to a multidisciplinary level of service when it is needed. Finally, MM is truly a life span condition. Evaluation of the condition often starts during fetal life and continues on into and throughout adulthood. Also, MM not only effects neurologic and general health but also causes varying levels of disability which must also be assessed and managed.

MM as a Malformation of the Nervous System

MM is the prototypic neural tube defect or spinal dysraphism. The term spina bifida has historically been used to describe these conditions. The term myelodysplasia has also been used. This term is confusing in that it is also used to categorize various neoplastic conditions of blood and bone marrow. It also does not give any indication that MM (and other forms of spinal dysraphism) is conditions that begin during embryogenesis. Spinal dysraphism fulfills this criterion as it refers to the fact that the embryologic tissue sheets, the ectoderm, mesoderm, and endoderm work in harmony to induce each other to result in differentiated tissues such as the nervous system. Proper inductive events are required to form the nervous system, and deviations in this process lead to nervous

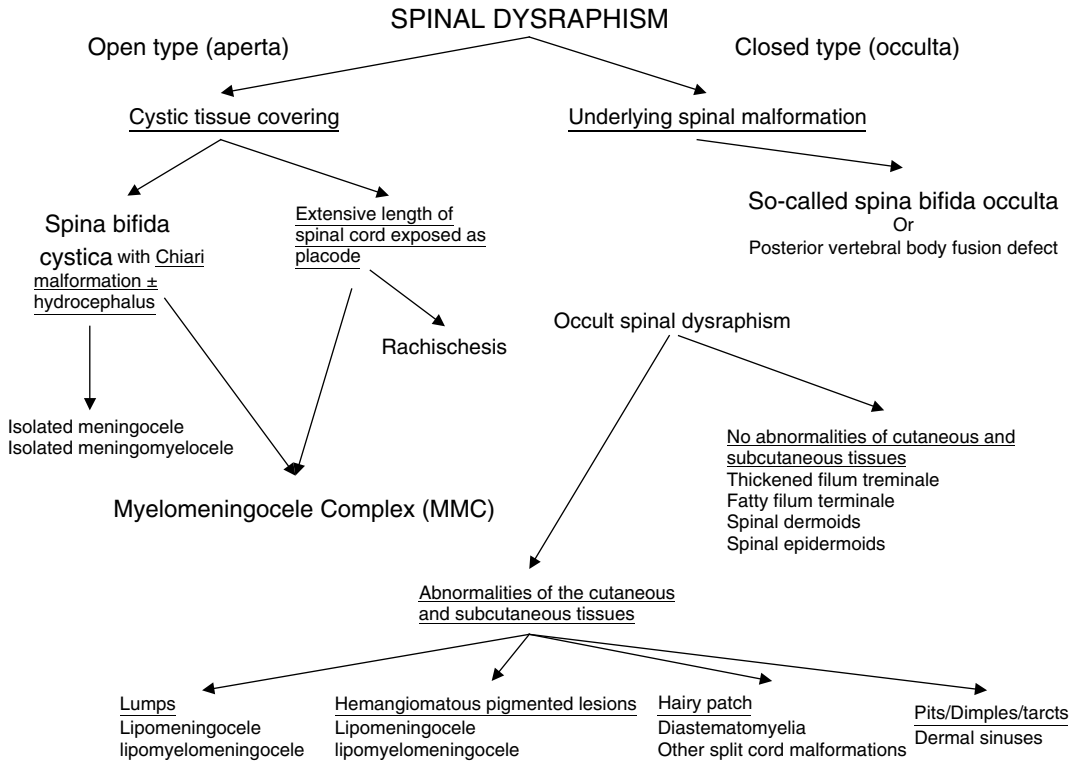

FIGURE 108-1. Algorithm for types of spinal dysraphism.

system malformations such as MM. The term spinal dysraphism also is inclusive and can be used to describe both open (aperta) and closed (occulta) forms of the condition, as well as forms of spinal cord malformations where the spinal processes are not bifid (such as certain forms of tethered spinal cord). It also allows for a more unified approach to categorizing malformations of the spinal cord, as well as malformation of the nervous system in general. Given what we now know about the biology of such CNS malformations as holoprosencephaly, one could argue we should call such cephalic midline malformations of the brain forms of cerebral or cranial dysraphism (as we do for encephaloceles).

MM almost always involves abnormalities along the entire neuroaxis, including the cerebrum, brainstem, cerebellum, and the remainder of the spinal cord above the spinal malformation. Some of these associated conditions are true malformations/dysplasias, whereas others are more likely deformations, such as the cerebellar vermis herniation or Chiari II malformation. Only deformations are likely to respond to surgical procedures such as decompression. A clearer understanding of these issues will require better longitudinal studies, better knowledge of the underlying mechanisms leading to spinal dysraphism, and more detailed analysis of the variability seen in this condition.

The most important roles the neurologist plays in providing services to people with spinal dysraphism include as follows: knowledge of the various conditions, their presentations, and the variability they express. Appreciation of this variability and complexity is important for assigning potential causal relationships between presenting symptoms and signs and abnormalities of structure and function. Most importantly, years of experience with this condition teaches one that many clinical problems are multifactorial and care must be taken in assigning causative association to one variable. This is particularly true when surgical intervention is being considered. On the other hand, surgical intervention is often needed in managing this condition and its deteriorations in function that present throughout the life span. Surgery is often a critical factor in maintaining and/or gaining health and function in MM. This is true not only for neurosurgical interventions but urological, orthopedic, and general surgical procedures as well. Examples of this include posterior fossa decompression, spinal cord untethering, and bladder augmentation.

Role of the Neurologist

Below are basic principles the author uses to assess people with MM throughout the life span. The tables provide a checklist of issues to specifically address.

Fetal Issues

The neurologists with experience in spinal dysraphism and MM can play an important role in prenatal assessment through their experience with this complex condition throughout the life span. A significant number of families presented with the diagnosis of fetal spinal dysraphism welcome the opportunity to be further educated about a condition that most lay people know very little about (Table 108-1). This is particularly true now that the option of closure of the open dysraphic defect through fetal surgery is a reality. At this writing, this procedure is being evaluated in a National Institutes of Health-sponsored clinical trial and a moratorium exists on performing the procedure outside the trial.

Newborn Issues

The neurologist can help the MM team by doing a thorough assessment of the newborn's neurologic functions and impairments (Table 108-2). It is important to acknowledge that single examinations do not reveal the whole picture and that there can be a period of decreased function after MM closure. Serial examinations of motor and sensory function over several months is the best way to determine the level of motor impairment and begin to talk about prognosis for motor function and ambulation. Most newborns who exhibit a L3 motor and/or sensory level have a good prognosis for ambulation at least through childhood. Sometimes MM is part of a syndrome, evaluation (with other team members) for the presence of any dysmorphologies or other malformations suggestive of an underlying syndrome (such as a possible chromosomal or genetic disorder) or environmental etiologic syndrome (eg, valproic acid embryopathy) is critical in the newborn period. Helping the team assess the newborn for evidence of increased intracranial pressure from hydrocephalus and whether or not cerebrospinal fluid/ventricular shunting is required is also the job of the neurologist.

TABLE 108-1. Prenatal Assessment in Myelomeningocele

Determine whether lesion is a myelomeningocle or some other form of spinal Dysraphism (e.g. diastematomyelia)
Determine the anatomical level of the lesion
Assess for the presence and severity of
Chiari malformation
Hydrocephalus
Associated brain malformations
Extremity deformities
Congenital kyphosis and/or scoliosis
Abnormalities of other body organs (kidneys, ureters and bladder, heart, etc.)
Prognosticate with caution. Discuss the spectrum of disability and illness seen in this condition.

TABLE 108-2. Management of Newborns in Myelomeningocele

Assess for the presence and severity of brainstem syndrome (unexplained Apnea, dysphagia, changes in eye movements and gag reflex)
Look for post closure alterations including
CSF leaks
Decompensation of hydrocephalus
Decompensation of brainstem and cerebellar function from compression, i.e. tight
Posterior fossa
Development of syrinx
Development of pseudomeningocele
Review latex allergy precautions
Assessment of genitourinary tract structure and function (renal sonogram, voiding cystourethrogram and urodynamics)
Assessment of anorectal function (anal wink and anal sphincter tone)
Initial assessment of feeding, swallow and GE reflux issues (based on symptoms and observation)
Initial assessment for sleep apnea (CR monitoring and consider sleep study)

Infant Issues

The neurologist is in a pivotal position to educate the family about all the aspects of this condition and how they stem from the underlying neurologic impairments (Table 108-3). A well-educated family is better prepared to negotiate the complexity of this condition as it manifests throughout the life span in their child. By developing a longitudinal relationship with the child and family, the neurologist will be better positioned to help the family during the likely crises, surgeries, and periods of uncertainties that arise for the majority of those affected by spinal dysraphism. Also, the neurologist

TABLE 108-3. Management of Infants with Myelomeningocele

Ongoing assessment of
Intracranial pressure (head circumference, fontanelle status, head sonogram, CT and MRI scans)
Brainstem and cerebellar function
Bladder pressure, GU reflux, and voiding (urological studies if changes in function-introduction of clean intermittent catheterization (CIC) and anticholinergic medications if bladder pressure is elevated)
Presence or absence of GU infection (urine for microscopy and culture)
defecation and neurogenic constipation
Joint mobility and contracture development
Latex and other allergies (serologic testing, avoidance counseling)
Efficacy and side effects of medications used to manage the bladder (anticholinergics, sympathomimetics, prophylactic antibiotics)
Continue screening for the presence of sleep apnea and other disorders of sleep
Assessment of
Tone abnormalities and their effects on motor development and posture*
fine motor, language, problem-solving, and social development*

* If changes, assess for shunt malfunction, increased intracranial pressure, posterior fossa compression on cerebellum and/or brainstem, and tethered spinal cord.

will be better able to keep the family focused on the overall picture of facilitating their child's growth and development while coping with the extra challenge of a complex health condition and disability. In this author's experience, many families exhibit periods of withdrawal from health services after traumatic hospitalizations, surgeries, or changes in function. A trusted health professional with whom the family has worked over time can help them refocus, overcome their anxieties, and better plan for the future.

Childhood Issues

The primary role here is the methodical and consistent assessment of nervous system function over time (Table 108-4 and 108-5). Although new problems in those with MM often present with the development of new symptoms, serial neurologic assessments are also critical in identifying the development of new problems within the nervous system in those with spinal dysraphism. The likelihood of potentially reversible nervous system deterioration in spinal dysraphism is real, particularly in MM (Table 108-5). If one includes shunt malfunction, the vast majority of individuals with MM will develop a new potentially reversible CNS problem within their lifetime. The goal of all MM services should be to identify these processes while they remain potentially reversible. Working with the rehabilitation team and the prescription of adaptive equipment is also important (Table 108-6).

Adolescent Issues

As the neurologist can educate the parents/caregivers of infants with MM about the condition, the opportunity to repeat this process again for the person with spinal dysraphism themselves arises during adolescence (but should ideally begin in childhood). An organized and thorough approach to this education will pay big dividends in helping the person with MM transition successfully to adulthood. One cannot assume responsibility for one's own health care without understanding why one needs that health care, particularly when that health care is as complex and time-consuming as it is with MM. The neurologist should also, along with the rest of the spina bifida team, advocate for a formal transition plan to help move the adolescent toward adulthood and ideally into adult health services. Ideally, this transition plan will integrate with the educational-based transition plan mandated by law and also with community-based support services. It is

TABLE 108-4. Childhood Issues In Myelomeningocele

Ongoing assessment of
Developmental attainments or losses*
Functional attainments or losses (including social)*
School function*
Seizures, headaches, tics, stereotypies*
Self-image and social self
The child's knowledge of their condition
Interventions for contractures and deformities*
Frequent assessments of the child's mental health and parent-child relationship
Assessment of the family and environment
Siblings and Friends
Ample opportunities in accessible environmen and physical activities (structured and unstructured)
Nutritional issues
Undernutrition
Beginnings of obesity
Assessment of growth and concern of early puberty and its adverse effects on growth
Psychosexual development

* If changes, assess for shunt malfunction, increased intracranial pressure, posterior fossa compression on cerebellum and/or brainstem, and tethered spinal cord.

TABLE 108-5. Potential Deterioration seen in Myelomeningocele

Decompensation of hydrocephalus with evident increases in intracranial pressure
Acute
Subacute/Chronic
New onset deterioration in brainstem function
Dysphagia
Sleep apnea
Eye movement changes
Other bulbar impairments (tongue deviations, fasiculations, altered gag relex)
New onset deterioration in upper extremity function
Atrophy of hand muscles
Arm weakness and/or grip weakness
Radicular neck/arm/hand pain
Tremor and dis-coordination of arms/hands
Carpal tunnel/median nerve symptoms and/or signs
New onset deterioration in lower extremity function
Neurological causes of decreases in gait
New onset leg weakness
Radicular back/hip/leg pain
Neurological causes of contracture development
Development of scoliosis and/or kyphosis.

TABLE 108-6. Rehabilitation Aspects of Myelomeningocele

Sacral and low lumbar (L4, L5 and Sacral lesions)—often ambulate into adulthood
Ankle-foot orthoses
Dynamic or floor reacting ankle-foot orthoses
Mid-lumbar (L3, L3/4)—can walk into adulthood, but often with significant difficulty after early childhood
As above plus crutches and/or walker
Wheelchair for distances (particularly in late childhood)
High-lumbar and thoracic (L2 and above)—can be trained to ambulate in early childhood with extensive bracing and aids
Recipricating gait orthoses
Hip-knee-ankle orthoses plus walker or crutches
Wheelchair for distances (particularly in late childhood)
Early use of wheelchair (strong consideration for power mobility)

this author's experience that this transition plan is very important in setting a good foundation for early adult functioning and health. Without it, fragmentation of services, neglected areas of health, and functioning and failure in independence are possible (and even likely). As the stakes for deterioration in health (and the real possibility of death) and loss of function (and quite possibly independence) are high, more effort needs to be paid to this area. Identification of high risk individuals and families will help us to focus on those most in need, as resources to provide this more intensive and integrated form of health care remain limited (Table 108-6).

Adult Issues

The child neurologist should not have to provide service to an adult population in a system of services in which adult neurologists and other health providers (eg, physiatrists) are adequately trained and experienced to deliver these services to those who have grown up with a neurologic impairment and disability. Ideally, adult health care services should be introduced through a transition team that includes both pediatric and adult providers. As the young adults and their parents become comfortable with the adult team, full participation in the "adult-only" program begins. The development, organization, and maintenance of these teams are difficult and expensive. Although their merits and effectiveness have been documented in the literature, they remain rarities on the landscape of American (and for that matter World) health care. Because of these above issues, it is becoming increasingly common to see pediatric providers evaluating and treating adults with MM. As the issues outlined for childhood continue to be the dominant health care issues, the compromise is not entirely a bad one (at least for the time being) (Table 108-8). It is important to remember that occult (and not so occult) shunt malfunction continues to occur into adulthood and may manifest as such subtle and often overlooked problems as asymptomatic papilledema, chronic headaches, subtle functional changes in cognition, energy levels, and lower and upper extremity function. It should never be assumed that because years have gone by without symptoms or signs of increased intracranial pressure that the ventricular shunt is no longer needed. All people with cerebrospinal fluid shunts should be evaluated as if shunt failure is a potential cause of their problems.

Also, in this author's experience, the problem of pain becomes a dominant issue for a significant number of adults with all forms of spinal dysraphism. Musculoskeletal and neurologic problems are the most common causes of pain. Early use of so-called neuropathic pain medications such as tricyclic antidepressants or gabapentin when pain appears to have a neuropathic quality should be considered. Early use may prevent the development of difficult and sometimes intractable chronic pain syndromes.

TABLE 108-7. Adolescent and Adult Issues in Myelomeningocele

- Ongoing assessment of growing independence (or lack thereof) with regards to
  - Homework
  - Chores
  - Social planning
    - Dating
    - Friends
  - Career aspirations
- Transition issues (i.e. plans for dealing with new environments and challenges in health care, education, vocation and living)
- Begin to assess for carpal tunnel syndrome (median nerve compression) in those who use crutches and/or extensive manual wheelchair use
- Additional adult issues
  - Reproductive issues
  - Work-related issues
  - Pain (It's causes and management)
  - Multi-dimensional assessment of deterioration in health and/or function (if and when it occurs)
  - Aging issues and their effects on function and disability.

Acknowledgments

The author wishes to thank his former colleagues at the Spina Bifida and Related Conditions Center at the Kennedy Krieger Institute for their years of hard work, dedication, and collaboration in helping those with spinal dysraphism remain healthy and achieve their functional potentials.

TABLE 108-8. Essential Evaluations for Myelomeningocele

- Infants
- Serial head cicumference measurements
- CT scan to assess ventricular system (baseline and as needed based on head growth)
- MRI of brain (include cervicothoracic spine) if dysfunction of brainstem and/or upper extremities
- Renal sonogram (assess kidneys, particularly for hydronephrosis)
- Urodynamic evaluation (to assess for abnormal bladder pressure and dysynergy)
- Voiding cystourethrogram (to assess for vesiculoureteral reflux)
- Beyond infancy
- Once or twice yearly assessment of optic discs for papilledema
- CT scan of head and shunt series (AP and lateral of head, chest and abdomen) every three to five years or when symptoms dictate
- MRI of brain (include cervicothoracic spine) if deterioration of brainstem and/or upper extremities and/or lower extremities functions
- MRI of lumbosacral spine if deterioration of lower extremities function, but also if deterioration inbrainstem and/or upper extremities functions (particularly if change in manual muscle testing) (Neurological causes of changes in bladder function as well)
- Yearly renal sonogram and serum BUN/Creatinine
- Urodynamic evaluation if a change in urinary voiding function (incontinence, or urinary tract infections.

Suggested Readings

Botto LD, Moore CA, Khoury MJ, Erickson JD. Neural-tube defects. N Engl J Med 1999;341:1509–19.

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Kirk VG, Morielli A, Gozal D, et al. Treatment of sleep-disordered breathing in children with myelomeningocele. Pediatr Pulmonol 2000;30:445–52.

Rickwood AM. Assessment and conservative management of the neuropathic bladder. Semin Pediatr Surg 2002;11:108–19.

Rintoul NE, Sutton LN, Hubbard AM, et al. A new look at myelomeningoceles: functional level, vertebral level, shunting, and the implications for fetal intervention. Pediatrics 2002;109:409–13.

Practitioner and Patient Resources

Spina Bifida Association of America
<http://www.sbaa.org>
The site of the Spina Bifida Association of America includes resources for medical professionals and individuals with spina bifida and their families. Updates on most important topics including latex allergy and folic acid supplementation. A new "Health Guide for Parents of Children Living with Spina Bifida" can be ordered through the site.

Association for Spina Bifida and Hydrocephalus
<http://www.asbah.org>
The site of the Association for Spina Bifida and Hydrocephalus for England, Wales, and Northern Ireland provides information complementary to the SBAA site.

Centers for Disease Control and Prevention
<http://www.cdc.gov/ncbddd/folicacid>
Centers for Disease Control and Prevention site with comprehensive information about folic acid and the prevention of neural tube defects.

Lipomyelomeningocele Family Support Network
<http://www.lfsn.org>
The site of the Lipomyelomeningocele Family Support Network includes information on this variant of spinal dysraphism and the tethered spinal cord.
<http://www.clinicaltrials.gov/show/NCT00060606>
Information on the Myelomeningocele Repair Randomized Trial, the NIH-sponsored trial to determine whether fetal closure of the myelomeningocele provides benefit over postnatal closure. This study is slated to end March 2007.

Hydrocephalus Association
<http://www.hydroassoc.org>
The site of the Hydrocephalus Association includes information packets and other resources for patients and families. Also includes a section on adult-onset hydrocephalus.

Hydrocephalus Center
<http://www.patientcenters.com/hydrocephalus>
The site of the Hydrocephalus Center an e-resource and companion to the Hydrocephalus Book. Both are informative resources about hydrocephalus and cerebrospinal fluid shunts.
<http://www.patientcenters.com/wheels>
The companion Web site to the book Life on Wheels. This book is for people who use a wheelchair for mobility. It also includes information on bladder and bowel function for people with spinal cord dysfunction.

CHAPTER 109

NEUROCOGNITIVE COMPLICATIONS OF SICKLE CELL DISEASE

FENELLA J. KIRKHAM, MB BCHIR, FRCPCH

ALEXANDRA M. HOGAN, PHD

Children with sickle cell disease, a chronic hemolytic anemia, present with a wide variety of neurologic syndromes, including ischemic and hemorrhagic stroke, anterior and posterior territory transient ischemic attacks, "soft neurological signs," seizures, headache, coma, visual loss, altered mental status, cognitive difficulties, and covert or "silent" infarction. Those with ischemic stroke usually have stenosis or occlusion of the distal internal carotid and proximal middle cerebral arteries diagnosable using magnetic resonance angiography or transcranial Doppler (TCD) ultrasound. For hemorrhagic stroke, aneurysms are common in adults but not in children, who often present with hypertension after transfusion or corticosteroids. Covert infarction may be detected on magnetic resonance imaging in around 25%. Cognitive difficulties, characteristically affecting attention, executive function, memory, arithmetic, and processing speed, are also common, particularly in those with covert infarction and large-vessel disease. Indefinite transfusion prevents recurrence in the majority of those who have had a stroke and prevents stroke in those with TCD velocities > 200 cm/s. In addition to the possibility of cure from transplantation, hydroxyurea, aspirin, and overnight respiratory support to prevent nocturnal hypoxemia are under investigation as strategies to prevent neurologic complications. The modifiable effects of blood pressure control, poor nutrition, and chronic infection on stroke risk should be explored.

Background

General

Sickle cell disease (SCD) is one of the most common genetically determined disorders and particularly affects those of African origin. In SCD, an abnormal β-globin gene codes the substitution of the amino acid valine for glutamine in the β-globin chain. The resulting hemoglobin S is unstable and has an increased propensity to polymerize under certain physical conditions. Historically, the sickle gene has conferred a selective advantage by virtue of a relative resistance to falciparum malaria in heterozygotes (those with one copy of the sickle gene). However, homozygotes (with both hemoglobin genes coding for hemoglobin S, HbSS) have a serious life-threatening disease, sickle cell anemia (SCA). There are two other common genotypes included under the term SCD: hemoglobin SC disease and sickle cell-β thalassemia, where one hemoglobin gene codes for hemoglobin S and the other codes for another abnormality of the β globin chain (either hemoglobin C [HbSC] or β-thalassemia [HbSβthal]).

SCD is characterized by both acute and reversible, as well as chronic and irreversible, changes in the properties and deformability of sickle red cells. Intracellular hemoglobin polymerization, combined with abnormal membrane properties, results in abnormal rheology of the blood. The primary determinant of the amount of polymer formation within the sickle red blood cell is the degree of oxygen saturation.

The clinical features of SCD are caused by a chronic hemolytic anemia combined with intermittent vaso-occlusion. Although disease severity is variable, many

suffer repeated episodes of bone pain and progressive organ damage, resulting in a poor quality of life and reduced life expectancy. Pain is a cardinal feature and typically restricts normal activities and requires strong analgesia. Other common complications in infants and children include dactylitis, splenic sequestration, aplastic anemia, chest crisis, skin ulceration, priapism, stroke and educational impairment as a result of memory and attentional problems, decoding difficulties, and abnormalities in visual motor integration.

The main causes of death in childhood are sepsis, acute splenic sequestration, chest syndrome, and stroke. Neonatal screening, combined with prophylactic penicillin and immunization, has had a dramatic impact on deaths due to sepsis, and the establishment of specialist clinics has allowed prompt intervention in life-threatening complications. The challenge now is to improve quality of life by reducing the frequency and morbidity of complications, particularly those affecting the brain.

Neurologic Complications

Epidemiology

Stroke is 250 times more common in children with SCD than in normal children, with an incidence similar to that for a general population of elderly adults, yet there has been relatively little research into risk factors and prevention. Stroke and transient ischemic attacks (TIAs) occur with an incidence of 0.61 and 0.52 to 0.74/100 patient years in children and young adults, respectively, with homozygous SCA (HbSS). The prevalence of stroke in children aged 2 to 19 is 2 to 6% and in those over 30 is 7 to 9%. In patients with the other genotypes (HbSC and HbSβthal), stroke is less common than in those with HbSS but is still much commoner than the general childhood population. For those with SCD who survive into adult life, major organ failure, including stroke, is the most common cause of death. Approximately 25% of patients with SCA and 10% of those with HbSC will have had a stroke by the age of 45 years.

Pathology

Although it was assumed in the past that stroke in SCD was the result of sickeling in the small cerebral vessels or disorders of coagulation, angiography shows that the majority of SCD patients with stroke have narrowing of the arteries of the Circle of Willis at the base of the brain, usually involving the distal internal carotid (ICA) and proximal middle cerebral arteries (MCAs) (Figure 109-1). Pathologic examination of these arteries shows endothelial proliferation, fibroblastic reaction, hyalinisation, and fragmentation of the internal elastic lamina. In some cases, recent thrombus may be seen either within the narrowed lumen or occasionally without associated arterial wall changes. In a proportion, fibrous occlusion of these arteries is associated with the development of very thin collateral vessels which bypass the occlusion. The appearance of these collaterals is known on angiography as moyamoya, from the Japanese expression describing the angiogram appearing like a "puff of smoke" (see Figure 1D; see Chapter 105, "Stroke and Cerebrovascular Disease"). The arterial stenosis and occlusion (with or without moyamoya) leads to cerebral infarction either in the MCA territory or more characteristically in the superficial and deep borderzones between the anterior and the MCA territories. Subarachnoid and intracerebral hemorrhage also occur, sometimes as a result of rupture of the fragile moyamoya vessels or of aneurysms usually located at the bifurcations of major vessels, most commonly in the posterior circulation. Sinovenous thrombosis may be associated with infarction or hemorrhage. Pathologic changes in the small vessels are also well described, and it is well recognized that both infarction and hemorrhage may occur in the absence of arteriographic changes.

Cerebral infarction has been reported to be the most common cause of stroke in the first two decades of life and from the fourth decade onwards, while hemorrhagic stroke occurs more commonly in the third decade.

Clinical Presentation

There is a broad spectrum of acute presentation with cerebrovascular accident (CVA) and other neurologic complications in patients with SCD. In addition to clinical stroke, with focal signs lasting > 24 hours (see Chapter 105, "Stroke and Cerebrovascular Disease"), patients with SCD also have TIAs with symptoms and signs resolving within 24 hours, although many of these individuals are found to have cerebral infarction or atrophy on imaging (Figure 109-2). The insidious onset of "soft neurological signs," such as difficulty in tapping quickly, is usually associated with cerebral infarction. Seizures are also more common in the SCD population, affecting around 10%. In addition, coma and headache are common presentations of infarctive and hemorrhagic stroke and cerebrovascular disease in children with SCD. Hyperventilation, eg, during an electroencephalography, occasionally provokes transient and permanent neurologic deficits, usually involving the posterior circulation territory. Altered mental status—with or without reduced level of consciousness, headache, seizures, visual loss, or focal signs—can occur in numerous contexts, including infection, acute chest syndrome, and acute anemia as well as apparently spontaneously. These patients are classified clinically as having had a CVA, although there is a wide differential of focal and generalized vascular and nonvascular pathologies, often distinguished using acute magnetic resonance (MR) techniques (see Chapter 105, "Stroke and Cerebrovascular Disease"), with important management implications.

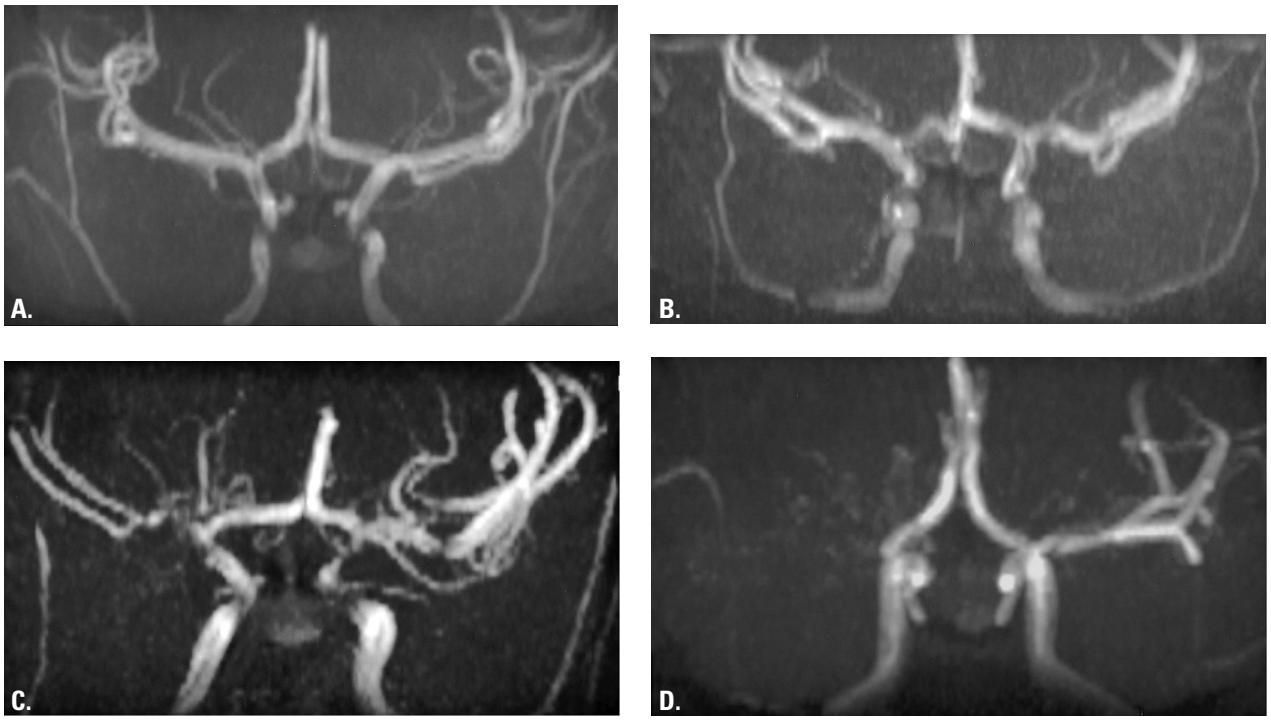

FIGURE 109-1. Magnetic resonance angiography in sickle cell anemia.

Risk Factors for Acute Neurologic Complications

High white-cell count, low hemoglobin, and oxyhemoglobin desaturation predict neurologic complications. In addition, risk factors for overt ischemic stroke include hypertension and previous TIA or chest crisis. For hemorrhagic stroke, aneurysms are common in adults but not in children, who often present with hypertension after transfusion or corticosteroids. Seizures are more common in those with cerebrovascular disease and covert infarction.

Recurrence

Around two-third of children with SCD presenting with their first stroke will have a further episode if untreated. Regular simple, manual, or automated (erythrocytapheresis) transfusion to a hemoglobin S of < 30% reduces the recurrence rate over the longer term to around 10%. The risk of ischemic stroke recurrence is higher for patients presenting spontaneously, those who underwent simple transfusion at presentation and those with moyamoya on arteriography.

Covert Cerebral Infarction

Cerebral infarction can be demonstrated on magnetic resonance imaging (MRI) in patients with SCD without symptoms of either stroke or TIA (see Figure 109-2). This covert or "silent" infarction affects around 20 to 25% of children and adolescents, characteristically in the anterior and/or posterior borderzones, and is associated with hyposplenism and relatively infrequent pain. Neurologic examination is normal, although these patients may have had subtle TIAs, headaches, or seizures.

Cognitive Sequelae

By mid-childhood, there is a reduction in the intelligence quotient of patients with SCD compared with siblings and other controls, which may be progressive, particularly in those with moyamoya syndrome. Impaired cognitive function appears to be related to covert stroke, poor growth, low hemoglobin level, and high platelet count, as well as lowered level of oxyhemoglobin saturation. Arithmetic may be particularly affected, and subtle deficits in attention and executive function have also been demonstrated in association with covert infarction.

Diagnosis

Brain Imaging in Acute Neurologic Complications

Computed Tomography or MRI

Computed tomography (CT) may be performed rapidly to exclude hemorrhage, although MRI is usually required to demonstrate the extent of infarction as early as possible, as well as potentially reversible pathologies such as

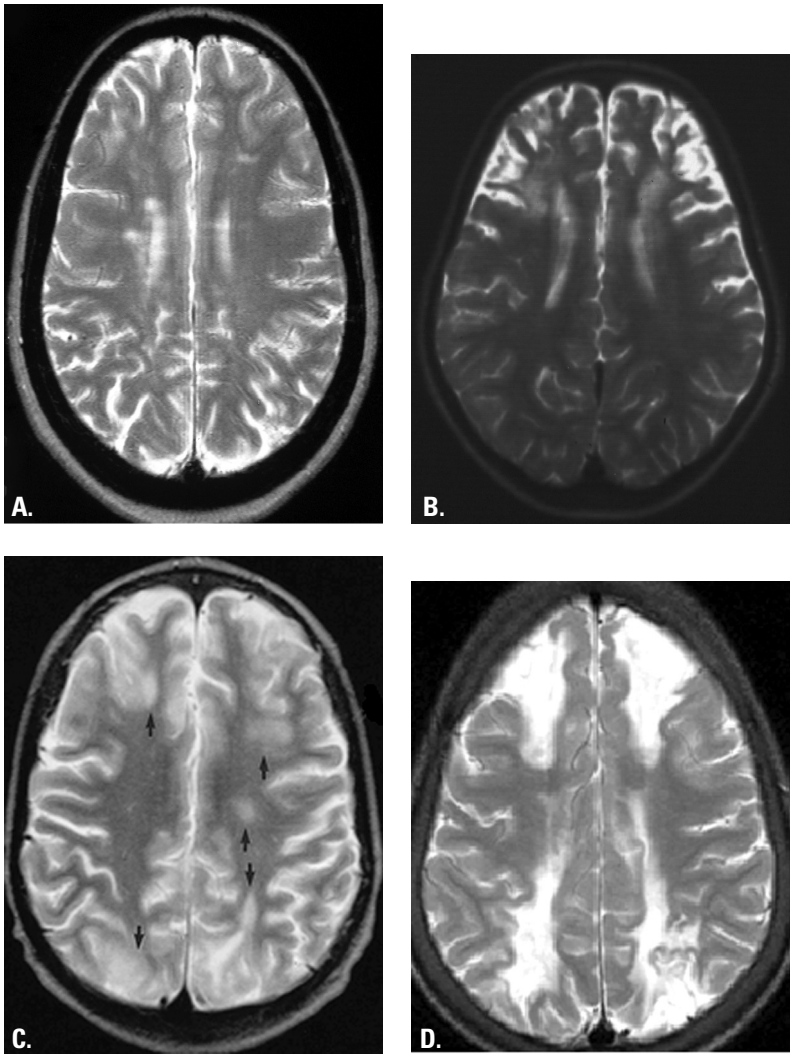

FIGURE 109-2. Magnetic resonance imaging demonstrating covert or "silent" infarction in children who did not have a clinical stroke.

posterior leukoencephalopathy (see Chapter 105, "Stroke and Cerebrovascular Disease"). Subarachnoid and intracerebral hemorrhage occur often in the context of acute hypertension or as a result of sinovenous thrombosis, rupture of aneurysms (usually located at the bifurcations of major vessels, particularly in the vertebrobasilar circulation), or rupture of fragile moyamoya collaterals. In patients presenting with clinical stroke, likely findings include large infarct in the distribution of the MCA, smaller lesions in the basal ganglia, or deep white or grey matter of the borderzones. Occipitoparietal or thalamic involvement should suggest sinovenous thrombosis.

MR or Conventional Arteriography

Between 60 and 90% of children with SCD and acute stroke in an arterial distribution have abnormal findings on conventional angiography or magnetic resonance angiography (MRA) (see Figure 109-1). Typical abnormalities include stenosis or occlusion of the distal ICA or MCAs. Moyamoya syndrome and, occasionally, rarer patterns such as vertebral or ICA dissection and small vessel vasculitis have also been documented. Sinovenous thrombosis is probably underdiagnosed because many patients do not undergo acute vascular imaging; if emergency MRA is available and the results are found to be normal, MR or CT venography should be considered.

Screening for Preventable Pathology

MRI

Covert or "silent" infarction can be detected using T2-weighted clinical MRI at 1.5 tesla (see Figure 109-2) but cannot be recommended as routine as there is currently no

evidence base for preventing progressive covert infarction or clinical stroke. Focal abnormalities in perfusion demonstrated using MRI (arterial spin-tagging or gadolinium as tracer) (Figure 109-3A,B) or positron emission tomography are associated with cognitive deficits. Compared with controls using voxel-based morphometry, there is evidence of damage in the white matter of the borderzones even in patients with SCA and normal T2-weighted MRI, but this cannot currently be used for diagnosis in individual patients. Improvements in MRI, including more powerful magnets (eg, 3 tesla) or additional sequences (eg, diffusion tensor imaging), are likely to reveal more pathology, but a considerable amount of work will be required to determine clinical significance and these will remain in the research arena for some time to come.

Transcranial Doppler for Cerebrovascular Screening

Stenosis may be diagnosed before stroke occurs as high time-averaged maximum velocity on transcranial Doppler (TCD) ultrasound (see Figure 109-3D). Adams and colleagues (1997) categorized the highest time-averaged maximum velocity on either side into 3 groups:

1. those with normal TCD, defined as ICA/MCA velocity < 170 cm/s.
2. those with conditionally abnormal ICA/MCA velocities, ie, between 170 and 200 cm/s, who had a 7% risk of stroke over the next 3 years.
3. those with abnormal ICA/MCA velocities, ie, > 200 cm/s, who had a 40% risk of stroke over the next 3 years.

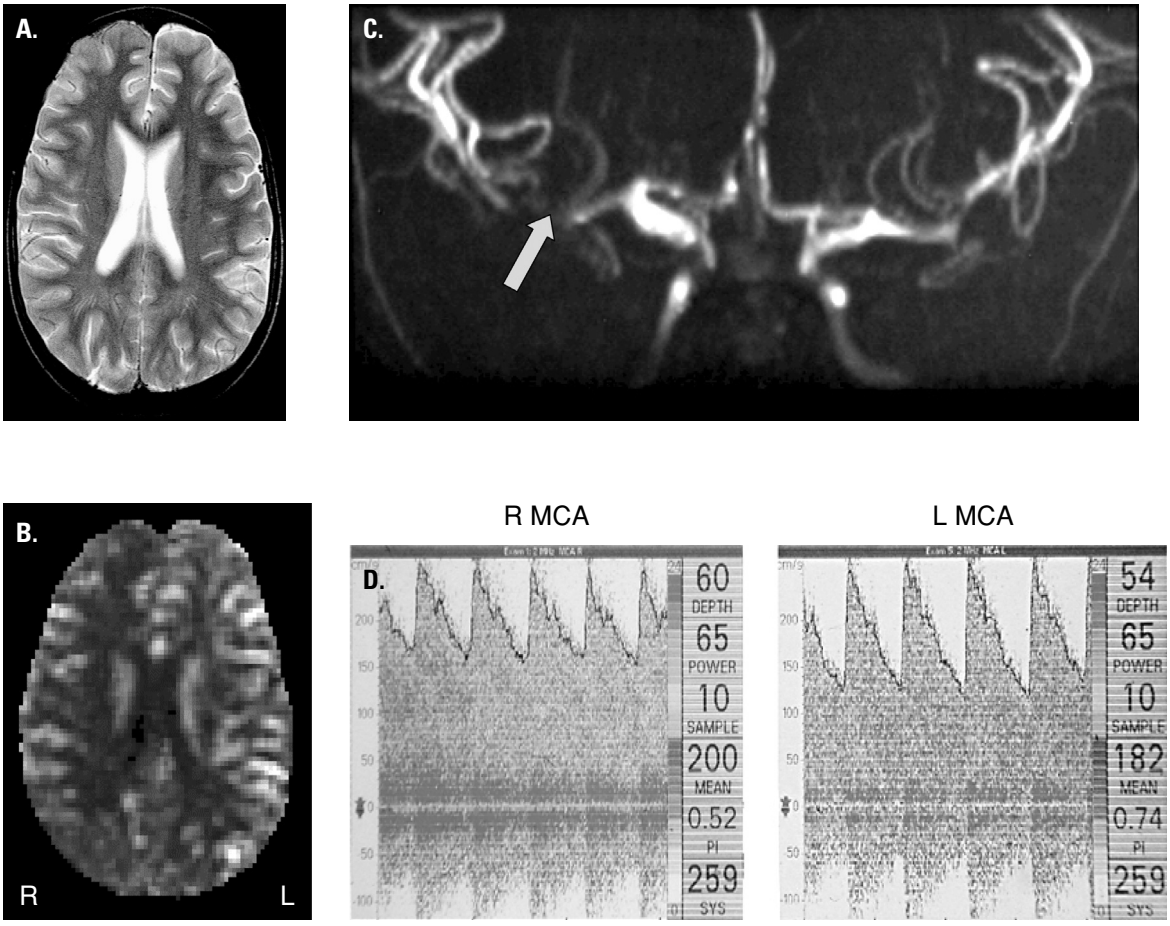

FIGURE 109-3. Images from a child who had recently presented with a chest crisis. (A) normal T2-weighted magnetic resonance imaging (MRI), (B) perfusion MRI showing reduced perfusion posteriorly on the left and throughout the right hemisphere, (C) bilateral turbulence on MR angiography, and (D) transcranial Doppler showing conditional velocities on the left and abnormal velocities on the right.

Cognitive Testing

Patients with SCA are at risk from infancy for neurodevelopmental delay, which can be detected using the Bayley Infant Neurodevelopmental Screener. In older children, covert infarction is associated with poor performance on tests of attention. Executive dysfunction is associated with TCD abnormality and, in adolescents with silent infarcts, reflected in reduced amplitude of event-related potential components associated with frontal lobe function. Memory may also be a problem which may be remediable with specialist education. A combination of the California Verbal Learning Test-Children's Version and Block Design from the Wechsler Abbreviated Scale of Intelligence may be a relatively cost effective method of screening for covert infarction, and the "TOVA" test of attention has also demonstrated sensitivity (86%) to covert infarct. Appropriate cognitive screening batteries are likely to emerge once there is an evidence base for prevention or remediation.

Management

Emergency Management of Stroke in SCD

This therapy has evolved through hematologic clinical experience rather than being subject to rigorous evaluation by randomized controlled trial. Hemoglobin and sickle hemoglobin percentage should be measured at presentation with any neurologic complication, and packed red blood cells (20 mL/kg) should be cross-matched as quickly as possible. The goal should be to begin the exchange transfusion within 2 to 4 hours of presentation, particularly if the deficit is persisting or progressing, although no data. Blood should be leukocyte-depleted and sickle-, C-, E-negative as well as human immunodeficiency virus-, cytomegalovirus-, and hepatitis C-negative and compatible with the recipient's ABO, Rhesus D, K, Fy, Jk, and MNS red cell phenotype to minimize the risk of alloimmunization. If available, exchange rather than top-up transfusion is recommended by most hematologists and appears to be associated with reduced risk of recurrence, although there are no randomized data. Immediately after presentation, exchange transfusion should be undertaken to reduce the hemoglobin S percentage to < 20% and raise the hemoglobin to 10 to 11 g/dL with a hematocrit of > 30% and can be accomplished using a manual regime or an automated cell separator for erythrocytapheresis. If manual exchange is performed, 2 to 3 procedures are usually required, whereas automation usually allows the exchange to be completed in a single session. Ideally two intravenous lines should be placed so that saline may be infused while blood is withdrawn in the other line, although it is possible to exchange through one large vein using a 20 mL syringe and a three-way tap and a diaphragm bung into which the venesection bag needle is inserted. A central line is needed if peripheral access is impossible. The volumes for the exchange are calculated once the hemoglobin is known and are recalculated at the halfway stage depending on the repeat hemoglobin. Exchange transfusion must be conducted slowly (100 mL/h and 5–10 mL/kg/aliquots) and with caution in view of the occasional association with neurologic deterioration, perhaps related to increasing viscosity and/or blood pressure. Aliquots should be recalculated to be no more than 5 mL/kg if the patient is acutely unwell or hypoxic. If the patient has had a neurologic event in the context of severe anemia (eg, splenic sequestration or aplastic crisis), or if exchange transfusion is going to be delayed for more than 4 hours, urgent top-up blood transfusion of 20 mL/kg should be considered. Although published cases are rare, once diagnosed on appropriate neuroimaging, there is no known contraindication to management of hemorrhage, sinovenous thrombosis, or dissection as outlined in the protocols for nonsickle stroke (see Chapter 105, "Stroke and Cerebrovascular Disease"). Interventional Neuroradiology with coils has been successfully used for the management of aneurysms in SCD and represents a reasonable alternative to surgery.

Prevention of Recurrent Stroke

Although there has never been a controlled trial, several cohort studies have shown that recurrent stroke is reduced to around 10% in those on a chronic transfusion regime, at least 6 weekly, to reduce the sickle cell hemoglobin (HbS) level below 30%, compared with a recurrence rate of between 66 and 90% in untreated patients (Royal College of Physicians Intercollegiate Paediatric Stroke Working Group, 2002; Hulbert and colleagues, 2006). Until further evidence is available, children with SCD who have had a stroke should be transfused long-term to achieve a hemoglobin S below 30% for 3 years and below 50% subsequently, as there is considerable, albeit anecdotal, evidence that this is an effective method of reducing recurrence. Hydroxyurea, bone marrow transplantation, and revascularization for moyamoa are options for some patients, particularly those who cannot tolerate chronic transfusion or experience recurrent events despite reduction of the hemoglobin S percentage to < 30%.

Primary Prevention

Blood Transfusion

Stroke Prevention Trial The Stroke Prevention Trial in Sickle Cell Anemia (STOP I) trial recruited 130 children aged 2 to 16 years with SCA (HbSS) or sickle β zero

thalassemia (HbSβ0) and no history of stroke were screened for abnormal TCD, defined as ICA/MCA velocity > 200 cm/s, from sickle cell centers across the United States. They were randomly allocated to either blood transfusion or observation with an end point of clinical stroke, defined as a new focal neurologic deficit lasting more than 24 hours. The study was terminated early because of the benefit of transfusion in preventing first stroke in children with SCD. Preliminary epidemiologic evidence suggests that implementation of TCD assessment in routine medical care of children with SCA is associated with a reduction in stroke.

STOP II developed from the STOP I trial. Recruitment was from a pool of children with SCD and abnormal TCD on screening that had received 30 months or more of regular transfusion on the STOP protocol and had converted from a high risk to a low risk on TCD. These children were screened with MRA to ensure that there was no evidence of severe lesions. Patients were then randomly allocated into two arms. One arm continued with blood transfusions, the other stopped transfusions. Patients had a TCD every 3 months and an annual brain MRI or MRA. Follow-up continued for 2 to 4 years. Three likely outcomes were predicted. First, a stroke would develop, if this occurred, blood transfusions would resume; secondly, the patient would remain low risk on TCD, in which case the participant would continue in the study; thirdly, the TCD results reverted to abnormal, in this event participants would resume transfusion. The Data and Safety Monitoring board recommended closure to STOP II due to safety concerns when interim analysis showed reversions to high risk (14 TCD endpoints and 2 others with stroke), all in the nontransfusion arm.

Current policy in the USA and Europe arising from STOP I and STOP II is that children with SCA (HbSS) or HbSβ0 thalassemia should be screened with TCD to find those with velocities > 200 cm/s and those children should then be transfused indefinitely; this policy has been endorsed in official guidelines in the USA and UK. The number needed to treat is six.

Silent Infarct Transfusion Study This six-year study commenced late 2004 comprises 29 sites in the United States, Canada, England, and France and will report in 2013. The main goal is to determine the efficacy of blood transfusion therapy as a treatment for preventing silent infarctions.

Issues with Chronic Blood Transfusion

There are major drawbacks with chronic blood transfusion therapy. Fifteen percent of patients in the STOP trial crossed over from the transfusion arm, primarily due to finding the treatment unacceptable. A further 15 and 8% developed alloimmunization or required central venous catheterization, respectively. In addition, children undergoing regular transfusion are at risk of organ failure due to iron overload and must be given subcutaneous deferoxamine several nights a week to prevent this; unfortunately, compliance is frequently an issue. For that reason, there is a good rationale for examining alternative strategies for preventing neurologic morbidity in SCD.

Alternative Approaches

Several studies looking at prevention of neurocognitive morbidity have now started. Endpoints include MRI and TCD abnormality as well as cognitive testing, including memory, attention, and processing speed.

Bone Marrow Transplantation

Although there has not been a randomized controlled trial, it is clear that successful bone marrow transplantation cures SCD. National centers quote survival rates of > 90% while > 80% are disease-free. However, there is a possible risk of a fatal cerebral hemorrhage in the acute phase. Approximately 20% of patients will have seizures despite phenytoin prophylaxis and supplementary magnesium. Although recurrent clinical stroke is rare after transplantation, even if transplantation is performed for the indication of a previous stroke, individuals who have already had a silent infarction are at risk of an extension. Relatively few patients and their families are willing to undergo transplantation in view of the mortality risk.

Hydroxyurea

A large randomized controlled trial in adults with SCD showed that the frequency of painful crisis was reduced in patients taking hydroxyurea compared with placebo. Hydroxyurea increases fetal hemoglobin, which has a higher oxyhemoglobin affinity, and probably also reduces inflammation. In preliminary studies, there is evidence for a beneficial effect on TCD abnormality and cognition. However, many patients are reluctant to embark on this drug because of the uncertainty of the long-term risk of cancer. For patients who have had a stroke, there is currently a trial recruiting which compares long-term blood transfusion treatment with switching to hydroxyurea after several years of blood transfusion treatment (SWITCH). Examining whether this drug has a role in primary prevention of neurocognitive abnormality in the BABYHUGS trial has proved difficult because of the requirement to sedate very young children to undergo MRI.

Aspirin

Aspirin has been shown to reduce secondary stroke in adults and has been investigated as a method of primary prevention, although the risk of bleeding may outweigh any benefit, as has been shown for the general population with a low risk of stroke. Two small trials in the early

1980s showed that aspirin had no effect on the number of painful episodes in SCD; however, importantly, no major adverse effects were reported. The Sickle cell Two center Aspirin Response Trial to establish safety, feasibility, and compliance is underway.

Management of Sleep Disordered Breathing

Young people with SCD are at high risk of sleep disordered breathing, and there is some evidence for an effect on stroke risk. However, surgery, eg, adenotonsillectomy has long waiting lists, and there is no evidence of benefit. Oxygen supplementation is problematic because of the discomfort of the cold gas as well as the fire risk. Conventional continuous positive airway pressure (CPAP) has proved difficult to use in children, but autoCPAP, which only triggers when the patient obstructs, is the treatment in the Prevention of Morbidity in SCD pilot trial, which is mainly looking at safety, feasibility, and compliance but has a processing speed endpoint.

Infection, Blood Pressure, Nutrition, and Family Support

Children with SCD should be vaccinated against Pneumococcus and Haemophilus and should take regular penicillin. Blood pressure is lower in the majority of patients with SCD but is relatively increased in those with stroke; there is no evidence on whether control of hypertension reduces recurrence risk. A good diet, including at least 5 portions of fruit and vegetables a day and regular exercise within the limits of tolerance, may also reduce the risk of stroke. Support for families and appropriate role models for good parenting is likely to be of benefit, as there is evidence that a "learned helplessness" parenting style is associated with cognitive problems and that behavior problems are more likely if there is family conflict. Trials of educational remediation are under way.

Specific Treatment Schedules

See Chapter 105, "Stroke and Cerebrovascular Disease" for general management

Transfusion Therapy

- For acute stroke or other central nervous system (CNS) complications of SCD, if hemoglobin < 10 g/dL: simple transfusion as soon as possible to raise hemoglobin to 10 g/dL
- For all patients with acute stroke or other CNS complications of SCD: manual or automated (erythrocytapheresis) exchange as soon as possible to reduce hemoglobin S to < 30%
- For secondary prevention in patients with previous ischemic stroke: regular simple, manual, or automated (erythrocytapheresis) exchange to maintain hemoglobin S < 30% indefinitely
- For primary prevention of stroke in patients with SCD and maximum ICA/MCA velocity > 200 cm/s: regular simple, manual, or automated (erythrocytapheresis) exchange to maintain hemoglobin S < 30% indefinitely.

Hydroxyurea

- For primary prevention in patients with previous ischemic stroke who cannot tolerate regular blood transfusion: hydroxyurea 15 mg/kg/d escalating to 30 mg/kg/d if hematologic toxicity. Regular full blood counts must be obtained, and the hydroxyurea stopped if neutropenia supervenes.
- For secondary prevention in patients with previous ischemic stroke who cannot tolerate regular blood transfusion or who have recurrent neurologic events despite HbS < 30%: hydroxyurea 15 mg/kg/d escalating to 30 mg/kg/d if hematologic toxicity. Regular full blood counts must be obtained, and the hydroxyurea stopped if neutropenia supervenes. Transfusions should be continued for an overlap period. Patients with iron overload may benefit from phlebotomy.

Surgery/Interventional Neuroradiology

- For secondary prevention in patients with previous ischemic stroke who have moyamoya on angiography: referral to an experienced vascular surgeon who can consider revascularization.
- For secondary prevention in patients with previous ischemic stroke who have an aneurysm on angiography: referral to an experienced vascular team who can consider surgery or interventional neuroradiology for extirpation.

Rehabilitation

- For children with stroke: referral to a team experienced in rehabilitation of acute injuries.
- For children with cognitive difficulties: referral to educational services for additional support in school targeted at specific learning difficulties identified in the individual child.

Discussion

This is an exciting time for those caring for patients with SCD as greater understanding of the pathophysiology has led to evidence-based treatments for the primary and secondary prevention of neurologic and cognitive morbidity which are starting to become widely available in parallel with evidence of benefit to the population. However,

many have side effects or are an unacceptable burden to the child, and further research, in partnership with the children and their families, is urgently required. There is greater understanding of the risk factors for cognitive impairment, which may eventually lead to evidence-based prevention as well as educational rehabilitation. Large scale randomized controlled trials will need to involve multiple sites across continents, but the studies conducted to date have shown that this is an achievable aim.

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Practitioner and Patient Resources

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Chapter 110

Pain Management

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A clinical approach to evaluate childhood pain is presented, with emphasis on the means of assessment, most common types of pain found in neurological patients and approaches to treatment unique to pediatric patients.

"Children experience pain on a number of levels, from bumps and bruises whilst playing to disease-related and chronic pain resulting from illnesses, such as cancer and juvenile arthritis. I know from my own research that they also feel pain from a very early age. The sad truth is that we have the ability to treat and prevent children's pain but all too often we don't, particularly when children are being seen outside the pediatric environment." Al Aynsley-Green

Pain is a ubiquitous occurrence, a fundamental part of the human experience. The critical role of pain in protecting an organism from potentially damaging experiences can be fundamentally observed in watching a child dealing with an injury, learning the valuable lesson that whatever led to the hurt, might be something that should be avoided in the future. However, nothing can be as devastating as watching a child in pain, particularly a child in chronic pain. And neurology is a unique environment, in that many of the syndromes that lead to pain through pathology of the nervous system provide a unique clinical challenge.

Pain brings many patients to the physician's door, and it opens a powerful window to view the potential underlying pathology. Until quite recently, pain was virtually untreated in children, and many health care providers maintained that children did not feel pain the same as adults. In the past two decades, there has been a push to improve pain management in the pediatric population. Revolutionary work has addressed the role of pain in children and the unique approach a clinician must use in addressing pain in the pediatric environment.

To better manage pain, the practitioner should understand the different types of pain that children encounter and the means by which children communicate their pain experiences, particularly at different stages of development. This exploration must begin with an exposition of the nature of pain itself.

The Definition of Pain

According to the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Pain is a subjective experience, not an objective one, and according to the IASP, each individual learns what pain is through experiences related to injury in early life. Physiologists and biologists recognize that stimuli that cause pain are likely to be those that cause tissue damage. Accordingly, pain is the subjective experience we associate with actual or potential tissue damage. Pain is also an emotional experience, and the IASP contends that pain is always unpleasant. Experiences that are similar to pain but are not unpleasant, such as pricking, should not be considered pain. Unpleasant experiences, such as paresthesias and diasthesias, including tingling and buzzing, may also be considered pain on report but may not genuinely be painful because they may not have the usual

sensory qualities associated with pain. Some sensory experiences may be emotionally experienced as painful but by definition are not pain. For example, dyesthesias, or unpleasant sensations in response to normal stimuli, may be reported by the patient as an unpleasant experience. This becomes particularly critical in the pediatric population, in that pain must basically be what the person experiencing it claims it to be. In children, the concept of pain may be different than that found in adults, but pain remains subjective, so in the end analysis, we must rely on the report of the child, if the child is old enough for self-report.

What sensory qualities are associated with pain? One of the most fascinating ways to explore this phenomenon is to ask individuals to define their experiences (Table 110-1). Note the unique perspective that some children, particularly athletes, have with respect to pain.

Although these definitions of pain do show similar patterns, the role of age and experience can clearly be seen in the way individuals characterize their definitions of pain. Most important, we would argue that the manner in which individuals define pain can significantly influence the way in which they experience potentially noxious events.

Pain in the Absence of Tissue Damage

One of the most critical aspects of the study of pain respects that individuals can report pain in the absence of tissue damage or any pathophysiologic cause. This can happen because of psychologic reasons or due to centralized pain. Psychologic factors, such as anxiety and depression, may lead to the amplifications of unpleasant stimuli to the realm of pain.

Centralized pain often derives from chronic experience with pain that leads to changes in the nervous pathways that remain after the damage has healed. Nociceptive pathways can be hypersensitive, following injury or overstimulation. There is usually no way to distinguish the experience of those with psychogenic or neurogenic pain, or pain resulting from psychologic disturbances or from alterations in the nervous system that are not necessarily derived from tissue damage, from pain due to tissue damage. If individuals regard their experiences as pain, and they report those experiences in the same way as pain caused by tissue damage, those reports should be accepted as pain. This definition of pain, as presented by the IASP, avoids tying pain to the stimulus. Individuals can experience noxious events without experiencing pain, just as individuals can experience pain in the absence of tissue damage. Our studies with high-level athletes have shown that even highly noxious events do not produce pain reports in many athletes, although tissue damage clearly occurs. This may be evident in their definitions of pain reported above.

Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain. Pain, by this definition, is always a psychologic state, even though we may appreciate that pain most often has a proximate physical cause. Pain is, by its nature, a subjective experience. Pain is, at its core, defined by the child or adult experiencing it.

TABLE 110-1. Individual Definitions of Pain

Age	Gender	Definition
6	Girl	"When you fell, did you have a big scab or a little scab?"
7	Girl	"Not too bad, hurts, not too much but sometimes a lot."
6	Boy	"Hurt. Sometimes you get a little cut…it's like twisting your ankle…that hurts bad, very bad, and not useful."
10	Boy	"An uncomfortable feeling when something is injured."
11	Girl	"Something that hurts very much."
13	Boy	"Something hurts you, makes you sad, upset."
15	Boy	"Reaction of nerves telling your brain that some damage is being caused to your body."
17	Female	"Something that hurts."
18	Male	"Unpleasant sensation."
19	Male	"A signal that tells you that you should not be doing something. Tells you that something you are doing is bad."
17	Female	"Pain means that you should stop."
18	Male	"Something I don't like. Try to avoid."
18	Female	"Something bad, can be physical or emotional. Something you want to stay away from."
19	Female athlete	"…when it is unbearable – for me to stop, something has to be unbearable."
18	Female athlete	"…intense, sharp, agony."
17	Male athlete	"anything that keeps me from doing what I have to do."
18	Male athlete	"…more of an unpleasant feeling—not an option whether you tolerate it or not—you just do."
18	Male athlete	"Pain is something that causes disturbances in my abilities to do things."
17	Male athlete	"unpleasant sensation that causes activity to cease."

Children's reports adapted from McGrath PA, (1990).

Pain in the Body

Nociceptors (receptors that carry information regarding stimuli that approach tissue-damaging ranges) are capable of a remarkable form of adaptation, called sensitization, whereby stimulation in the periphery that would not be normally perceived as painful are perceived as frankly painful (allodynia). Most interestingly, the process can occur at the peripheral level, the nociceptor or input level, and more centrally at the level of either the spinal cord or cortically. Certainly, the role of the pain system as potential protector, as well as an early warning system, becomes evident in an examination of the phenomena of sensitization.

After cutaneous injury, both the injured skin and the adjacent uninjured skin become more sensitive to specific types of sensory stimulation. Empiric research emphasizes the role of central mechanisms in the maintenance of many types of hyperalgesic response or responses that are perceived as more painful than would be expected. Hyperalgesia can be maintained even after anesthetizing the region of pain. However, administration of anesthetics prior to noxious stimulation prevents the development of sensitization. The administration of anesthetics, however, cannot undo sensitization, once it has evolved. Thus, while peripheral inputs are required for the development of hyperalgesia, peripheral inputs from the injury site are not required for maintenance of the hyperalgesic effect.

This brief review makes the argument for aggressive treatment of pain, even in our younger patients. Exposure to nociceptive stimulation can lead to centralization of pain responses, such that even in the absence of any evident tissue damage, pain may still be present. This type of learning may allow for the maintenance of pain even when the initial injury has healed. Many studies indicate that early pain experiences can also lead to potential alterations in responses of children. Although these studies are speculative, the potential implications are profound and certainly require that physicians who work with children with a malleable nervous system be particularly cognizant of significant early pain experiences. Every effort should be made to reduce clinical pain.

These early experiences with pain may play a role in the development of pain pathways and may significantly alter normal pain pathway development. This could lead to excessively sensitive interpretation of painful inputs. Children who experience significant stressors may develop unique modifications of the nociceptive systems, which may make them more vulnerable to the development of certain types of somatic pain syndromes. Again, while many of these research findings are still speculative, they raise concern for the treatment of children and emphasize the importance of management of pediatric pain.

Pain in the Clinic

Pain is not simply the product of tissue damage but is the amalgamation of nociception, psychologic factors, cultural factors, and experiences that result in the perceptual experience of pain (Figure 110-1). This biopsychosocial model frames the necessity for multimodal treatment of pain. Most important, these factors do not interact through a serial process but function through a parallel processing model, interacting through multiple levels and acting at multiple points in the pain experience, to influence the subjective experience of pain. Each of these factors can influence subjective pain and are critical to acknowledge in order to take an adequate pain history. Particularly with a pediatric population, the history becomes crucial, as children who cannot deal adequately with stressors may express their frustration through physical pain, and, as with adults, many psychologic factors can amplify the pain response in children. This makes the history an important first place to start in a discussion of pediatric pain.

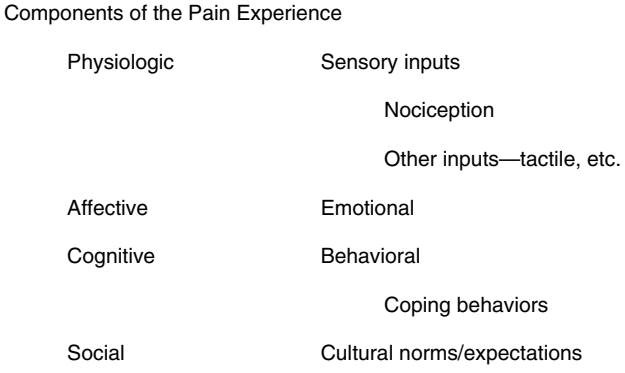

FIGURE 110-1. Components of the pain experience.

Taking a Pain History

When taking a pain history, inquiries should be directed to the child as much as possible. In general, children from approximately the age of 3 years should be able to provide beneficial information about their pain, including information about alleviating and aggravating factors, contextual factors, and the nature of the injury/insult. Most importantly, psychosocial factors can play a critical role in the manifestation of pain behaviors in children. When possible, information should be collected from the child in both the presence and the absence of the parents, as the parents may be playing an inadvertent role in either amplifying or minimizing pain.

In young children, pictures are helpful for localization of pain, in addition to pointing to the area on the body. Multiple queries are beneficial to try to get accurate information regarding specific localization of pain, keeping in mind that many types of severe pain can be difficult to localize even for adults, especially if the pain is radiating. In any assessment of pain in a child, patience is important. Avoid leading questions if possible, and allow the child to tell the story as much as she is able.

An index of the impact of pain on activities can be informative to the pediatric clinician as an index of pain severity. However, as these types of complaint can also permit young persons to avoid onerous tasks, this type of assessment also suggests the importance of multiple levels of pain assessment in children. This again emphasizes the need to talk to both the child and the parent about the impact of the pain on the child's daily activities.

Does the pain keep the child out of school but not off the playground? Many aspects of pain are difficult to characterize, but the more of these aspects we can assess, particularly the impact of pain on daily living, the better our potential understanding of the potential etiologies and aggravating factors surrounding pain.

An assessment of family history of illness can be imperative in the interpretation of a child with vague complaints of pain. Particularly in the context of neurologic pain, where many times sources of pain are not obvious, care must be taken not to overinterpret a family history of chronic pain complaints. But if a relative has recently died of a brain tumor, and a child presents with chronic headaches, this certainly merits further investigation, as psychologic factors can play a critical role in pediatric pain, as both genesis and amplifiers of pain.

Any discussion of pain has to include a discussion of the primary means of pain assessment. Pain measurement in adults is difficult. In children, the problem becomes even more complex, particularly with younger children.

Pain Measurement in Children

In infants and younger children, behavioral and physiologic measures, including facial expressions and heart rate measures, provide primary means for pain assessment (Table 110-2). One of the difficulties with use of these types of pain assessment resides in their indirect nature. Although pain ratings are by their nature subjective, these "objective" measures of pain are also colored with their own indirect issues. Health care professionals who interpret behavioral pain measures, such as body posturing, facial expressions, or crying, may attribute a cry to pain that may be due to other emotions or these behaviors may be interpreted quite differently. Several studies have shown that interrater reliability for these measures, particularly when comparing ratings of health care professionals to parents, remains quite poor. Multiple assessments by different observers are critical, as well as consistent assessment using the same observers over time.

TABLE 110-2. Methods for Pain Assessment in Children

Appropriate Age	Type of Scales	Examples
Infants/young children	Physiologic scales	Heart rate Respiration rate Reflex responses
Young children	Behavioral responses	Body posture Facial expression/ grimacing Distress behaviors Crying—loudness and duration
3 yr +	Subjective scales/ self report	Interviews/ questionnaires Pain thermometers
4–5 yr		Facial scales Color scales Visual analog scales Drawings
6–7 yr +		Numeric scales Magnitude matching

These behavioral measures do provide a valuable means for monitoring pain progress during pain treatment, particularly for young patients experiencing acute, sharp pain. These measures are quite valuable to assess changes of pain over time in acute pain situations in these younger patients, most appropriately if the same observers keep track of pain in the child. However, these behavioral rating scales are not as effective for more chronic types of pain, or for duller, aching types of pain.

As a child approaches the age of 3 years, faces pain scales, color scales, and simple numerical scales become more appropriate. Similarly, body pictures on which the child can draw the site, or even use the color she thinks is appropriate for her pain, can provide a unique and informative means to convey pain change. In children, measures of absolute pain states as a ratio scale are difficult. However, measuring pain severity in general and pain change become more accessible as children age, and with judicious work on the part of clinicians and nurses powerful information can be divined from the child herself. Parents can also provide important information about the child's level of activities and play in response to pain treatment. A good initial pain history and pain assessment can provide a baseline that enables a better understanding of changes in pain course, particularly for recurrent or chronic pain problems in children.

In general, subjective measures of pain are ideal when they can be used. The type of method most appropriate depends not only on the type of pain and age of the child

but the purpose of the assessment. If the assessment is to be used as a diagnostic tool, a drawing would provide more information than a simple numeric rating, whereas the simple numeric rating might be more useful in a medication management setting, where changes in pain level are the target for measurement. Tools should not be absolute, but should be varied, based on the child and the type of problem encountered. Creativity and engaging the child, particularly for younger children, can provide a wealth of information, including the use of colors for different types of pain, drawings, and types of magnitude matching, including a simple measure, such as squeezing a nurse's hand when pain increases during a potentially noxious procedure. Most of these tools provide a means of assessing pain change over time, and particularly pain improvement, rather than an absolute measure of pain.

Finally, when using a given type of subjective scale, it is important to maintain a standard format across multiple visits. Even minor modifications of anchors of a given pain scale can lead to significant changes in pain ratings, using the simple faces pain scales often used in pediatric populations. A shift in the anchors, from a frowning face to a nonsmiling face without a frown, or the number of faces used in the scale, can significantly change the ratings children will report. Consistency is important, particularly if pain ratings are used to assist medication and treatment choices. Also, the use of pain diaries, both as electronic and paper and pencil tools, can provide important information for those with more chronic or recurrent problem, allowing a better assessment of the potential environmental and psychologic factors that might influence a child's pain.

Pain Problems in the Pediatric Patient

Pain remains a ubiquitous problem, particularly the pain of everyday injury. But the types of pain that children present with clinically can be different from those found in adults. In general, pain is classified into three primary types: (1) acute pain, (2) recurrent pain, and (3) chronic pain.

Acute pain is characterized by a well-defined noxious stimulus, associated with tissue damage and relatively short duration. Acute pain usually provides important biologic information that something is wrong and usually resolves when tissue damage heals. Recurrent pain syndromes are pains that occur in otherwise healthy children, such as headaches, abdominal pains, or limb pains. Recurrent pain syndromes are not symptoms of physical disease, and although chronic in nature, are not usually considered chronic pain syndromes, which are represented by syndromes characterized by persistent pains of underlying prolonged disease processes.

Acute Pain

The most common acute pains in children are superficial skin injuries, including the classic cuts, scrapes, and bruises of childhood. Similarly, the pain of medical procedures, including dental visits and vaccinations, remain rites of passage for children. Certainly, individual experiences create a range within these acute pain experiences, such as those of young active children. For the neurologist, these types of injury can also be marked by nerve entrapment, nerve shearing, and other types of nerve injury. Similarly, neurologists may be required to induce acute pain on their young patients, through the use of painful medical procedures.

One of the most critical factors in acute medical pain experiences appear to be related to perceived level of control. Children who are unable to appropriately cope with pain and may need to be restrained during a procedure may ultimately experience reduced pain if they are given a sense of control over the situation. This can be produced by offering the child the ability to manipulate their environment, such as holding a favorite stuffed animal or mother's hand. Similarly, some children may want information regarding the nature of the procedure. Allowing them exposure to the procedure room, the equipment, and the participants may assist in alleviating anxiety for these children. Two types of coper in general have been identified for these types of acute pain experience: (1) associative copers, or those who want more information and want to be involved in the procedure, and (2) dissociative copers, or those who prefer to know as little as possible and just "get it over with." A few quick questions to the child and the parents can make particularly complicated medical procedures much more pleasant for all those involved, particularly if the procedure is adjusted based on the primary type of coping that the child finds most effective.

In general, children should be informed about medical procedures, to their level of understanding, but not in ways that will lead them to be frightened. More focus should be placed on the sensations and procedures that they can expect to encounter than on potential pain. But children should also be made aware that pain is to be expected and the pain should not be minimized. This enables children to use the coping skills they are most familiar with and to prepare themselves for potentially noxious events. Telling a child that an event will not hurt, when it clearly will, is no more amusing for a child than for an adult and can create a distrust of the medical environment. Many adults who are reluctant to visit a dentist often report a painful experience in their childhood that was often minimized. "White coat syndrome," or fear of physicians and those in white coats, may be attributable to this type of misinformation, which leads to distrust of those in the medical environment—the "This won't hurt

a bit" when most know that it will. It is better to be honest with a child, and to deal with the consequences, than to falsely represent the situation and deal with the longer-term consequences that may even keep that individual as an adult away from health care.

For the acute nerve injury or fracture, pain management is often limited to the use of standard anti-inflammatories or, in severe acute injury, perhaps more aggressive pain medications, including short-term use of narcotic analgesics. However, for children, one of the most critical components may lie in respecting the child's pain as much as possible, validating the child's responses rather than belittling them. Explain to the child to her level of understanding what can and what cannot be done. In acute injury, local anesthetics can also be used to reduce pain, particularly if bones have to be set, nerves are inflamed, or a longer-term stay in the hospital is required. Also in the acute pain setting, adjunct nonpain medication measures, such as counseling, soothing, and biofeedback can be helpful, and as the classic standbys, such as ice, heat, and rest. Similarly, if the injury is severe, mild antianxiety medications can be useful. Anxiety acts to amplify pain responses in both adults and children. However, care should be taken not to overmedicate a child to make the child more manageable, when talking to the child might accomplish the same result. Using a child's innate coping skills to maximal efficiency is not only critical in the acute setting but also enables the child to use those same coping strategies again in similar situations.

In the context of acute injury, one of the most common presentations for children in emergency rooms can be extremity injuries. Broken bones and lacerations can also involve nerve injuries, which may not be adequately treated. Similarly, difficult births may lead to damage to different components of the brachial plexus, which can bring the infant to the attention of a neurologist. Chronic regional pain syndrome type II (CRPS, also called causalgia) can occur when nerve injuries do not resolve adequately. Children with burning pain and neurovascular abnormalities resulting from nerve injury may present to a neurologist many years following the initial incident. In these cases, a detailed history can be critical to provide the best treatment. We will discuss CRPS with the chronic pain syndromes. Here, we want to highlight the importance of aggressive early treatment of nerve injury, to prevent centralized chronic neurogenic pain, as discussed below. Early identification and judicious use of anti-inflammatories and other pain medications including narcotics, may prevent the development of a CRPS.

Recurrent Pain Syndromes

Recurrent pain syndromes in children include headache, limb pains, and recurrent abdominal pains. Recurrent pain is a repeating pain that occurs in otherwise healthy children. In neurology, the primary recurrent pain found in children is migraine headache. One of the primary steps in any type of recurrent pain is establishing patterns, if present.

The use of pain diaries can provide powerful insights into associated factors, particularly with limb pains and headaches in children. A multimodal approach to childhood pain becomes particularly crucial in the evaluation of a child with recurrent pain, where a clear etiologic factor is often elusive.

Migraine headache is discussed in detail in Chapters 9 through 16 in this book. Recommended abortive and preventive therapies are discussed in Chapter 16 "Current Pharmacotherapy for Pediatric Migraine." Tension headache is also possible in children, and when possible, psychological factors are amenable to modification should be evaluated. The use of pain medications like acetaminophen can be useful in chronic tension headache, although aspirin should be avoided, due to the potential role in the development of Reye's syndrome.

Recurrent limb pain is also a common presentation in children. Limb pain syndromes in children may have an underlying neurologic component, particularly if nerves are compressed or if recurrent activity leads to nerve injury. Thorough evaluation of patterns and history again provides the key to a neurologic approach to assessment of limb pains in children. Classic "growing pains" is a diagnosis of exclusion and requires a thorough evaluation. Generally, growing pains present as symmetrical pain in the thighs, knees, calves, and shins and are usually of short duration.

Recurrent pain in children provides a unique challenge because the pathology is often elusive, and prophylaxis is often preferable to palliation of the pain once it has resurfaced. Close examination of patterns and factors that can generate and amplify pain provide the best means to assist the neurologist in dealing with these types of pain in young patients.

Chronic Pain Syndromes

Chronic pain syndromes most frequently encountered in children include arthritis, hemophilia, and sickle cell anemia. Children can also have difficulties with phantom limb phenomena if they have either traumatic or surgical amputation, and development of CRPSs has been identified in children who have suffered nerve injuries. Also, children can present with hereditary peripheral neuropathy, fibromyalgia, facial nerve disorders, and many types of neurogenically maintained pain. These types of pain problem can be particularly difficult to treat, especially if they are longstanding.

Neurogenic types of pain can be extremely difficult to cope with, both for the patient and the treating physician. Many of the normal types of coping strategies that individuals use, including rest, ice, heat, and elevation, simply may not be effective with many types of chronic pain and can

aggravate some types of neurogenic pain. Often described as burning or tingling, neuropathically maintained pain can be very difficult to eliminate. Recent advances in medication and therapies have provided some outlets for those patients who face chronic neuropathic pains.

Fibromyalgia has been characterized in children and may find itself in the pediatric neurologist's office. Many theories of fibromyalgia still maintain a potential neurologic basis for at least some of the symptoms. In children, recurrent aching pain and tenderness are found in local points of tenderness, as characterized by the American Rheumatological Association. These children may also have sleep problems, fatigue, and stress symptoms. Recommendations for treatment include rest and reassurance, massage at sites of local tenderness, nonsteroidal anti-inflammatory drug (NSAID) therapies, amitriptyline, transcutaneous electrical nerve stimulation (TENS), relaxation and biofeedback, and, in severe cases, corticosteroids and local anesthetic injections (which although proven successful in adults, it have not received as much support in pediatric cases). Research to date does not report significant success of specific medications for fibromyalgia in children. In general, research points to coping ability of children as one of the primary factors in the health status of children with fibromyalgia. Thus, psychologic management and reassurance may be as critical as medication management, for young patients facing fibromyalgia.

Similarly, an amorphous term called "growing pains" can also be applied to deep pains in the limbs, mostly the legs. These pains often occur bilaterally. Both these types of pain syndromes occur more frequently in the context of emotional upset and in families where family members report other pain problems. In chronic pain syndromes, the psychologic and emotional factors may be particularly important, especially in syndromes resistant to medications and more traditional therapeutic approaches. The role of psychologic factors in pain has been well established, in pain amplification and in impeding ability to cope with pain. Cognitive and behavioral therapies may provide an important augmentation to medication management.

CRPS types I and II are also syndromes of chronic limb pain, associated with hyperesthesia, episodic coolness, and sometimes swelling of the involved extremity. CRPS I, also called reflex sympathetic dystrophy, has no clear association with a nerve injury, whereas CRPS II, or causalgia, has a clear association and distribution that indicates previous nerve injury and is associated with a documented nerve injury. Patients can have loss of mobility and functioning in the involved limb. Interestingly, as with both fibromyalgia and "growing pains," CRPS in younger patients is often coincident with stressful family situations. This should not be taken to mean that these syndromes are psychosomatic, but it certainly indicates that stress has a profound impact on pain in children, and for those children who do have chronic pain problems, it can reduce their ability to cope with that pain. With CRPS, treatment recommendations should begin with physical therapy and TENS, as well as NSAID therapies to reduce swelling, if present. Relaxation and biofeedback have also been effective for milder cases, but psychologic assessment and psychotherapy can be important for these children to reduce anxiety and other potential complicating factors. Alterations in the sympathetic nervous system have been implicated as one of the potential causes of CRPS. For more severe cases, where mobility can be limited such that physical therapy and relaxation therapies may not be realistic, local anesthetic sympathetic blocks can be attempted. In only the most severe cases, sympathectomy and systemic vasodilators may be used, but no data indicate the effectiveness of these procedures in children, although they may be very effective in adults with CRPS.

Neuropathic pain can also present as posttraumatic or postsurgical peripheral neuropathy, neuropathic pain due to tumor involvement of the peripheral or central nervous system, neurodegenerative disorders, metabolic and toxic neuropathies, and pain after direct injury to the nervous system. In general, psychologic and cognitive/behavioral treatments can assist children in coping with the difficult sensations involved with neuropathic pain. Relaxation training, biofeedback, and instruction in coping techniques are particularly useful. Similarly, physical therapy can be of significant benefit in assisting these children in learning how to deal with these types of pain. Drug therapies can be very complex and often involve the use of tricyclic antidepressants (TCAs), as well as other antidepressants (particularly, if the child expresses depressed mood), anticonvulsants, infusions of lidocaine and opioids. The role of both TCAs and anticonvulsants in management of severe neuropathic pain has been well documented in pediatric patients and adults. Similarly, antidepressants may play a role in severe pain, not only for the psychiatric benefits but also as a potential analgesic therapy. However, a multimodal approach to neurogenic pain is particularly critical, as responses to these medications do not tend to be uniform across pain syndromes but tend to be unique to each patient.

Chronic pain management in children should, for the most part, try to rely on multimodal management, rather than only on medications, as much as possible. However, for many types of chronic pain, particularly for neurogenic pain, medications are essential. For severe pain, chronic opioid use may be warranted to allow the child to actively participate in activities of daily living, and as many of these syndromes respond to negative psychologic states, increasing activity and locus of control may assist in decreasing pain. Pain therapies should not be unidimensional and should include counseling, physical therapy, and

other tools to enable the child to cope with the pain to the best of her ability. Pain medications should be kept at the lowest effective dose, a rescue medication should be available for "bad days," and other resources should be available.

Cancer and Pain

Although the most common types of cancer in children are not associated with pain, leukemias require many frequent painful medical procedures as forms of treatment. Similarly, the distress caused by a life-threatening illness not only to the child but also to the child's family can significantly amplify pain symptoms. All attempts should be made to identify the specific means the child and the family can use to better cope with painful procedures.

As with adults, children show tremendous variability in their ability to cope with pain. Some children benefit from as much information as possible regarding potentially painful medical procedures, whereas others prefer to know as little as they can. However, physicians and parents need to be aware that even young children may know more than they might appear. When the adults step outside with the doctor and start talking in hushed voices, children may soon realize that something aversive is soon to follow. Also, even when children are not able to cope and might be hoped, they should still be praised, rather than just told that the aversive experience is over. This will simply lead to further expectations that similar experiences will be equally aversive. If restraint is necessary, the child should not simply be told that it was not all that bad or to be a "big girl" or a "big boy." Even the smallest amount of positive coping should be praised, to reinforce positive coping skills.

In cancer, aggressive pain management can be critical, particularly if the cancer is life threatening or end-of-life issues are addressed. The debate over the use of opioids in cancer treatment still rages, but the general consensus in research has resolved that patients with severe pain do not develop addiction to opioids, although they do become tolerant. Opioids are an important tool for cancer pain in children and should be used. But as with all types of pain in children, other methods should also be used, to ensure that the child has an adequate arsenal of support to assist in her pain management.

Conclusion

Pain provides a powerful tool, both in diagnosis and as a means of alleviating suffering. Children are wonderfully resilient. When children and their parents are educated, and the child becomes an active member in the pain management team, working with the child in pain becomes a much less arduous task. Even for children who cannot communicate their pain, behavioral signals provide ample cues to those who want to alleviate pain in children. For those willing to invest the time, this assists in providing better patients in the long run and allows us to be better health care providers.

In conclusion, we present a general paradigm for approaching a child in pain (Table 110-3). These are provided as general guidelines only—each child is different, and the appropriate assessment of pain is critical to allow adequate treatment.

TABLE 110-3. General Paradigm for Pain Management in Children

1. Increase control as much as possible in children
   - Even in patients who must be restrained, the child should be allowed to make choices, and should be informed, as much as possible, regarding what to expect
   - Treat the child with respect
     - Even if the child yells and screams, do not belittle the response
     - Respond positively to appropriate behavior and minimize those that are negative
2. Nonpharmacologic treatments
   - As much as possible, nonpharmacologic treatments should be used
     - Counseling
     - Biofeedback
     - Anxiety management
     - TENS
     - Ice
     - Heat
   - Avoid minimizing the child's pain
   - Behavior should not be overly solicitous, which may encourage secondary gain, nor should it be overly brazen
   - Pain should be recognized, as should the child's ability to cope with the pain. However, as pain is subjective, the ultimate decision for more aggressive treatment needs to rest with the child—base on child's ratings of pain, as much as possible
   - Has adequate pain relief been found?
3. NSAID therapies
   - For headache and recurrent pain in normally healthy children, NSAIDs may provide an important therapy for minimally intrusive pharmacologic intervention
   - Also, acetaminophen can help manage relatively minor chronic pain
4. Local anesthetics
   - Use of a local anesthetic and local blocks may provide respite without need for systemic medications, particularly for severe postsurgical pain
   - Also, local blocks can be used in an acute injury situation, to reduce need for potent pain medications
5. Narcotic pain medications
   - Opioid medications are completely appropriate for children in acute pain
   - Similarly with adults, chronic opioid use for chronic pain in children should be reserved for those with pain that is unresponsive to other therapies
   - Opioids should never be used in isolation and should only be used with monthly monitoring for potential side effects
   - In general, opioids do not tend to be addictive for patients with chronic pain.
   - However, pediatric pain patients may have other psychosocial issues that complicate their pain that should also be treated
   - Although these are certainly issues with adults, the difficulty in communication for children requires aggressive assessment of potential psychological factors that might complicate pain

NSAIDS = nonsteroidal anti-inflammatory drugs; TENS = transcutaneous electrical nerve stimulation.

Suggested Readings

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Deshpande JDT, editor. The pediatric pain handbook. St Louis (MO): Mosby; 1996.

Skevington SM. The psychology of pain. Wiley, John, & Sons, Inc; 1996.

Anand KJ, McGrath PJ, Stevens BJ. Pain in neonates. 2nd ed. Elsevier Science; 2000.

Patient and Practitioner Resources

American Pain Society
4700 W. Lake Ave.
Glenview, IL 60025
Phone: (847) 375-4715
Fax: (877) 734-8758 [Toll-free]
E-mail: info@ampainsoc.org
<http://www.ampainsoc.org>
The American Pain Society has established several goals in seeking to improve the care of patients with pain. These goals include advancing treatment by ensuring access to treatment, removing regulatory barriers, and educating practitioners and policymakers in all settings about advances and economics of effective pain treatment.

The International Association for the Study of Pain
IASP Secretariat
909 NE 43rd St, Suite 306
Seattle, WA 98105-6020
Phone: (206) 547-6409
Fax: (206) 547-1703
E-mail: iaspdesk@juno.com
<http://www.iasp-pain.org>
The International Association for the Study of Pain (IASP) is a nongovernmental organization affiliate of The World Health Organization and is dedicated to furthering research on pain and improving the care of patients with pain. Membership in IASP is open to all those who have special interest in the diagnosis and treatment of pain.

The American Pain Foundation
97 N. Charles St., Suite 710
Baltimore, MD 21201-4111
Phone: 1-888-615-7246
E-mail: webmaster@painfoundation.org
<http://www.painfoundation.org>
The American Pain Foundation serves people suffering with their mission to improve the quality of life of people with pain by raising public awareness, providing practical information, promoting research, and advocating to remove barriers and increase access to effective pain management.

CHAPTER 111

BRAIN DEATH IN CHILDREN

STEPHEN ASHWAL, MD

Head injury, infection, and asphyxia are among the most common causes of brain death in children. Because of fundamental differences in how nervous system functions are assessed in young children, it can be difficult to ascertain brain death. Thus, observation periods are often extended in infants before declaring that the absence of brain function is clearly irreversible.

In 1987, guidelines for the determination of brain death in children in the United States were proposed by a task force that represented several major professional medical and legal societies (Table 111-1). These guidelines emphasized the importance of history and clinical examination in determining the etiology of coma so that remedial or reversible conditions were eliminated. In addition, age-related observation periods and the need for specific neurodiagnostic tests were recommended for children younger than 1 year of age. In children older than 1 year, it was recommended that the diagnosis of brain death could be made solely on a clinical basis and that laboratory studies were optional.

Since their publication in 1987, these criteria have been generally accepted. In addition, they have served as explicit guidelines for physicians who asked to diagnose brain death in pediatric patients who may be potential organ donors. At the time these guidelines were developed, criteria for term infants younger than 7 days old and preterm infants were excluded because of lack of sufficient data. More recent studies have found that the criteria used in infants under the age of 2 months can also be applied to preterm and term infants.

Epidemiology

In the past decade, studies from pediatric intensive care units have reported that the incidence of brain death in older infants and children ranges from 0.65 to 1.2% of admissions. In one study, brain death represented 31.4% of all deaths in children older than 1 month of age and 6.3% of deaths in neonates. Researchers at Loma Linda University Children's Hospital reported that the percentages of brain deaths and overall deaths in their pediatric and neonatal units were 2.1 and 28%, respectively.

Brain death most commonly occurs in children younger than 1 year of age and is uncommon in adolescents (Table 111-2). The most frequent cause of brain death in

TABLE 111-1. Guidelines for Brain Death Determination in Children

A. History: determine the cause of coma to eliminate or exclude reversible conditions
B. Physical examination criteria
    1. Coma and apnea
    2. Absence of brainstem function
        a. Midposition or fully dilated pupils
        b. Absence of spontaneous oculocephalic (doll's-eye) and caloric-induced eye movements
        c. Absence of movement of bulbar musculature, corneal, gag, cough, sucking, and rooting reflexes
        d. Absence of respiratory effort with standardized testing for apnea
    3. Patient must not be hypothermic or hypotensive
    4. Flaccid tone and absence of spontaneous or induced movements, excluding activity mediated at spinal cord level
    5. Examination should remain consistent for brain death throughout the predetermined period of observation
C. Observation period according to age
    1. 7 days to 2 months: two examinations and EEGs 48 hours apart
    2. 2 months to 1 year: two examinations and EEGs 24 hours apart or one examination and an initial EEG showing ECS combined with a radionuclide angiogram showing no CBF, or both
    3. More than 1 year: two examinations 12 to 24 hours apart; EEG and isotope angiography are optional

Adapted from Ad Hoc Committee on Brain Death (1987).

CBF = cerebral blood flow; ECS = electrocerebral silence; EEG = electroencephalography.

TABLE 111-2. Age Ranges and Etiologies of Brain-Dead Infants and Children

Term	Percentage of Patients (%)
Age (*n* = 219)	6
0–4 mo	12
4–12 mo	15
1–2 yr	17
2–5 yr	32
5–10 yr	8
10–18 yr	10
Etiology (*n* = 590)	
Head injury	30
Near drowning	9
CNS infection	16
Asphyxia	14
SIDS	5
Metabolic	5
Cerebrovascular	5
Miscellaneous	16

Adapted from Ashwal S (2001).

CNS = central nervous system; SIDS = sudden infant death syndrome.

children is traumatic brain injury (usually from child abuse) and, less often, motor vehicle accidents. Asphyxial injury is also common and occurs after near drowning, as a complication of shock, from strangulation or suffocation, or from sudden infant death syndrome (SIDS). Brain death secondary to meningitis may be seen in patients who develop massive cerebral edema with the onset of herniation within 12 to 24 hours of hospitalization. Miscellaneous causes of brain death involve rare metabolic diseases, perioperative central nervous system (CNS) insults, and acute obstructive hydrocephalus.

Declaration and confirmation of brain death in the majority of pediatric patients presenting in coma after a serious CNS injury are usually completed within the first 2 days of hospitalization. Most children are subsequently removed from life support systems or are referred for organ donation within a 2-day period once the diagnosis of brain death is confirmed. Rarely, pediatric patients who are brain dead have been maintained on ventilator support for prolonged periods, but these patients suffer cardiac arrest at an average of 17 days after brain death is suspected. Longer survival (eg, "chronic brain death") has been reported. There are no reports of children making good neurologic recovery if they met adult brain death criteria on examination.

Clinical Examination

By definition, all patients who are declared brain dead are comatose and apneic and lack brainstem reflexes. These criteria may not be present on admission in all children; they usually evolve during the first days of hospitalization. Serial examinations are frequently helpful; it is also important to make sure that reversible conditions associated with altered metabolic states, toxin exposure, fluid and electrolyte abnormalities, hypothermia, hypotension, or medication effects have been excluded. Hypothermia occurs in about 50% of children who are comatose after catastrophic brain injuries. Thus, there is a need to rewarm patients before completing the examination and obtaining neurodiagnostic tests.

Coma

Assessment of lack of consciousness may be difficult in infants and children. Although there is no absolute way to be certain that a neonate or young infant has lost all conscious awareness and is "unreceptive and unresponsive," as stated in the original task force criteria, testing by tactile, visual, and auditory stimulation is comparable with that performed in the older child. When attempting to diagnose brain death, even in infants and young children, one is assessing the complete loss of all responsiveness rather than trying to detect subtle conscious behaviors. In most instances, and regardless of the child's age, the bedside clinical examination can satisfactorily accomplish this goal. Documenting the absence of any form of repetitive, sustained purposeful activity is important, as is differentiating brain death from other states of unconsciousness, such as the vegetative state. If the neurologic examination remains unreliable or if there is uncertainty that the child is unresponsive, confirmatory neurodiagnostic studies, such as electroencephalography (EEG) and measurement of cerebral blood flow (CBF), are required.

Loss of Brainstem Function

In preterm and term neonates, one must take into account that several of the cranial nerve responses are not fully developed. For example, the pupillary light reflex is absent before 29 to 30 weeks' gestation, and the oculocephalic reflex may not be elicitable prior to 32 weeks. Term and preterm infants are difficult to examine because their small size makes it technically difficult to adequately assess cranial nerve function. Assessment of pupillary reactivity can be compromised at the bedside because of difficulty accessing the infant who is in an incubator or because of corneal injury, retinal hemorrhages, and other anatomic factors, such as swelling or partial fusion of the eyelids. Because of the smaller amount of pigmentation and the smaller size of the newborn's pupils, visualization of changes in the size of the pupil can make assessment of the loss of pupillary reactivity difficult.

Likewise, assessment of ocular motility can be very difficult in intubated infants, and frequently, the examiner will need assistance, particularly when performing ice-water caloric stimulation. The procedure does not differ

substantially when performing this test in newborns versus older children. It is more difficult to adequately assess the caloric response in neonates, as they have small external ear canals; therefore, it is always important to examine both the oculocephalic (doll's-eye) and the oculovestibular (caloric) reflexes.

Although the corneal reflex is perhaps the easiest brainstem reflex to examine in neonates and infants, it is frequently the least reliable. Contact irritation, dehydration and maceration of the cornea, use of lubricant drops, wearing of eye patches for treatment of hyperbilirubinemia, and use of analgesics frequently affect the tactile surface sensory receptors of the cornea in a negative way. However, it remains important to test for this reflex as its presence indicates preserved brainstem function.

Assessment of lower cranial nerve function is also limited and is usually confined to examination of the gag reflex. There may be a substantial amount of adhesive tape around the face and cheek to secure the endotracheal tube, and this impedes the clinician's ability to perform this part of the neurologic assessment. When infants are intubated (either by the oral or by the nasogastric route), testing their gag reflex usually can only be accomplished with stimulation of the endotracheal tube.

Apnea

The normal physiologic threshold for apnea (minimum carbon dioxide tension at which respiration begins) for children has been assumed to be the same as adults (pCO_2 > 60 torr). In most studies, there will be a gradual increase in pCO_2 over a 5- to 10-minute period, usually with maintaining the arterial pO_2 at >200 torr while supplying 100% tracheal oxygen. Recent reports concerning apnea testing in children have raised questions about the effects of brainstem compressive lesions, potential recovery of brainstem respiratory drive, and the pCO_2 threshold in children. It is important to note that treatment of compressive brainstem lesions might reverse severe neurologic deficits that mimic brain death. Interestingly, a report exists describing the case of a 3-month-old infant who met the 1987 Task Force criteria for pediatric brain death and developed two to three irregular breaths per minute on day 43 of hospitalization. This infant died 71 days after presentation. At issue is whether this should be considered a return of respiratory function and, if so, whether return of irregular breathing is an "improvement" in the absence of other brainstem functions.

The third issue relates to a case report involving a 4-year-old child with a posterior fossa pilocytic astrocytoma who suffered a cardiac arrest. This patient met the clinical criteria for brain death, except for the results of apnea testing, which showed minimal respiratory effort after 9 minutes and 23 seconds, when patient's pCO_2 measured 91 torr. This child's spontaneous breathing was insufficient to maintain life, and assisted ventilation was necessary. It was thought that this child's higher pCO_2 threshold was due to hypoxic-ischemic injury. This case raised questions about whether this was a phenomenon unique to children and whether the current standard of a pCO_2 of 60 torr is correct.

The technique of apnea testing in children is similar to that in adults using apneic oxygenation after disconnecting from the ventilator. Therefore, normalization of the CO_2 tension and core temperature and preoxygenation for 5 to 10 minutes before beginning the apnea challenge are recommended. Careful monitoring of the heart rate and blood pressure during the procedure, while watching the chest cage for movement, is needed. Most studies recommend that pCO_2 levels be determined at 5-minute intervals and continued for 15 minutes if the pCO_2 has not reached 60 torr and if the pO_2 has not fallen below 50 torr. Prolonged bradycardia or development of hypotension during testing is due to irreversible brainstem failure, acidosis, or hypoxemia; at this juncture, the infant should be placed back on the ventilator.

Neurodiagnostic Testing

EEG documentation of electrocerebral silence (ECS) and the measurement of the absence of CBF remain the most widely available and useful methods to confirm the clinical diagnosis of brain death. However, in the past decade, practitioners have begun to rely more on repeated clinical examinations that demonstrate coma, apnea, and absent brainstem function than to use confirmatory testing in children or adults.

EEG

Guidelines for brain death recordings were developed by the American Electroencephalographic Society in 1994. The role of EEG in confirming the diagnosis of brain death in infants, children, and neonates has been described extensively in the literature. Problems with obtaining an EEG in infants and children include shorter interelectrode distances; external artifacts caused by technologies in newborn and pediatric intensive care units; rapid cardiac and respiratory rates of infants and children compared with those seen in adults; shorter distances between the heart and the brain, making the electrocardiographic contribution disproportionately large in children; reduced amplitude of cortical potentials in preterm and term neonates; longer duration of the effect of depressant drugs; greater tendency for suppression burst patterns in infants with neurologic disorders; and the presence of congenital CNS malformations (eg, hydranencephaly) associated with ECS.

It is well recognized that a certain number of brain-dead infants, children, and adults will have persistent EEG activity. Most of these EEG patterns show low-voltage θ or β activity or intermittent spindle activity. Its persistence in functionally dead brains may continue for days. Data from several studies have found that the initial EEG in brain-dead children is isoelectric in 51 to 100% of patients (mean 83%). In the majority of children who initially have EEG activity, follow-up studies usually show evolution to ECS.

Typically, when the initial EEG in children demonstrates ECS, a repeat EEG will remain isoelectric. However, there have been reported cases of recovery of EEG activity. In these reports, the findings were either inconclusive or the patients had retained some brainstem or cerebral function and, thus, did not meet the clinical criteria for brain death. Since Green and Lauber's report over 30 years ago of two infants who had return of some EEG activity after an initial ECS recording, there have only been a few additional reports of infants in whom EEG activity returned. Thus, concerns about the return of EEG activity have been overemphasized. In addition, none of these infants recovered. It should be emphasized that ECS may occur soon after a child has had a cardiac arrest. In infants in whom the initial EEG, 8 to 10 hours after cardiac arrest, shows ECS, a repeat study 12 to 24 hours later may show diffuse low-voltage activity. Most of these infants die from associated complications of the acute catastrophic insult; those who survive usually go on to a permanent vegetative or minimally conscious state. Similar observations have been reported in adults.

Overall, the available data in children suggest that demonstration of ECS on the initial EEG is sufficient to support the clinical diagnosis of brain death. However, as previously noted in the 1987 Task Force guidelines, it is not necessary to obtain an EEG in children older than 1 year as long as the neurologic examination remains unchanged for the appropriate observation period.

In children, the most common drugs causing reversible loss of brain electrocortical activity include barbiturates (eg, phenobarbital), benzodiazepines, narcotics, and certain intravenous (thiopental, ketamine, fentanyl, and midazolam) and inhalation (halothane and isoflurane) anesthetics. A study in 92 children reported data suggesting that therapeutic levels of phenobarbital (ie, 15 to 40 μg/mL) do not affect the EEG.

CBF Determination

Neuroimaging techniques can be used to document the absence of CBF. These include cerebral angiography, radionuclide angiography, transcranial Doppler ultrasonography, computed tomography (CT) with contrast injection or xenon inhalation, digital subtraction angiography (DSA), single photon emission CT, and positron emission tomography. Of these, radionuclide angiography remains the most widely used in children because it is portable, relatively sensitive, and easy to perform. Documentation of the absence of CBF confirms brain death and has been reviewed elsewhere in detail.

Radionuclide Imaging

Studies in children have shown that radionuclide imaging is accurate and reproducible. It has been favorably compared with other methods of detecting the presence or absence of CBF. The absence of CBF in brain death is due primarily to low cerebral perfusion pressure (mean arterial pressure–intracranial pressure [ICP]) and secondarily to release of vasoconstrictors from vascular smooth muscle and brain parenchyma.

A certain percentage of pediatric patients who are brain dead may have CBF early after diagnosis. In studies reported by Drake and colleagues, 15 of 47 brain-dead children had evidence of intact CBF as determined by radionuclide imaging. About two-third of the patients who had repeat studies showed loss of CBF 2 to 3 days later. This occurred regardless of whether these patients had ECS or some EEG activity recorded when the first CBF study was obtained. In a more recent report, 5 of 18 clinically brain-dead preterm and term infants retained CBF. Greisen and Pryds also described two suspected brain-dead newborn infants with ECS who had preserved CBF documented by xenon scanning. Overall, it is clear that CBF may be present in infants and children who are clinically brain dead. In most patients, repeat CBF studies 24 to 48 hours later will likely, but not uniformly, document loss of CBF.

Transcranial Doppler Ultrasonography

Transcranial Doppler ultrasonography has been advocated because it is a portable and noninvasive way to ascertain cerebral circulatory arrest. Reports in pediatric patients since 1983 have validated the specificity and sensitivity of transcranial Doppler ultrasonography. Doppler changes seen in brain-dead patients include loss of diastolic flow, appearance of retrograde diastolic flow, diminution of systolic flow in the anterior cerebral artery with unchanged flow in the common carotid artery, and, finally, the loss of any detectable flow in these vessels.

DSA

DSA is another technique used to assess the intracranial circulation. This technique can be performed intravenously or by intra-arterial injection. A small amount of nonionic contrast material is injected while DSA of the cerebral vasculature is done, similar to conventional cerebral angiography. This allows visualization of contrast within the major intracranial vessels; lack of such visualization indicates absence of CBF. There are very few reports of this technique in children and

only one recent case report in a brain-dead neonate. A recent report using intravenous DSA in 110 patients with clinical signs of brain death observed that the initial study documented absent contrast enhancement in 105 patients. Repeat studies conducted within several hours in the remaining five patients also confirmed cessation of CBF.

Evoked Responses

Brainstem auditory evoked response (BAER) testing has been extensively studied as an alternative confirmatory method. Its portability and noninvasiveness seem ideal, but several studies have raised doubt as to the BAER's reliability in determining brain death, particularly in children younger than 6 months old. More recent studies, however, have suggested that BAER testing reliably confirms brain death in children. In one report, almost 90% of 51 brain-dead children had loss of the BAER (complete loss in 27 patients; loss of waveforms III–VII in 18 patients). It was also shown that loss of BAER preceded the development of ECS. This finding suggested that BAER testing might be more useful than EEG for earlier laboratory confirmation of brain death. However, if testing is performed too early, a false-positive result may occur.

Somatosensory evoked potentials (SEPs) possibly may have greater discrimination in the confirmation of brain death. Recent studies of SEPs in children found that only 62.5% of patients had complete absence of SEPs or just a cervical cord (but no thalamocortical) response, suggesting SEPs are of limited use as a confirmatory test in children.

Brain Death in the Newborn

About 550 newborns of a total of 4.9 million live births may be annually diagnosed as brain dead. Etiologies of brain death based on data from 87 newborns younger than 1 month of age included hypoxic-ischemic encephalopathy (61%), birth trauma (8%), malformations (6%), cerebral hemorrhage (6%), infection (7%), SIDS (7%), nonaccidental trauma (4%), and metabolic causes (1%).

Preterm and term neonates younger than 7 days of age were excluded from the 1987 Task Force pediatric brain death guidelines. The ability to diagnose brain death in newborns is still viewed with uncertainty. This is due to the small number of brain-dead neonates reported in the literature. Several years after publication of the guidelines, data on 18 brain-dead neonates were published, and it was suggested that brain death could be diagnosed in term infants and preterm infants of greater than 34 weeks' gestational age within the first week of life. Because the newborn has patent sutures and an open fontanelle, increases in ICP after acute injury are not as significant as in older patients. Thus, the usual cascade of events of herniation from increased ICP and reduced cerebral perfusion is less likely to occur in newborns. Brain death in newborns (even those age < 7 days) can be diagnosed, provided the physician is aware of the limitations of the clinical examination and laboratory testing. It is important to carefully and repeatedly examine these infants, with particular attention to examination of brainstem reflexes and apnea testing. An observation period of 48 hours is recommended to confirm the diagnosis. If an EEG is isoelectric or if a CBF study shows no flow, the observation period can be shortened to 24 hours. Although there are few cases of preterm infants who become brain dead, it is likely that the same time frame would be applicable. There have been few instances of neonates or older infants who showed minimal transient clinical or EEG recovery, but none appears to have regained meaningful neurologic function, and all died within brief periods of time.

Because of the significant physiologic and cerebrovascular differences in the neonatal response to injuries resulting in brain death, previous studies have observed a much higher incidence of newborns with EEG activity or cerebral perfusion. In addition, some newborns with ECS showed preserved CBF. Conversely, others without CBF showed EEG activity. In the neonate, even though CBF and mean arterial blood pressures are much lower, increases in ICP after acute injury are less dramatic. Recent data on 30 newborns who had EEGs and radionuclide perfusion studies found that one-third with ECS showed evidence of CBF and 58% of those with absent CBF had evidence of EEG activity.

Data on 37 of 53 brain-dead newborns in whom EEGs were performed revealed the following: ECS ($n = 21$), very low voltage ($n = 13$), burst-suppression ($n = 1$), seizure activity ($n = 1$), and normal ($n = 1$). Almost all patients whose first EEG showed ECS had ECS on the second study, and most patients who initially did not show ECS on their first EEG did so on a repeat study. The data suggested that for confirmation of brain death, only one EEG showing ECS is necessary, provided the examination remains unchanged.

CBF data have shown that it is absent in 72% of brain-dead newborns. In some infants who initially had CBF, repeat studies demonstrated the absence of flow. No significant differences were observed in the median duration of brain death in those neonates with CBF (4 days) compared with those without CBF (3 days). These findings, as well as those described earlier, emphasize the limitations of both CBF determinations and EEG findings for confirmation of brain death in neonates.

Organ Procurement in Brain-Dead Children

Because brain death is more frequently due to severe asphyxial injury in children than in adults, concerns that similar injury to other organs would preclude transplantation have been raised. Inotropic agents to support

blood pressure and cardiac function may also be necessary, particularly if the etiology of brain death was related to a pre-existing global asphyxial insult that may have caused hypoxic myocardial injury. Recent data, however, suggest that organ transplantation, including heart transplantation, can be successfully accomplished from pediatric donors. Likewise, although brain-dead child abuse victims have rarely been considered organ donors because of legal issues, many centers now try to obtain surrogate consent. With cooperation from the medical examiner's office, they have been able to successfully obtain organs from such donors.

The loss of neuroendocrine function must be treated in order to accomplish successful organ donation. Perhaps the most common problem is diabetes insipidus, which can be easily controlled with low-dose vasopressin (3–5 U intramuscularly or 0.05–0.1 U/kg intravenously, as needed). Some patients may also require supplemental corticosteroid therapy, as impairment of the hypothalamic-pituitary-adrenal axis may occur. Adequate respiratory support to maintain organ function is also important. In addition, treatment and prevention of infection will minimize cardiovascular instability. In most instances, the time available for this type of monitoring and support is relatively short (2 days) before organ donation occurs. Support for the grieving family and for the nursing and other medical staff is extremely important and perhaps is one of the most vital services a physician can provide. The responsibilities of the physician involved in the declaration of brain death must always be clearly demarcated from those physicians interested in organ procurement.

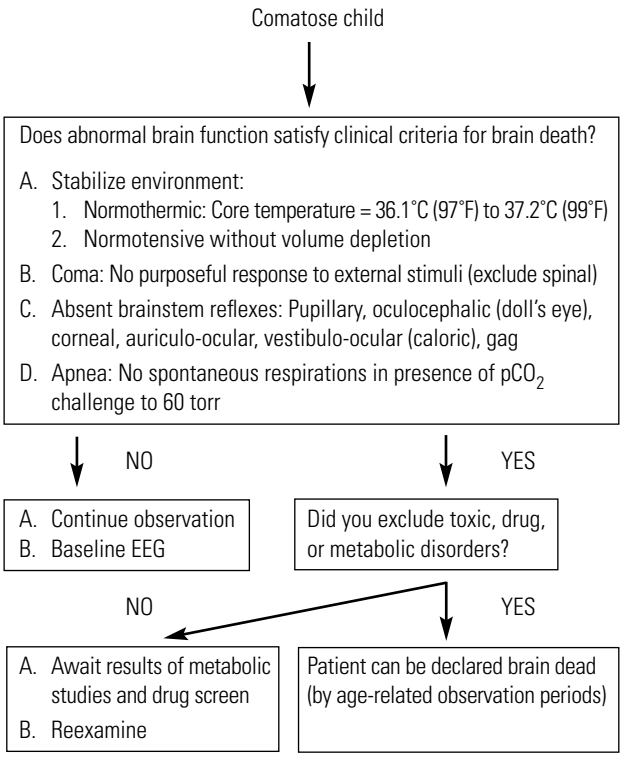

FIGURE 111-1. Protocol for determination of brain death.
A. Newborn to 2 months: Examinations 48 hours apart remain unchanged with persistence of coma, absent brainstem reflexes, and apnea. Supportive testing with EEG or CBF studies should be considered.
B. 2 months to 1 year: Examinations 24 hours apart remain unchanged. Supportive testing with EEG or CBF studies should be considered.
C. > 1 year of age: Examinations 12 to 24 hours apart remain unchanged. Supportive testing with EEG or CBF studies are optional.

Summary

The diagnosis of brain death in pediatric patients is based on the same principles as in adults. Although the neurologic examination is difficult because of the size of the patient, immaturity of certain developmental reflexes being tested, and pathophysiologic differences such as the presence of open sutures and fontanelles in the neonate and infant, the fundamentals of the examination (coma, apnea, and absent brainstem reflexes) allow for accurate diagnosis. It is clear that a certain percentage of infants and children, like adults, will not have "confirmatory" neurodiagnostic testing. As is the case in many other areas of medicine, clinical judgment and serial examinations allow for the establishment of a definitive diagnosis. Better understanding of the pathophysiology of the evolution of brain death in neonates and infants should help decide whether the recommended age-related periods of observation are based on differences in developmental neurophysiology or cerebrovascular regulation. A paradigm for the diagnosis of brain death is given in Figure 111-1.

Suggested Readings

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Practitioner and Patient Resources

The Compassionate Friends, Inc
P.O. Box 3696
Oak Brook, IL 60522-3696
Phone: (630) 990-0010 or (877) 969-0010
Fax: (630) 990-0246
<http://www.compassionatefriends.org>
The mission of The Compassionate Friends is to assist families toward the positive resolution of grief following the death of a child of any age and to provide information to help others be supportive.

The Dougy Center, The National Center for Grieving Children and Families
P.O. Box 86852
Portland, OR 97286
Fax: (503) 777-3097
<http://www.dougy.org>
The mission of The Dougy Center for Grieving Children is to provide loving support to families and organizations seeking to assist children grieving a death locally, nationally, and internationally by allowing individuals to share their experiences as they move through their healing process.

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