PEDIATRIC
NEUROLOGY

GREGORY L. HOLMES

Pediatric Neurology

"Dr. Holmes, a consummate clinician, has succeeded in writing a masterpiece for the care of children with neurological disorders. The book's concise and well-referenced case discussions are packed with important teaching points and clinical pearls. Keep this on your desk!"

—*Elaine Wyllie*, MD, Professor of Pediatrics, Epilepsy Specialist,
Director of the Center for Pediatric Neurology,
Cleveland Clinic, Cleveland, OH

"This is an essential book for the busy paediatrician. It presents important, specific diagnostic problems in paediatric neurology and how the clinician should think about the differential diagnosis. It is admirably strong on clinical aspects of history taking and examination and selective on the use of investigations. It has chosen problems in which there is commonly a differential diagnosis between serious and mild conditions. Acute neurological and chronic disabling conditions are included. The book contrasts with traditional textbooks by taking the clinical presentation of a patient at primary care doctor level as the starting point. The reader is taken through the diagnostic and management process by an experienced paediatric neurologist. This is an easy and friendly way of developing clinical decision making skills and acquiring knowledge. I strongly recommend it."

—*Professor Brian G R Neville*, Professor of Childhood Epilepsy,
Neurosciences Unit, UCL Institute of Child Health,
London, United Kingdom

"*What Do I Do Now? Pediatric Neurology* is an imminently enjoyable and exquisitely useful book. It contains 28 mini-chapters each containing a case vignette of an important pediatric neurological problem encountered by general parishioners and specialists alike. These vignettes are then succinctly analyzed, the subsequent management is discussed and the condition briefly reviewed with appropriate and useful bibliography. The chapters are all to the point and contain all the important clinical "pearls" that would benefit general practitioners and even specialists.

The book, as the author, who is a world renowned pediatric neurologist and epileptologist, states is targeted toward pediatricians, family practitioners, adult neurologists, medical students and nurse practitioners to help in the management of pediatric neurological cases particularly when a pediatric neurologist may not be immediately available. The book easily achieves this goal and much more. It clearly can also serve as a template for case discussions for pediatric and adult neurologists in training and for continuing medical education for seasoned pediatric neurologists.

In addition, because of its format it provide a much more attractive and enjoyable reading experience than a regular textbook does.

In brief, this is book is a refreshing and a must have for all practitioners who could potentially encounter children with neurological problems."

—*Mohamad Mikati MD*, *Wilburt C. Davison* Distinguished Professor of Pediatrics, Professor of Neurobiology, Chief, Division of Child Neurology, Duke University Medical Center, Durham, NC

"No field has had more of an explosion of basic science knowledge than neurology. But the actual practice of neurology is learned case by case. This volume on pediatric neurology in the series, *What Do I Do Now?* serves a need and fills a gap since there are relatively few books in pediatric neurology that teach by the important case discussion. Dr. Holmes covers the main disorders encountered in practice with concise illustrative cases, a discussion that emphasizes the differential diagnosis and treatment, followed by key points and references. I recommend this book to everyone interested in pediatric neurology, from the student to the practicing physician. It will be especially useful to those providing the initial care for children with neurological disorders, including pediatricians and family practitioners, as it will inform them about the management of their patients. This book should be mandatory reading for medical students, residents in both pediatrics and neurology, child neurology fellows, nurse practitioners, physician assistants and all others in the ancillary professions that treat children with neurological disorders. I am frequently asked, 'What is the best book to use to learn pediatric neurology?' I now have the answer."

—*James J. Riviello, Jr., MD, George Peterkin* Endowed Chair in Pediatrics, Professor of Pediatrics and Neurology, Department of Pediatrics, Section of Neurology and Developmental Neuroscience, Department of Neurology, Peter Kellaway Section of Neurophysiology, Baylor College of Medicine, Houston, TX and Director of the Epilepsy and Neurophysiology Program, Director, Neurocritical Service, Section of Neurology, Chief of Neurophysiology, Texas Children's Hospital, Houston, TX

Pediatric Neurology

What Do I Do Now?

VOLUMES IN THE SERIES

Pediatric Neurology

Gregory L. Holmes, MD
Department Chair
Professor of Neurology and Pediatrics
Dartmouth Medical School
Dartmouth Hitchcock Medical Center
Hanover, NH

Acknowledgments

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Preface

Pediatric neurology is a challenging yet fascinating discipline that studies neurological diseases in a growing and maturing nervous system. The clinical presentation, response to therapy, and outcome are all closely related to a highly plastic, evolving nervous system. It is therefore not surprising that lessons learned in the adult may not always apply to the developing nervous system. For this reason, it is timely and appropriate for the editors of *What Do I Do Now?* to devote an issue to pediatric neurology.

The 28 cases that make up this book come from my experience as a pediatric neurologist over the past 30 years. Pediatric neurology has now developed into a broad specialty, incorporating disciplines ranging from neuromuscular disease to neurogenetics to neurometabolic disorders. The cases presented here are a brief snapshot of both common and less common disorders encountered by pediatric neurologists. This book is by no means a comprehensive review of any of the topics; rather, I compare this book to wine tasting, where one can sample wine in small aliquots; the interested reader has a brief taste of a variety of pediatric cases. The scenarios are designed to entice the reader to consider what he or she would do next. While I have included lists of differential diagnoses for many of the cases, most astute clinicians can reduce the differential diagnosis to a few possibilities after taking a history and performing an examination. I have therefore purposely tried to eliminate rare and unlikely conditions from the differential diagnoses.

This book is targeted toward pediatricians, family practitioners, adult neurologists, medical students, and nurse practitioners. Most of the cases presented here can be managed by interested healthcare professionals without formal pediatric neurology training, as in many parts of the country pediatric neurologists may not be readily available for consultation. Each case is short, encompassing salient features of the diagnosis. The cases are not meant to be tricky or misleading.

I hope this book will convey some of the excitement I have on a daily basis working with children with neurological disorders. Ideally this book will motivate readers to dig deeper into the literature to learn more about the disorders. If this book is successful in helping even a single child with a neurological disorder, I will feel the effort was worthwhile.

Gregory L. Holmes, MD
Hanover, NH

Table of Contents

Pediatric Neurology

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1   Absence Seizures

You are called by a pediatrician who is seeing a 7-year-old girl with staring episodes. According to the pediatrician, teachers have noted the child stares off into space frequently. During the episodes the girl does not respond to questions. The pediatrician suspects the child is daydreaming but calls you to see if he should obtain an EEG.

What do you do now?

When questioned about a child who is having staring episodes, the physician should consider daydreaming, attention-deficit/hyperactivity disorder (ADHD), or a seizure disorder. The correct diagnosis can usually be made by asking a few questions. The family or teacher should be asked:

- Can the episodes be terminated by questioning or touching the child?
- Are there any motor signs during the event?
- Does the child quickly return to baseline after the event?
- How long do the episodes last?

Absence seizures are generalized seizures, indicating bihemispheric initial involvement clinically and on EEG. Absence seizures have an abrupt onset and offset. There is typically a sudden cessation of activities with a blank, distant look to the face. As the seizure continues, there are often automatisms and mild clonic motor activity such as jerks of the arms and eye blinking. It is unusual for a child with typical absence seizures to simply stare without any other behavioral manifestations. An absence seizure typically lasts less than 30 seconds, usually less than 10 seconds.

Complex partial seizures may begin with an aura and then progress to a period of unresponsiveness. As in absence seizures, complex partial seizures are associated with automatisms such as lip smacking or gestures of the hands. Complex partial seizures are longer than absence seizures, typically averaging 1 to 2 minutes, and are often followed by a period of confusion and tiredness.

Daydreaming usually occurs in a child who is bored. The child may stare but does not have the distinct change in facial expression seen in children with seizures. Motor activity does not occur during daydreaming and there is no post-staring confusion or tiredness. Usually, the child can be redirected with questions. Children with ADHD, while inattentive, typically do not have long periods of staring. As with daydreaming, ADHD is not associated with motor activity or post-staring impairment. Children with autism frequently have episodes of staring. While the EEG in autistic spectrum disorder is often abnormal, rarely do the children have absence epilepsy.

It is important for any physician seeing a child with staring spells to have the child hyperventilate for 3 minutes. Even toddlers can be coaxed into

FIGURE 1-1 Generalized spike-wave discharge in a 7-year-old with absence seizures.

hyperventilating with a pinwheel. A very high percentage of children with untreated absence seizures will have an absence seizure with hyperventilation. It is far less likely that hyperventilation will elicit a seizure in a child with complex partial seizures.

If the physician is concerned that the child has epilepsy, an EEG can be very useful. The EEG signature of a typical absence seizure is the sudden onset of 3-Hz generalized symmetrical spike or multiple spike-wave complexes (Fig. 1.1).

Children with complex partial seizures are more likely to have temporal or frontal lobe spikes (Fig. 1.2). A normal EEG during wakefulness, sleep, hyperventilation, and photic stimulation would make the diagnosis of absence seizures quite unlikely. However, children with complex partial seizures can have normal EEGs.

The table provides a summary of key differentiating points between absence seizures, complex partial seizures, daydreaming, and ADHD.

FIGURE 1-2 Right frontal sharp waves (*arrows*) in a 9-year-old with complex partial seizures.

TABLE 1-1 Differential Diagnosis of Staring Attacks

	Absence Seizure	Complex Partial Seizure	Daydreaming	ADHD
Aura	No	Frequently	No	No
Duration	‹30 seconds	1–2 minutes	Minutes	Seconds
Automatisms	Frequently	Frequently	No	No
Frequency	Multiple daily	Infrequent, unusual to have ›2/day	Frequent, situation-dependent	Frequent
Post-staring impairment	No	Yes	No	No
EEG	Generalized spike-wave	Normal or focal discharges	Normal	Normal

After making the diagnosis, appropriate therapy can be initiated. For absence seizures, epilepsy therapy with ethosuximide, valproate, or lamotrigine should be considered. In the case of complex partial seizures the number of drugs that could be used is much broader.

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2   Acute Cerebellar Ataxia

You are called by a pediatrician who has a 4-year-old girl in his office who awoke from a nap with the inability to walk. The mother states her daughter was fine before the nap and now stumbles and falls when standing.

The girl had enjoyed good health except for occasional ear infections and upper respiratory infections. Four days ago, she developed a cold with rhinorrhea, coughing, and a low-grade fever. The child was treated with acetaminophen and ibuprofen and was recovering. The girl had been eating well and had no difficulties with vomiting or diarrhea.

The pediatrician says that the child is afebrile, playful, and alert. The general examination was unremarkable except for mild rhinorrhea. There were no rashes. The chest was clear on auscultation and the abdominal examination normal. No nystagmus was noted, visual fields appeared to be intact, and no facial asymmetry was found. The fundi were not examined. The child had no difficulty reaching for objects and did not have a tremor. Reflexes could not be elicited.

When the child was placed in the standing position her feet were more widely placed than usual. When she attempted to walk she was very unsteady and fell either to the right or left. Without help from the mother the child fell after taking a few steps. The pediatrician notes that the child does not appear to be upset by her inability to walk.

The pediatrician is concerned that the child has a cerebellar tumor and wishes to know if you want to obtain an MRI of the brain.

What do you do now?

You ask to see the child and confirm the pediatrician's findings on examination. You do a funduscopic examination and note there is no papilledema. Although you agree that the child should have an MRI of the brain, you reassure the mother that it is unlikely the child has a brain tumor.

With this history and neurological examination, the most likely diagnosis in this child would be acute cerebellar ataxia. Acute cerebellar ataxia usually occurs in children between 2 and 7 years of age. The onset is often explosive. As in this case, the child may wake up from a nap with the condition. Ataxia varies from mild unsteadiness while walking to complete inability to walk. Even when the ataxia is severe, the mental functioning is normal. Despite the difficulty walking, the child, unlike the parents, often appears totally unconcerned about his or her state.

While the sudden onset of ataxia is concerning, it is likely that the child has a benign condition. Often the first thought is that the child has a posterior fossa tumor, but the history of being fine before a nap and then having pronounced ataxia would be unlikely for a posterior fossa tumor, in which the onset of the ataxia is usually more gradual and headache and vomiting are common. The neurological examination is important. In addition to the ataxia, some children have nystagmus. However, this is not a universal finding and in this case nystagmus was not present. Typically in acute cerebellar ataxia the child looks healthy and is not distressed by the condition.

Other conditions that could lead to acute ataxia are listed in the table. Obtaining a urine toxic screen would be reasonable in this case. Rare causes of acute ataxia include the myoclonus/opsoclonus syndrome and the Miller Fisher syndrome. In the myoclonus/opsoclonus syndrome there are unusual chaotic eye movements (opsoclonus) in addition to myoclonic jerks of the trunk and extremities and ataxia. Former terms used for the syndrome include dancing eyes and dancing feet syndrome. This condition is a paraneoplastic condition and requires a vigorous search for a neuroblastoma, which may be occult. If deep tendon reflexes cannot be elicited, the Miller Fisher syndrome should be considered. The Miller Fisher syndrome is characterized by ataxia, ophthalmoplegia, and areflexia. It is sometimes associated with pupillary abnormalities, but limb weakness does not occur. It is considered a variant of Guillain-Barré syndrome and recovery is almost

always complete. In addition, Guillain-Barré can also present with ataxia as the initial symptom and rapidly progress to the point where ventilator support is required. Children with discitis may refuse to walk but this is due to back pain rather than cerebellar dysfunction.

In acute cerebellar ataxia, a history of a preceding viral illness can usually be elicited. Varicella is a particularly common viral illness occurring before the onset of acute cerebellar ataxia. Because of the concern about posterior fossa conditions, a head CT or MRI is typically obtained. While the CT is quicker and easier to obtain, the MRI provides better resolution. MRI using FLAIR (fluid attenuation inversion recovery) images will often pick up signal changes in the white matter not only within the cerebellum but also in other white matter areas. A subset of patients with acute disseminated encephalomyelitis (ADEM) have primarily cerebellar involvement. Although it is not usually necessary in straightforward cases, the spinal fluid examination may show a mild elevation of protein and a few lymphocytes.

Symptoms usually begin to remit after a few days, although a full recovery may take weeks. Most children have a full recovery.

KEY POINTS TO REMEMBER ABOUT ACUTE CEREBELLAR ATAXIA

- Onset is usually abrupt.
- Ataxia occurs in the context of an otherwise healthy-appearing child.
- Posterior fossa lesions must be ruled out.
- Recovery usually occurs but may take months to years.

TABLE 2-1 **Common Causes of Acute Ataxia**

Cause	Comments
Drug ingestion and toxicity	Antihistamines, anticonvulsants, psychotropic medication
Brain tumor	Headache, emesis; ataxia has insidious onset
Acute cerebellar ataxia	Common, usually post-infectious
Miller Fisher syndrome	Associated with ophthalmoplegia and areflexia

TABLE 2-1 *Cont.*

Cerebellar abscess	Rare, usually associated with fever, infection elsewhere
Labyrinthitis	Dizziness, vertigo common
Head trauma	Ataxia may last days and weeks even after seemingly minor head trauma.
Opsoclonus/myoclonus syndrome	Paraneoplastic process
Cerebellar hemorrhage/posterior fossa subdural hematoma	Rare, associated with multiple etiologies, may be spontaneous
Discitis	Child may refuse to stand or walks awkwardy due to back pain
Conversion disorder	Rarely occurs in children age <10 years

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3   Alternating Hemiplegia of Childhood

You are consulted by parents who believe their 7-year-old son has been incorrectly diagnosed with epilepsy. The parents tell you they became concerned about the child during the first year of life when he was felt to be more "floppy" than their two other children at a similar age. They also noted that the child was delayed in regards to sitting and walking and had bizarre, darting eye movements. During the second year the boy began having episodes where he would develop the sudden onset of right- or left-sided weakness. The weakness would last minutes to hours. The weakness would sometimes seem to alternate between the right and left side during the same attack.

The boy was diagnosed with epilepsy by the neurologist. However, the parents said the neurologist was puzzled by the fact that EEGs during the attacks failed to show clear seizures. The neurologist concluded that the seizures must be arising from a focus deep in the brain.

Over the years the parents described episodes of eye jerking and problems with balance. The child is now quite

delayed and is receiving special educational services. He currently is taking clonazepam, valproate, and lamotrigine. The family feels these drugs, like many other antiepileptic drugs, have not reduced the number of attacks, although they believe that clonazepam has made the attacks less severe and shorter in duration.

You ask to examine the child. You noted he had a short attention span with poor eye contact. He spoke slowly and was dysarthric. On examination you found he had nystagmus, which increased on lateral gaze bilaterally and had a rotatory component. He had diffuse hypertonia, hyperreflexia, and ataxia. During the examination he had an attack where his right arm dropped to his side and he began to bend to the right. When he started crying you noted that he had no clear facial weakness. The attack lasted about 10 minutes and resolved without any intervention.

What do you do now?

This child has alternating hemiplegia of childhood. It is not surprising that the neurologist made an incorrect diagnosis since this is a very rare condition that often mimics epilepsy. Indeed, some children may also have epilepsy as a manifestation of the disorder. The EEG is often abnormal but during the attacks there are no ictal discharges. Unfortunately, there are no diagnostic tests for alternating hemiplegia and the diagnosis is made on clinical criteria.

There are seven criteria for the diagnosis:

1. Onset before 18 months of age
2. Repeated episodes of hemiplegia involving the right or left side of the body
3. Episodes of bilateral hemiplegia or quadriplegia
4. Other paroxysmal disturbances including tonic/dystonic attacks, nystagmus, strabismus, dyspnea, and other autonomic phenomena during hemiplegic attacks or in isolation
5. Immediate disappearance of all symptoms on going to sleep, with recurrence 10 to 20 minutes after awakening in long-lasting attacks
6. Evidence of developmental delay, learning disability, neurological abnormalities, choreoathetosis, dystonia, or ataxia
7. Not attributed to another disorder

As in this child, early hypotonia and floppiness and abnormal eye movements precede the onset of hemiplegia, usually by several months. Frequent attacks of hemiplegia emerge as the predominant manifestation in the first decade. The episodes of hemiplegia last from minutes to days, although the attacks can usually be aborted with sleep. Cognitive delays become more severe with time. Between attacks the child is rarely normal. Dyspraxia, dysarthria, dysphagia, dystonia, chorea, tremor, ataxia, weakness, and spasticity often occur. Bilateral hemispheric involvement is common during the attacks. The swallowing difficulties are particularly concerning since aspiration pneumonia can occur.

The cause is unclear. A genetically determined channelopathy is likely, although a mitochondrial disorder has also been considered.

Treatment of alternating hemiplegia of childhood has not been optimal. Sleep can relieve an attack. Benzodiazepines such as buccal midazolam have

been used. Flunarizine, a drug that blocks calcium channels, has been widely used, although it does not stop acute attacks. The drug is rarely totally effective.

KEY POINTS TO REMEMBER ABOUT ALTERNATING HEMIPLEGIA OF CHILDHOOD

- The duration of hemiplegia in the condition can vary considerably, lasting from seconds to hours.
- The EEG is critical to the diagnosis, showing central and midtemporal spikes.
- Sleep relieves the symptoms.
- A wide variety of neurological problems occur, including movement disorders such as dystonia.
- There are no diagnostic tests; laboratory studies are primarily used to rule out other conditions.

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4   Benign Neonatal Sleep Myoclonus

You are called by the neonatologists in the neonatal intensive care unit to see a 7-day-old girl with seizures. The child was born at term after an uneventful pregnancy, labor, and delivery. She was noted by the mother at age 6 days to have episodes where she would have bilateral jerks of the arms and legs. The jerks occurred in paroxysmal bursts lasting approximately 2 minutes. The child would flex the arms at the elbow and had rhythmic, to-and-fro movements of the forearms and legs. When informed of the events the pediatrician told the mother to bring her daughter to the emergency room; there, the emergency room staff witnessed an event and concluded the child was having clonic seizures and administered a loading dose of phenobarbital (15 mg/kg) and admitted her to the hospital.

The child had electrolytes, glucose, CBC, calcium, magnesium, blood ammonia, liver function tests, a spinal fluid examination, and an MRI, all of which were normal. Despite the phenobarbital, the child continued to have periodic episodes of myoclonic paroxysms. The child had an EEG and had an event of myoclonus during

the recording. The neurologist reviewed the recording and concluded that the myoclonic jerks were associated with theta and delta slowing with intermixed spikes. The child was then given a loading dose of phenytoin (15 mg/kg) without resolution of the myoclonus. The girl was then transported to your medical center.

When you examine her you are impressed with how normal the child appears. She is alert and vigorous. The neurological examination is totally normal.

What do you do now?

Seizures in newborns are very serious events and often portend an ominous diagnosis and prognosis. While infants with normal neurological examinations can certainly have seizures, it is a little unusual to see this many seizures in an otherwise healthy newborn. After hearing the story, you question the mother about the events and whether these ever occurred when the child was awake with the eyes opened. The mother could not recall any events that occurred when the child was awake. The EEG from the referring hospital was reviewed and it was concluded that the record during and between myoclonic episodes was normal. The intermixed interictal spikes noted were thought to be muscle artifact.

Based on the story and normal EEG you conclude that the child has benign neonatal sleep myoclonus. You tell the neonatologists no further workup is warranted and discontinue the phenobarbital and phenytoin and discharge the child home. On follow-up 2 months later you learn that the girl no longer has myoclonus and is doing well developmentally.

Benign neonatal sleep myoclonus is characterized by myoclonic jerks in an otherwise healthy infant. The myoclonic jerks are usually bilaterally symmetrical with involvement of both the upper and lower extremities. The jerks are seen during sleep and are never present when the child is fully awake. Benign neonatal sleep myoclonus is a non-epileptic condition and is not associated with epileptiform discharges on the EEG. While the myoclonic jerks may be confused with clonic or myoclonic seizures, as shown in the table, there are distinguishing features that should lead to the correct diagnosis.

Benign neonatal sleep myoclonus occurs primarily in term infants. The onset of the myoclonus is very early, with the majority of the children having myoclonus during the first 2 weeks of life. All of the children outgrow their myoclonus and development is usually quite favorable.

Although the exact incidence of benign neonatal sleep myoclonus is not known, it does not appear to be a rare disorder. Although the condition has been well described in the literature, benign neonatal sleep myoclonus continues to be misdiagnosed by pediatricians, primary care physicians, and even pediatric neurologists. This misdiagnosis has often resulted in unnecessary diagnostic studies and inappropriate antiepileptic drug therapy.

TABLE 4-1   **Benign Neonatal Sleep Myoclonus**

Features	Clonic Seizures	Myoclonic Seizures	Benign Neonatal Sleep Myoclonus
Sleep state	Awake/sleep	Awake/sleep	Sleep
Movements	Clonic	Myoclonic	Myoclonic
Symmetry	Usually asymmetrical	Usually symmetrical	Usually symmetrical
Eyes	Open	Variable	Closed
EEG	Epileptiform discharges contralateral to side of body jerking	Markedly abnormal with generalized spike-wave	Normal, artifact is common
Response to antiepileptic drugs	Often effective	Moderately effective	Ineffective

KEY POINTS TO REMEMBER ABOUT BENIGN NEONATAL SLEEP MYOCLONUS

- Symmetrical irregular jerking of the upper and sometimes lower extremities.
- Myoclonic jerks can be quite dramatic.
- Occurs only during sleep and ceases when the child is awakened.
- EEG is normal during the events.
- No treatment is required.

Further Reading

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5   Benign Rolandic Epilepsy

A pediatrician calls you about a 7-year-old boy whom he is seeing in his office. The parents brought the child in emergently because they believed the child was having a stroke. That morning while eating breakfast the boy suddenly stopped talking and developed a left facial droop and drooling. When asked a question the child did not respond but pointed to his mouth. The parents felt he understood the question but could not speak. Some left facial twitching was noted. The event lasted less than 5 minutes and cleared rapidly. At no point did the parents feel the child had impaired consciousness.

When his pediatrician examines him, he finds no neurological deficits. He tells you the child is in the second grade and is doing well from an academic and social standpoint. The pediatrician wonders if this was a transient ischemic attack and whether Coumadin is indicated.

What do you do now?

This is a classic presentation of benign epilepsy with centrotemporal spikes (BECTS), also referred to as benign rolandic epilepsy. BECTS is a genetic disorder, confined to children, that is characterized by nocturnal generalized seizures of probable focal onset and diurnal partial seizures arising from the lower rolandic area and an EEG pattern consisting of a midtemporal-central spike focus (Fig. 5.1). The disorder always begins during childhood. The age range is from 3 to 13 years, with a peak of age incidence at 7 to 8 years. The disorder occurs more frequently in boys than girls. Most children have normal neurological examinations and intelligence.

The key features in this child were the motor impairment of the face and motor aphasia without impairment of consciousness. The observation that the child could understand the question but not speak is a characteristic finding. Somatosensory symptoms may also occur, with the child noting tingling of the tongue, lips, and face during the initial phases of the seizure.
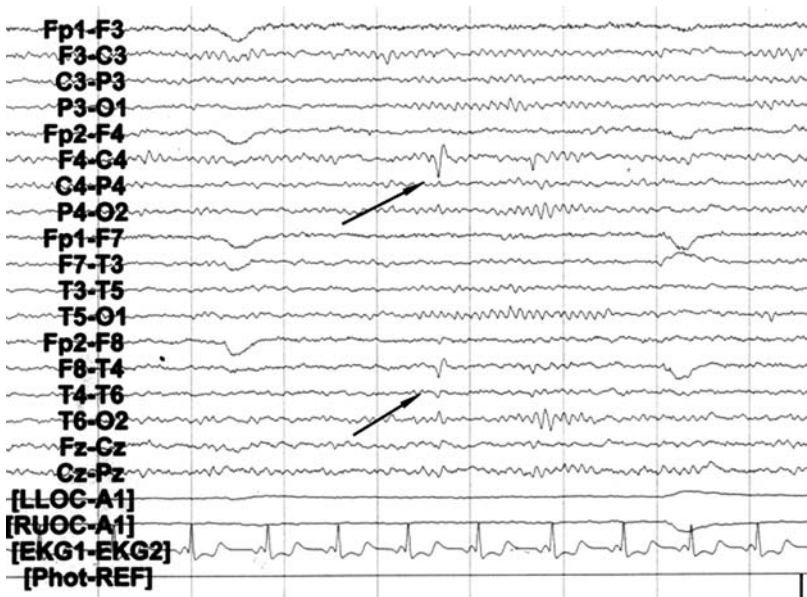
FIGURE 5-1 Seven-year-old with centrotemporal spikes (*arrows*) on the EEG. The child has benign rolandic epilepsy.

Some children have only diurnal simple partial seizures, whereas others have partial seizures with secondary generalization during sleep. In nocturnal seizures, the initial event is typically clonic movements of the mouth with salivation and gurgling sounds from the throat. Secondary generalization of the nocturnal seizure is common. The initial focal component of the seizure may be quite brief and is often missed by the parents, who find the child in the midst of a generalized tonic-clonic seizure. Postictal confusion and amnesia are unusual after seizures in BECTS.

The seizures may occur both during the day and during the night, although in most children seizures are most common during sleep. Daytime and nocturnal seizures are both brief. The frequency of seizures in BECTS is typically low, and it is unusual for status epilepticus to develop.

If the patient has a clinical history and the EEG characteristics of BECTS and a normal neurological examination, further workup is not necessary. If the neurological examination is abnormal or the EEG demonstrates abnormalities other than the typical epileptiform discharge, further evaluation with MRI is recommended.

Because of the benign nature of BECTS, many physicians choose not to treat the first or second seizure. If treatment is initiated, the seizures are usually controlled with a single antiepileptic drug. Drugs used for partial seizures (e.g., phenobarbital, phenytoin, carbamazepine, oxcarbazepine, and valproic acid) are usually effective.

The EEG is not a good predictor of recurrence risk. Most patients can be tapered off medications after 1 to 2 years of seizure control, regardless of whether the EEG normalizes.

The prognosis of BECTS is generally good, with the majority of children going into remission by the teenage years. However, a few patients with BECTS develop deficits in verbal memory or language skills. Children with BECTS should be monitored closely for school performance.

The characteristic interictal EEG abnormality is a high-amplitude, usually diphasic spike with a prominent following slow wave. The spikes (<70 ms) or sharp waves (<200 ms) appear singly or in groups at the midtemporal (T3, T4) and central (rolandic) region (C3, C4).

- It is unusual for staring to be the only manifestation of an absence seizure.
- Must be differentiated from complex partial seizures and non-epileptic events.
- Seizures are short but occur frequently.
- Readily diagnosed with hyperventilation.
- EEG shows generalized spike-wave activity.

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6 Brain Abscess

A pediatrician calls you about a 9-year-old girl he is seeing because of migraine headaches that have not responded to ibuprofen and aspirin. According to the pediatrician the child began having headaches about 2 weeks ago. The headaches initially began in the morning, sometimes awakening the child. Over the past week the headaches have increased in frequency and the girl complains about them constantly. The child denied any visual auras before the headaches. Some of the headaches are associated with emesis. The headaches are worse when the child is lying than when sitting. The pediatrician also reported that she had a temperature of 38°C. He noted that 3 weeks ago the child had bacterial pneumonia, which was successfully treated with antibiotics. A recent chest film was normal.

The pediatrician tells you that the child's neurological status seems fine. Because of a strong family history of migraine the pediatrician wishes to start sumatriptan but asks if you would see the child.

What do you do now?

This is a worrisome story. Several aspects of the history should raise concerns about the pediatrician's diagnosis of migraine. The number of the headaches per day is quite unusual for migraine. While migraine can occur upon awakening, this history should elicit concern for a more ominous diagnosis. In addition, a history of worsening of the headaches when lying down is worrisome since it would not be typical of migraine. Headaches in the early morning hours may indicate a structural lesion in the brain; when the child is lying down the intracranial pressure is greater than when the child is standing or sitting.

You ask to see the child in your office. You are surprised at how ill the child looks. The parents tell you that the child has always had headaches, but over the past 2 weeks they have become debilitating. While the parents acknowledge there is a history of migraine in the mother, father, and sister, they believe these headaches are not due to migraine.

On examination you find the girl has a temperature of 38°C. She is crying about the headache, saying she has trouble even thinking. On neurological examination you note she is inattentive and has full visual fields and no nystagmus on lateral gaze. However, on examination of her fundi you find optic discs that have blurred margins. Venous pulsations are not present. The remainder of the examination is normal.

The presence of papilledema and headaches constitutes a medical emergency requiring prompt evaluation. You order an MRI, which shows a large cystic lesion in the left frontal lobe.

In this case the onset of new headaches after a bout of bacterial pneumonia should raise the possibility of a brain abscess. Migraines can start at any time, but the frequency of the attacks in the face of a febrile illness should cause you to consider other possibilities. Chronic headaches in a child with a prior history of pneumonia would put a brain abscess in the differential diagnosis. In this case the possibility of a brain abscess should have occurred to you before the MRI was ordered. If the MRI did not show the cystic lesion, the child should have a spinal tap to rule out meningitis or encephalitis.

Brain abscesses present as mass lesions. Abscesses can be bacterial, fungal or parasitic. In bacterial brain abscesses, aerobic and anaerobic organisms are usually present. In children, the most common etiological agents in

FIGURE 6-1 MRI from a 9-year-old girl with *Staphylococcus aureus* brain abscess (*arrows*). The child developed fever and headache after surgery for a pulmonary arteriovenous fistula.

brain abscesses are *Staphylococcus aureus* and streptococci. Direct spread to the central nervous system can occur as a result of sinusitis, meningitis, otitis media, pneumonia, dental abscesses and congenital heart disease. There is an initial cerebritis with subsequence encapsulation and eventual rupture of the abscess.

Typically the MRI reveals single or multiple ring-enhancing lesions (Fig. 6.1). The cerebrospinal fluid is usually not diagnostic, and in this child a spinal tap could even be dangerous. The diagnosis is made by aspiration or biopsy and cultures. Surgical treatment of abscesses is indicated if there is impending herniation. Otherwise, depending on the size or location, antibiotic treatment after biopsy is recommended. When diagnosed quickly the mortality rate is low, but a significant number of patients are left with a subsequent neurological deficit.

The clinical symptoms of brain abscess are similar to those of any other space-occupying lesion. Headaches and seizures are common. If undiagnosed, brain abscesses may lead to hemiparesis and visual field cuts, depending on location.

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7 Breath-Holding Spells/Pallid Infantile Syncope

You receive a call from a nurse practitioner who wants you to see a boy with possible seizures. She tells you that this 16-month-old child has had multiple episodes where he loses consciousness and becomes quite limp and lifeless. After the first episode an EEG was obtained, which was normal. After the second episode the child was given phenobarbital and an EEG and MRI of the brain were obtained. Both studies were normal. Despite a phenobarbital level of 30 μg/mL, the boy continues to have the episodes, which are very frightening to the parents.

When you see the boy you learn that he was developing normally until the onset of these spells. When you ask the mother to describe them she says the episodes always appear to begin with a temper tantrum, often when the child hurts himself by falling, or when he does not get his way. He cries for a few seconds and then passes out and turns blue. He is usually limp, but the mother noted that on one occasion he became rigid. The child's eyes are always closed during the episodes. When asked whether he ever had an attack that did not

begin with crying the mother felt he may have done this once, although she is having difficulties remembering the details. He never has episodes when he is asleep. The mother remarked that since starting the phenobarbital the child has been irritable and has actually had more attacks.

What do you do now?

Based on the history alone you strongly suspect the child has breath-holding attacks. Since the child already had an EEG and MRI there is no need to repeat these studies. Instead, you ask the mother to videotape one of the episodes and taper the child off the phenobarbital.

Breath-holding spells are very common in infants and young children and are frequently mistaken for tonic seizures. Although they are a benign disorder, as in this case, the attacks can be very frightening to the parents. The table compares the salient features of breath-holding spells and pallid infantile syncope with the features of epileptic seizures. A key to breath-holding is that the spells usually begin with crying. However, in some children the trigger of crying can be quite brief, occurring after a sob or two. The child usually inspires and does not expire, becomes cyanotic, falls down, and becomes limp. Unlike epileptic seizures, the eyes are typically closed during the syncopal attack.

Pallid infantile syncope is precipitated by a stressful situation and leads to loss of consciousness. Pallor and sweating, as opposed to cyanosis, precedes the loss of consciousness. The attacks occur in toddlers and can be precipitated by minor events such as blows to the head, fright, and frustration. In the past, the clinical diagnosis was confirmed in the EEG laboratory using controlled ocular compression while monitoring both the EEG and EKG; ocular compression would lead to severe bradycardia followed by asystole and EEG slowing. Because of a concern about retinal detachment as well as provoking a severe attack, this study is no longer done.

Although in this child an EEG and MRI were performed, with a typical history, these tests are not needed. Children with long-QT syndrome have episodes of loss of consciousness that may be induced by injury, fright, or excitement, and an EKG should be obtained in a child with breath-holding or pallid infantile syncope. Since the condition appears to occur more frequently in children with iron deficiency anemia, obtaining a CBC and starting children with anemia on iron supplementation can be helpful. Children may have a convulsion as a part of the breath-holding sequence. The convulsive movements seen during breath-holding spells are reflex anoxic seizures and do not require antiepileptic drug therapy.

The prognosis is excellent, with the vast majority of children outgrowing the spells.

TABLE 7-1   **Breath-Holding Spells/Pallid Infantile Syncope**

Clinical Features	Breath-Holding	Pallid Infantile Syncope	Generalized Tonic or Tonic-Clonic Seizures
Age	6 mo–6 yr	12–18 mo	All ages
Precipitating factors	Invariably present	Invariably present	Usually none
Occurrence in sleep	Never	Never	Common
Family history	Often positive for breath-holding	Often positive for breath-holding	Often positive for seizures
Sequence of events	Crying → apnea → cyanosis → loss of consciousness → decreased tone → tonic-clonic or tonic seizure	Upset → pallor → loss of consciousness → hypotonia	Loss of consciousness → tonic-clonic or tonic seizure
Eyes open or closed	Closed	Closed	Open
Interictal EEG	Normal	Normal	Frequently abnormal
Postictal symptoms	Usually none	Usually none	Tired, confused, disoriented, sleepy

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8 Childhood Epilepsy with Occipital Paroxysms (CEOP)

A concerned and perplexed pediatrician calls you about a 5-year-old boy he is seeing because of episodes of nocturnal vomiting. The pediatrician has known this child since birth and tells you that the boy had been relatively healthy until about 6 months ago, when he started having episodes of vomiting, always at night. The parents would hear the child vomit and when they came into the room the child would be lying in bed in a pool of vomitus. Typically the boy would vomit two or three more times and then fall asleep. The episodes of emesis occurred once or twice monthly. The child's growth has been normal and the medical examinations have been consistently normal.

Initially, the pediatrician felt the child may have reflux, but treatment with proton pump inhibitors has been ineffective. The pediatrician has also considered the possibility of allergies, although the child has had no other allergic symptoms.

The reason the pediatrician calls you is that two nights ago the parents described a typical event of vomiting. However, when they went into the bedroom

they found their son with his eyes deviated to the right with some facial twitching. The eye deviation persisted for approximately 10 minutes, during which time the child did not respond to the parents' questions. The pediatrician wonders if the child could have abdominal epilepsy.

What do you do now?

Nausea and vomiting are common in children and are usually part of a mild, short-lived illness. Recurrent vomiting, particularly at night, can be a symptom of gastrointestinal reflux or allergies. The important clue here is the most recent episode, in which the child had eye deviation and was not responsive, signs of a likely seizure. When there is no obvious motor activity, determining whether children are having epileptic seizures can be difficult. When children are sick they may not respond normally, although they should not have eye deviation.

The pediatrician questioned whether the child had abdominal epilepsy. This is a reasonable concern and the pediatrician deserves kudos for considering the diagnosis. Abdominal epilepsy is a rare condition consisting of gastrointestinal disturbances caused by a seizure, usually arising from the temporal lobe. Most children with abdominal epilepsy have complex partial seizures with impaired consciousness and automatisms. In this case, abdominal epilepsy should be considered.

You ask to see the child and agree with the pediatrician that the past medial history and family medical history are non-contributory and that the neurological examination is normal. You suggest that the child have a head MRI and EEG. While it is unlikely this child has a posterior fossa lesion, a MRI will rule out the possibility. In addition, with this history a temporal lobe lesion is also possible.

The EEG showed normal background activity with occipital lobe spikes. Based on this EEG finding you suspect this boy has childhood epilepsy with occipital paroxysms (CEOP).

There are two distinct forms of CEOP. The early-onset type, or Panayiotopoulos syndrome, occurs in young children, with a peak onset of 5 years. The late-onset, or Gastaut, type has an age of onset of around 8 to 9 years. Both syndromes are associated with occipital spikes. Based on the age and clinical symptoms, this child likely has Panayiotopoulos syndrome, a disorder characterized by ictal vomiting and deviation of the eyes, often with impairment of consciousness with progression to generalized tonic-clonic seizures. The seizures are infrequent and often solitary, but in around one third of the children, the episodes evolve into partial status epilepticus. Two thirds of the seizures occur during sleep. The late-onset, or Gastaut, type consists of brief seizures with mainly visual symptoms such as elementary
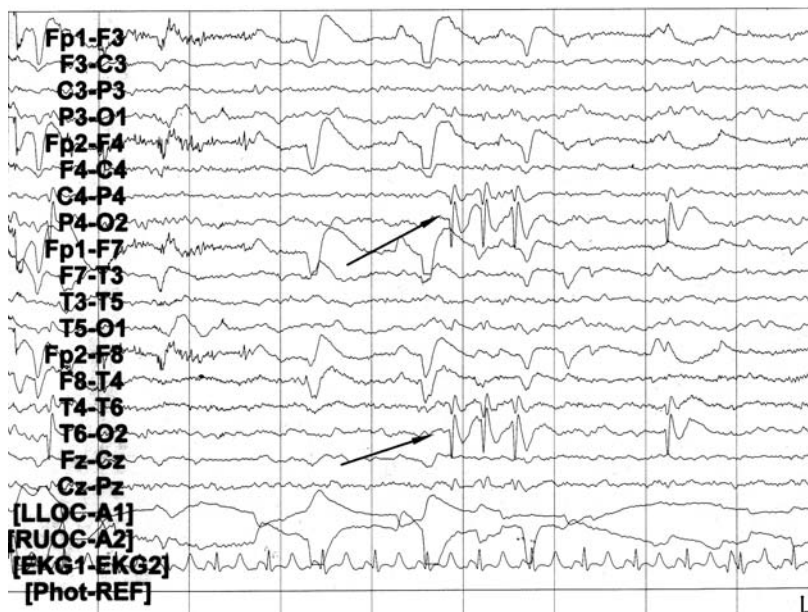
FIGURE 8-1 Right occipital spikes (*arrows*) in a child with childhood epilepsy with occipital paroxysms.

visual hallucinations, illusions, or amaurosis, followed by hemiclonic convulsions. Postictal migraine headaches occur in half of the patients.

The interictal EEG in both conditions is characterized by normal background activity and well-defined occipital discharges. The occipital spikes are typically high in voltage (200–300 mV) and diphasic, with a main negative peak followed by a relatively small positive peak and a negative slow wave. The discharges may be unilateral or bilateral and are increased during non–rapid eye movement sleep. An important feature in this syndrome is the prompt disappearance with eye opening and reappearance 1 to 20 seconds after eye closure.

The prognosis in the early-onset (Panayiotopoulos) type is excellent, and it typically resolves within several years of onset. The prognosis in the late-onset (Gastaut) form is variable, with some children having seizures persisting into adulthood.

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9 Congenital Myotonic Dystrophy

You are called to the neonatal intensive care unit (NICU) to see a 2-day-old boy with arthrogryposis. You learn that the child was the product of a 34-week pregnancy complicated by polyhydramnios and reduced fetal movements. The labor was prolonged and forceps delivery was eventually required. The infant had respiratory distress at birth and required a few minutes of ventilatory assistance with an Ambu bag in the delivery room. The neonatologists are concerned about a decreased activity level and poor feeding.

When you arrive in the NICU you find a child who is at the 3rd percentile for weight, height, and head circumference. The child appears dysmorphic, with a V-shaped mouth (upper lip forms an inverted V) and facial diplegia. The child is hypotonic and has absent reflexes and joint contractures at the elbow, knees, and ankles. The child has a poor suck. Despite these findings, the child looks remarkably alert. He follows well and responds to noxious stimuli with a cry, albeit a weak one.

What do you do now?

The constellation of findings of the tent-like mouth, hypotonia, and arthrogryposis in an alert infant would suggest a peripheral (nerve or muscle) rather than central disorder. The differential diagnosis would include:

- A congenital neuropathy
- Congenital muscular dystrophy
- Metabolic myopathies such as acid maltase deficiency
- One of the congenital myopathies such as central core disease, congenital fiber-type disproportion myopathy, minicore disease, myotubular myopathy, and nemaline rod myopathy

Before doing an extensive evaluation on the child, the mother should be examined for any possible weakness. When you examine the mother, you note some frontal bossing and mild facial diplegia (Fig. 9.1). When queried, the mother describes difficulty opening jars and turning doorknobs. When asked to squeeze your fingers and then let go, the mother has difficulty

FIGURE 9-1 Frontal bossing and high hairline in mother with myotonic dystrophy.
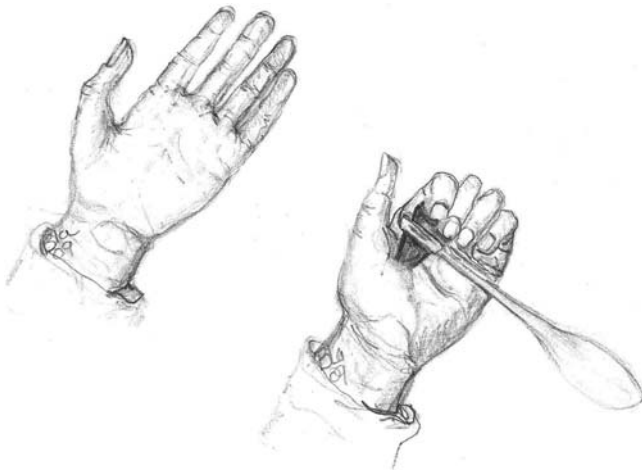
FIGURE 9-2 When the thenar eminence is struck with a reflex hammer, myotonia occurs and the thumb gets "stuck" in the palm.

relaxing her grip. When her thenar eminence is struck with a hammer, myotonia is induced (Fig. 9.2)

It is likely that the mother has myotonic dystrophy and the child has congenital myotonic dystrophy. The diagnosis can be confirmed by genetic analysis. Myotonic dystrophy is a multisystem disorder transmitted by autosomal dominant inheritance. An unstable DNA triplet in the *DMPK* gene (chromosome 19q13.2-13.3) causes the disorder. Repeat size changes from mother to child are greater than from father to child; this is why the mother is usually the affected parent when the newborn has the disorder.

While there is no direct therapy for the condition, physical therapy and orthopedic intervention can be very helpful.

KEY POINTS TO REMEMBER ABOUT CONGENITAL MYOTONIC DYSTROPHY

- Infants born to mothers with myotonic dystrophy are at risk for significant problems.
- Arthrogryposis, hypotonia, facial diplegia, and hyporeflexia are often presenting features.
- Examining the mother usually will establish the diagnosis.

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10 Discitis

You are asked by a pediatrician to see a 3-year-old boy who, for the past 3 days, has become upset when he attempts to sit up or walk. The parents say the child had been doing fine until he seemed to be having pain when he stood or sat. Although he had a viral illness a week ago, it was not severe and he seemed to recover without incident.

When you see the child, you find an alert boy who is quite content when he is lying on his side, but when you place him on his back he becomes agitated and starts crying. The crying becomes more vigorous when you attempt to sit him up or pull him to a standing position.

The neurological examination is otherwise within normal limits. Specifically, there was no weakness in either the upper or lower extremities. Reflexes were symmetrical. His abdominal examination was unremarkable. Although he appeared to have some pain over the spinous processes, this was not a consistent finding.

What do you do now?

A child who stops walking is a serious event that requires prompt investigation. The differential diagnosis would include acute myositis, a peripheral neuropathy, or a spinal cord lesion.

It would be unusual for a child to have a viral myositis without weakness, fever, or other signs of systemic illness. Likewise, inflammatory neuropathies such as Guillain-Barré syndrome would result in weakness and reduced reflexes. It is essential that an intrinsic or compressive spinal lesion be eliminated, even though spinal cord lesions typically result in weakness and corticospinal tract dysfunction with hyperreflexia. In addition, spinal cord lesions cause a sensory deficit due to a blockage of incoming sensation from sensory fibers entering the cord below the spinal cord lesion. This leads to a sensory level with decreased sensation below the spinal cord lesion and normal sensation above the level of the spinal cord injury. The negative neurological examination would be reassuring, but imaging the spine with MRI is essential.

The most likely diagnosis in this child is discitis. Discitis refers to an infection of a disc space and adjacent vertebral end plates. Children with discitis may refuse to walk, stand, or sit. Less commonly they may present with a limp, backache, abdominal pain, or irritability. The general and neurological examination is usually not helpful in establishing the diagnosis, although it may be useful in ruling out other conditions. Rarely, there may be localized tenderness on palpation of the spinous processes, muscle spasm and increased lumbar lordosis, or decreased motions of the spine.

The diagnosis is usually made through imaging. A MRI of the spine is the investigation of choice as it can detect early discitis and exclude spinal tumors. Typically there are signal changes in the vertebral bodies and disc space. Plain spine films may show narrowing of the intervertebral disk space. Technetium bone scans often shows increased pickup of tracer in the disk and vertebral body. The erythrocyte sedimentation rate is almost always elevated. White blood cell counts are usually normal.

Discitis in the neonate and young child most commonly affects the lumbar spine. In infants and young children, the cartilaginous vertebral end plates are traversed by numerous canals through which small vessels pass. These vascular channels serve as the location where the infection occurs. With age these vascular channels disappear, and discitis is rare in older children and adults.

The etiology of discitis is unclear. While blood cultures are often negative, when an organism is detected *Staphylococcus aureus* is the most common isolated bacterium. However, a variety of other bacterial agents have been reported. While some clinicians treat the children with antibiotics, there is no agreement about the need for treatment with antibiotics, since the outcome has been reported to be the same whether or not the patient receives antibiotics. If an antibiotic is prescribed, it should be one that is effective against *S. aureus*.

The prognosis is quite good, although disc space narrowing may be persistent. The long-term sequelae of such narrowing appear to be negligible.

KEY POINTS TO REMEMBER ABOUT DISCITIS

- A toddler who refuses to walk requires a prompt investigation to rule out spinal cord pathology.
- When the diagnosis of discitis is suspected, an MRI of the spine is the test of choice.
- Antibiotics are of questionable benefit.
- The prognosis is excellent.

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11 Dopamine-Responsive Dystonia

A 6-year-old girl is referred for problems with walking. The mother stated that the child never walked or ran normally. She tells you that the girl began walking at 18 months but was always clumsy and frequently fell, particularly when she was tired at the end of the day. The mother was initially told by her primary care physician that her daughter may have a mild form of cerebral palsy.

Over the past 2 years her condition has worsened. The mother notes that when the child walks, she intermittently switches from normal heel to toe walking when tired. In addition, she turns both feet inward when walking. Over the past several months she has had numerous bruises from falling. The mother became increasingly worried when the girl had some unusual stiffening of her right arm when she was walking or running. When the mother discusses her concerns with her pediatrician, he tells her that this cannot be cerebral palsy and sends the child to you for evaluation.

You learn that the child was born after a normal pregnancy, labor, and delivery. The mother feels her

daughter is bright, and she is doing well in the first grade. The child has a 1-year-old brother who is developing normally. A family history of neurological disorders could not be elicited. The mother emphasizes to you that her daughter walks much better in the morning than in the afternoon.

On the morning of the examination you find a delightful, precocious girl who seems quite bright. Cranial nerves II–XII are normal. There is no nystagmus. Finger-to-nose is done accurately and without tremor. Her strength is normal. Her reflexes are normal and her plantar response to stimulation was flexor. When she walked she had some mild in-turning of the right foot. Her gait was awkward and rather stiff. The mother tells you that on the morning you examine the child she is doing well and that later in the day her walking would become much worse.

What do you do now?

The pediatrician is correct: the progressive course of the disorder as described by the mother rules out the possibility that this child has cerebral palsy, a static disorder. The variation in severity of the gait disturbance over the course of the day described by the mother is an intriguing observation, so you schedule the patient to come to your office in the late afternoon and ask the mother to keep her very active before the appointment.

Three days later you see the patient. The findings have changed considerably from the prior visit. When the child walks into your room you immediately notice that there has been a dramatic deterioration in gait. The child struggles to walk into the room. The right foot is turned inward to such a degree that the child is walking on the side of her foot and both legs are stiff. You also note that there is a decreased arm swing, with both arms rigidly extended with the hands pronated. The hypertonus is of such a degree that it is difficult to bend the arms or legs. The child, while not in pain, clearly appears distressed by the muscle stiffness.

You recognize that you are dealing with dystonia, a condition characterized by abnormal tonicity of muscle, with prolonged, repetitive muscle contractions, often involving simultaneous contractions of both agonists and antagonists, leading to twisting of the extremities.

There are many causes of paroxysmal dystonia, so you order an MRI of the head and blood studies (Table 11.1). However, while you are waiting for the results to return you start the child on levodopa/carbidopa 25/100 mg bid, since you strongly suspect dopamine-responsive dystonia. A week later, the mother brings the child back and she is ecstatic. Since starting the levodopa/carbidopa the child is walking much better and for most of the day can run without a limp. The mother feels the drug has resulted in a miracle.

This patient likely has dopamine- or dopa-responsive dystonia, also known as hereditary progressive dystonia with diurnal variation or Segawa disease. It is an inherited dystonia typically presenting in the first decade of life. It is characterized by diurnal fluctuations, exquisite responsiveness to levodopa, and mild parkinsonian features. The disorder is most frequently due to a dominantly inherited mutation of the GTP cyclohydrolase I (GCH) gene on chromosome 14q 22.1–22.2. However, about 40% of dopamine-responsive dystonia do not carry the mutation of the GCH gene, Other inherited conditions such as mutations in the tyrosine hydroxylase

TABLE 11-1 **Differential Diagnosis of Episodic Dystonia in Children**

Diagnosis	Comments
Paroxysmal kinesogenic choreoathetosis	Characterized by episodes of chorea, athetosis, or dystonia, triggered by sudden movements or startle. Episodes may be preceded by an aura and generally last seconds to minutes, although they don't involve loss of consciousness. The frequency of attacks varies considerably, from multiple times in a day to as few as once a month.
Paroxysmal non-kinesogenic choreoathetosis	Attacks of dystonia, chorea, athetosis, and ballismus that occur spontaneously. The condition manifests as attacks lasting from a few minutes to several hours. Episodes happen only when the individual is awake, and he or she remains conscious throughout the attack. Episodes can occur multiple times per day or there may be weeks or months between attacks.
Exercise-induced dystonia	A clinical condition characterized by dystonic postures in parts of the body, most commonly affecting the lower limbs, after prolonged exercise, lasting 5 to 30 minutes and disappearing (in most cases) within minutes of cessation of the physical activity.
Alternating hemiplegia	A condition where children have alternating periods of hemiparesis lasting from seconds to hours. Dystonia may occur during the attacks.
Paroxysmal torticollis of infancy	A self-limited and benign entity characterized by recurrent episodes of head tilt, sometimes accompanied by vomiting, pallor, agitation, and ataxia, which subside spontaneously within a few hours or days and entirely disappear within months or years.

gene, aromatic L-amino acid decarboxylase and other defects of tetrahydrobiopterin metabolism can lead to dopamine-responsive dystonia. Dopamine-responsive dystonia is characterized by striatal dopamine deficiency with preservation of nigrostriatal terminals.

There is considerable variation in the age of onset of the disorder as well as the severity of the condition. The early signs, as in this child, typically involve a disorder of gait that fluctuates in intensity during the course of the day. Marked gait difficulties can occur, and it is not uncommon for the child to be diagnosed with cerebral palsy of the spastic diplegia type. Typically, the onset is in the first decade of life.

Dopamine production increases through the night with each cycle of rapid eye movement sleep. The activity at the nigrostriatal terminals peaks in the early morning and decreases during the day. Dopamine activity in the nigrostriatal terminals is reduced in patients with dopamine-responsive dystonia. This dopamine activity declines further during the day, leading to exacerbation of symptoms toward evening. It also decreases with increasing age, and thus the dystonia progressively worsens with age in many patients.

KEY POINTS TO REMEMBER ABOUT DOPAMINE-RESPONSIVE DYSTONIA

- Cerebral palsy is a static disorder. If there is neurological deterioration, you are not dealing with cerebral palsy.
- Fluctuation of the severity of the dystonia during the course of day is characteristic of dopamine-responsive dystonia, with the symptoms worsening toward the end of the day.
- If untreated the condition is progressive, but if diagnosed and treated early, patients do quite well.
- Because the disorder in inherited it is very important for the clinician to take a detailed family history in order to identify other affected family members.

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12 Duchenne Muscular Dystrophy

You are called by a pediatrician to discuss a 4-year-old boy whose parents feel he may have cerebral palsy. The pediatrician tells you he has followed the child since birth. Although the boy was somewhat slow in walking, the pediatrician felt this was a normal variant. However, recently the parents raised concern about his inability to keep up with his 3-year-old sister and the observation that he "waddles." The pediatrician is not concerned but wishes to run the case by you.

What do you do now?

The keys to the diagnosis are the history and physical examination. In this patient it would be important to see the family and examine the child. Comparing the development of the child with siblings can provide important clues to the diagnosis.

When you see the child you learn that while his sister was walking at 9 months, your patient started walking at 16 months, and the parents felt that compared to his sister he was quite clumsy. On examination, you find that the child is alert and interactive and appears quite bright. Cranial nerve examination is normal. On muscle testing you find some questionable weakness of the deltoids of the upper extremities but considerable weakness of the proximal muscles of the lower extremities. Toe walking and enlargement of the gastrocnemius muscles are observed. Tendon reflexes are difficult to elicit. When you ask the child to sit on the floor and then stand, the Gower sign is present, with the child using his hands and arms to push up to a standing position (Fig. 12.1).

This child likely has Duchenne muscular dystrophy, a dystrophinopathy. As in this child, the early symptoms are insidious and often dismissed by pediatricians and parents. Children with Duchenne muscular dystrophy may

FIGURE 12-1 Gower sign. Because of proximal leg weakness, the child uses his hands and arms to climb up his legs to get to a standing position.

present with developmental delay, particularly in speech. Only when difficulty arising from the floor and a waddling gait are observed, both signs of a proximal muscle weakness, is the diagnosis entertained. The majority of children maintain their ability to walk and climb stairs until 8 years of age. Eventually the child develops progressive loss of gait with loss of tendon reflexes and severe proximal weakness of both the upper and lower extremities.

Cerebral palsy can present with gait disturbances. However, cerebral palsy is an upper motor neuron disorder, and hyperreflexia and spasticity are the cardinal physical findings. Becker muscular dystrophy can be differentiated from Duchenne muscular dystrophy by the later age of onset (>5 years), unassisted ambulation after age 15, and survival into adult life. Muscle biopsy shows more dystrophin in children with Becker muscular dystrophy than those with Duchenne muscular dystrophy. The table lists the muscular dystrophies of childhood.

Duchenne muscular dystrophy is a genetic disorder due to a genetic defect at the Xp21 site. The abnormal gene product is a reduced muscle content of the structural protein dystrophin. The diagnosis of Duchenne muscular dystrophy can be made by genetic analysis. Creatine kinase (CK) levels are markedly elevated (10 times normal) in boys with Duchenne muscular dystrophy. While a muscle biopsy can also provide the diagnosis, it is no longer necessary since molecular diagnosis is available.

While Duchenne muscular dystrophy is not curable, it is treatable. Prednisone treatment and physical therapy can be quite helpful to the patient.

KEY POINTS TO REMEMBER ABOUT DUCHENNE MUSCULAR DYSTROPHY

- Mild early motor delay; onset is insidious.
- Children may present with developmental delay and unless the gait is observed carefully, the diagnosis may be missed and a further child may be born with the disorder.
- Becker muscular dystrophy has a later onset and a milder course.
- Waddling gait, enlarged calf muscles, and the Gower sign are keys to the diagnosis.
- Mutational analysis will provide the diagnosis.

TABLE 12-1 **Muscular Dystrophies of Childhood**

Type	Comment
Dystrophin-related disorders	
Duchenne/Becker muscular dystrophy	Becker muscular dystrophy is an allelic, milder form of Duchenne muscular dystrophy.
Severe childhood autosomal recessive muscular dystrophy	Phenotypically identical to Duchenne muscular dystrophy but with normal dystrophin content in muscle. Occurs in both sexes.
Non-dystrophin-related disorders	
Emery-Dreifuss muscular dystrophy	X-linked condition with contractures, weakness, cardiomyopathy
Facioscapulohumeral dystrophy	Facial diplegia, progressive proximal weakness, first affecting the shoulders and then the pelvis, often asymmetrical
Limb-girdle muscular dystrophy	X-linked disorder with progressive proximal muscle weakness
Congenital muscular dystrophy	
Congenital muscular dystrophy with central nervous system involvement (Fukuyama)	Early-life onset of proximal weakness, hypotonia, absent reflexes, seizures, developmental delay
Walker-Warburg syndrome	Severe lissencephaly, epilepsy, mental retardation, eye abnormalities such as corneal clouding, cataracts, retinal detachment, hypotonia, and weakness
Muscle-eye-brain (Santavuori) syndrome	Cortical dysplasia, epilepsy, mental retardation, complex eye abnormalities, weakness, contractures, and hypotonia

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13 Febrile Seizures

You are called to the emergency room to see an 11-month-old boy who had a generalized tonic-clonic seizure. According to the parents, the child was doing well until the prior evening, when they said he felt hot and obtained an axillary temperature of 38.2˚C. The boy was given 120 mg acetaminophen and was placed in the parents' bed. At approximately 3 a.m. the parents were awoken by the child kicking the mother. When the lights were turned on the parents found the child with the eyes open, staring straight ahead, with rhythmic jerking of the arms and legs. The family noted no color changes and estimated that the seizure lasted 5 minutes. The parents called 911 and the boy was transported to the hospital. The emergency medical service personnel noted no seizures en route to the hospital.

On admission to the emergency room the child had a temperature of 38.5˚C. The staff examined the boy and diagnosed acute otitis media. A spinal tap, which was normal, was performed and antibiotics and ibuprofen were started. CBC and electrolytes and glucose were normal. When you arrive, the boy is awake but is irritable.

You learn from the parents that there is not a family history of epilepsy. The birth history was unrevealing and the child's development has been normal. Your examination is unremarkable.

The emergency room staff has made arrangements to obtain a CT scan of the head and ask you whether it would be better to do a MRI.

What do you do now?

By the presentation, this boy had a simple febrile seizure. The seizure occurred in a child between 3 months and 5 years of age, was associated with fever, was generalized tonic-clonic in type, and lasted less than 15 minutes. With a normal neurological examination there is little reason to do any additional workup, and you should tell the staff that neither the CT nor MRI is necessary.

The most important test done when the child arrived in the emergency room was the spinal tap. While not all children with febrile seizures need to be tapped, the American Academy of Pediatrics recommends, on the basis of the published evidence and consensus, that after the first seizure with fever in infants younger than 12 months, a lumbar puncture be strongly considered because the clinical signs and symptoms associated with meningitis may be minimal. While clinical judgment is paramount, missing meningitis can be deadly and it is better to be cautious. The American Academy of Pediatrics also does not recommend the routine drawing of serum electrolytes, calcium, phosphorus, magnesium, CBC, or blood glucose. In this case, having a serum glucose to compare with the cerebrospinal glucose would be useful, particularly if the spinal fluid glucose was low, as can be seen in children with glucose transporter deficiencies. Furthermore, EEG and neuroimaging should not be done based on the history and neurological examination.

While additional testing is not necessary, it is important to counsel the family. While the risk of developing epilepsy after a simple febrile seizure is low, there is a substantial risk that the child will have another febrile seizure. As long as the seizures are brief and non-focal and associated with fever, it is not necessary to bring the child into the hospital. However, the cause of the fever should be investigated by the pediatrician.

Children who have focal seizures, prolonged febrile seizures (lasting >15 minutes), or more than one in 24 hours, have a higher likelihood of developing epilepsy. In these children, MRI and EEG may be helpful in differentiating children with benign febrile seizures from those in whom the febrile seizure was the first sign that the child is going to develop epilepsy.

Febrile seizures are rarely treated since for the most part they are quite benign and all of the antiepileptic drugs have some side effects. When children have prolonged febrile seizures, rectal diazepam can be used to abort the seizure.

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14 Fragile X Syndrome

You are called by a local pediatrician who wishes you to see a 6-year-old boy with autism who had a generalized tonic-clonic seizure. You learn from the pediatrician that the child was born after a full-term pregnancy to a G3P2→3 mom who had no difficulties with the spontaneous vaginal delivery. The child weighed 3,200 grams and had good Apgar scores. The mother was concerned about his development beginning with the first year of life. Compared to his 8-year-old brother and 9-year-old sister, he was never quite "right," even during the first year of life, when he rarely smiled and was delayed in rolling over, sitting and walking.

When you see the child, the parents tell you that the child was given a diagnosis of autism a year ago because of a combination of language delay, poor social interactions, and some self-stimulatory behavior, including hand biting. As you take the history you observe that the boy is quite hyperactive and disruptive to the point where the grandmother has to take the child out of the examining room. Once the child leaves the mother tells you the child will be held back in

kindergarten for another year. He is substantially delayed. He does not know his colors, can count only to six, and does not know his birthday, address, or phone number. The mother says he has a short temper and is argumentative and aggressive with members of the family.

Two weeks prior to your office visit the boy was found in the early morning having a generalized tonic-clonic seizure. The child's eyes were opened, with rhythmic jerking of the arms and legs. The parents described perioral cyanosis and incontinence. The seizure lasted approximately 2 minutes. When seen in the local emergency room he had a glucose level, electrolytes, CBC, and MRI, all of which were normal. He was started on phenobarbital.

When you bring the child back into the room you find him quite difficult to examine. The child has little eye contact with you. He does not follow commands and shows little interest in you, preferring to explore the room. His head circumference is normal, although he has a prominent forehead and jaw and large ears. The neurological examination is otherwise normal, although you have trouble visualizing the fundi.

What do you do now?

This child likely has fragile X syndrome, a disorder with a mutation on the X chromosome. Fragile X is a syndrome that occurs in males. Clues to the diagnosis are the developmental delay in a boy, his unusual face and ears, and his behavior. In this child the first step is to order genetic testing, a trinucleotide repeat sequence mutation in the fragile-X gene, *FMR-1*, and an EEG.

Boys with fragile X syndrome have mild to severe mental retardation (IQ 20–80). In addition, many have features of autistic spectrum disorder, consisting of abnormalities in social interaction and communication and repetitive behaviors or interests. Attention-deficit/hyperactivity disorder and conduct disorders are also common in the condition. Macro-orchidism can be an important clue to the diagnosis for the syndrome, but this may not be evident until after puberty.

Medical care for an individual with fragile X syndrome focuses on treating common problems and helping the individual achieve his developmental potential. Epilepsy occurs in approximately 25% of the boys and is usually not difficult to control. However, in this condition, which is often associated with aggressive behaviors and conduct disorders, phenobarbital would not be an ideal drug due to its association with hyperactivity and irritability. The EEG findings in this condition vary; some children have centrotemporal spikes.

Fragile X syndrome is caused by an expansion of a CGG repeat in the *FMR1* gene resulting in the absence of the *FMR1* mRNA and protein. The fragile X DNA assay has greatly improved both the sensitivity and the specificity of fragile X diagnosis. Chromosome analysis may be falsely negative, so DNA testing is important. The *FMR1* protein is proposed to act as a regulator of mRNA transport and of translation of target mRNAs at the synapse. Fragile X syndrome is seen as a loss-of-function disorder.

Fragile X syndrome exhibits the transmission pattern of X-linked inheritance. The disorder cannot be passed on by males to other males. However, both males and females can be affected, with girls less affected than males. Females with Fragile X full mutations may have cognitive impairment.

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15 Hashimoto's Encephalopathy

You are called to the emergency room to see a 14-year-old in status epilepticus. You are told the boy was found on the kitchen floor at 9 a.m. by his parents in the midst of a generalized tonic-clonic seizure. The emergency medical service was called and the child was transported to the emergency room. Upon arrival to the emergency room you find the child is intubated, and after 6 mg (0.1 mg/kg) of lorazepam and 1,200 mg of phenytoin (20 mg/kg) the seizure stopped. According to the parents and the emergency room staff, the seizure lasted approximately 120 minutes.

In reviewing the history you learn that the child had his first seizure 4 weeks before this admission. The seizures occurred while he was walking home from football practice and according to eyewitnesses was generalized tonic-clonic in type. After the seizure he was quite combative. He was treated with 2 mg haloperidol, 8 mg lorazepam, and 11 mg midazolam. He was admitted to the hospital and had a normal MRI, electrolytes, and glucose and a negative urine toxic screen. A spinal tap revealed a glucose level of 74 mg/dL, protein of 31 mg/dL,

3 white cells, and 0 red cells. An EEG, done 24 hours after the seizure, was diffusely slow.

The child gradually recovered with increasing alertness and activity, but he seemed excessively sleepy after the seizure. Thyroid function tests were obtained because of a recent weight gain and tiredness. Due to a reduced T4 (2.0, normal 4.6–12) and elevated TSH (12.1, normal 0.5–6.0) the patient was started on thyroid supplementation (25 ↔g). He was discharged home on no antiepileptic drugs. When seen in the clinic 1 week after a vacation at Disney World, the mother said that while he had had no additional seizures, he never returned to his baseline status. His neurological examination was normal and the mother said she believed it was likely that the thyroid medication was not yet fully effective.

One week later he was admitted to the hospital after a second seizure. While eating dinner he began acting strangely, dropped his fork, and began to mumble. He had a brief generalized tonic-clonic seizure. An EEG the following day was mildly abnormal because of slow background and left frontal delta. He was started on levetiracetam and the dose was titrated upward to 1,000 mg bid.

He did well for 3 weeks, although the mother said he remained somewhat sluggish. On the morning of his admission for status epilepticus, he behaved as if he had just woken up and seemed mildly confused and tired.

You learn there is no family history of epilepsy, although there is a strong family history of hypothyroidism.

The patient had been doing reasonably well in school, although his grades had dropped from the prior year. The emergency room staff did a CT scan, which was normal, and a lumbar puncture, which revealed a normal opening pressure, a protein level of 51 mg/dL, glucose of 63 mg/dL (serum glucose of 95 mg/dL), 2 red cells, and 6 white cells. Cerebrospinal fluid and blood cultures were negative.

What do you do now?

A somewhat unusual feature of this story is that the child never seemed to recover from the seizures. The mother described him as "not being right" after the first seizure. While this may be secondary to the hypothyroidism, one has to be concerned about an ongoing encephalopathic process such as a chronic infection, vasculitis, or metabolic disorder. The hypothyroidism may be an important clue to the diagnosis. While it is true that it takes a period of time before thyroid supplementation starts to show a clinical benefit, it is also possible that the child has Hashimoto's encephalopathy.

You learn that his thyroid peroxidase antibodies were grossly elevated at 2,105 (normal, 0–34), while the ANA, myeloperoxidase antibody, proteinase-3 antibody, and rheumatoid factor were negative. Repeat thyroid function tests show that the patient is now euthyroid.

While the endocrinologists say the findings are indicative of Hashimoto's thyroiditis, you suggest this child has Hashimoto's encephalopathy and elect to start the patient on 2 mg/kg prednisone. Within days the child is much brighter and more animated than he has been in the past 2 months.

Hashimoto's encephalopathy is a relatively new disorder, first described in 1966, and is the accepted name for the condition of encephalopathy associated with Hashimoto's thyroiditis. Because most patients with Hashimoto's encephalopathy improve with steroids or immunosuppressant treatment, some clinicians now refer to the condition as "steroid-responsive encephalopathy associated with autoimmune thyroiditis." Clinical manifestations of Hashimoto's encephalopathy include encephalopathic features such as seizures, behavioral and psychiatric manifestations, movement disorders, and coma. Although it has been linked to cases of Hashimoto's thyroiditis or thyroid dysfunction, the most common immunological feature of Hashimoto's encephalopathy is the presence of high titers of antithyroglobulin or thyroid peroxidase antibodies. Some endocrinologists doubt there is a relationship between thyroiditis and the encephalopathy, and it is unclear whether antithyroid antibodies represent an immune epiphenomenon in a subset of patients with encephalopathic processes or if they are really associated with the pathogenic mechanisms of the disorder. However, the responsiveness of Hashimoto's encephalopathy to steroids or other therapies such as plasmapheresis supports the hypothesis that this is a disorder that involves immune pathogenic mechanisms.

There is not a relationship between thyroid function and the encephalopathy. Patients with Hashimoto's encephalopathy can be hypothyroid or euthyroid.

This patient responded well to steroids and has been seizure-free for over 6 months. While most patients respond to steroids, other patients benefit more from intravenous immunoglobulins and plasmapheresis.

KEY POINTS TO REMEMBER ABOUT HASHIMOTO'S ENCEPHALOPATHY

- Consider the disorder in acute psychosis, status epilepticus, or unexplained coma.
- High titers of antithyroglobulin or thyroid peroxidase antibodies are clues to the diagnosis but are not diagnostic of the condition.
- Thyroid function tests can be normal.
- Patients typically have a dramatic response to steroids.

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16   Hydrocephalus

You are called by a pediatrician who is seeing a 2-year-old girl in his office who had been having episodes of early-morning vomiting. The child is well known to the pediatrician, who has been following her since birth. The pediatrician tells you that the girl was born after an uneventful pregnancy, labor, and spontaneous vaginal delivery. Apgar scores were normal and the child's birth weight, length, and head circumference were normal. The girl's routine office visits were uneventful.

Three weeks ago the parents noted the girl began having episodes of early-morning emesis. They would hear her gagging and frequently found her in a pool of vomitus. The child told the parents that both her stomach and head hurt during the event.

The pediatrician describes the child as being alert and active. Her general and neurological examinations were considered normal. However, of concern to the pediatrician was the fact that the girl's head circumference was above the 95th percentile. He wondered whether the child had hydrocephalus.

What do you do now?

The pediatrician has encountered a common problem, a large head circumference in an apparently normal young child. Since the girl has morning vomiting, the concern is somewhat more acute. Increased intracranial pressure can result in emesis, particularly in the morning, after the child has been lying flat during the night. Lying flat increases intracranial pressure, whereas standing or sitting reduces intracranial pressure. Therefore, the history of morning emesis should raise concern about increased intracranial pressure and warrants prompt evaluation.

Macrocephaly means a large head, commonly defined as two standard deviations above the normal population. This definition indicates that 2% of the normal population has macrocephaly. Since macrocephaly may be familial, the first step in this child is to measure the head circumferences of the parents. If both of the parents had head circumferences above the 95th percentile, the findings in the child would be less concerning.

When you measure the head circumferences of the parents, you note that they are both normal, making the elevated head circumference in this child more worrisome. The causes of a large head include hydrocephalus (excessive volume of cerebrospinal fluid in the skull), megalencephaly (enlargement of the brain), thickening of the skull, and hemorrhage into the subdural or epidural spaces.

Hydrocephalus is divided into two types: communicating (non-obstructive) or non-communicating (obstructive), depending on whether cerebrospinal fluid communicates between the ventricles and subarachnoid space.

Hydrocephalus often presents with headache, weight loss, sleepiness, high-pitched cry, failure to thrive, and emesis as well as increasing head circumference. On physical examination one typically sees a bulging fontanel, splayed sutures, enlarged head, and "sunsetting" (deviation of the eyes downward).

In this child the next step would be to obtain an MRI to rule out hydrocephalus or a structural lesion or other cause that could lead to megalencephaly (Table 16.1).

The MRI showed enlargement of the lateral and third ventricle, with a normal fourth ventricle (Fig. 16.1).

Aqueductal stenosis is eliminated as a possibility because the fourth ventricle is enlarged. The findings are indicative of communicating hydrocephalus.

TABLE 16-1 **Causes of Megalencephaly**

Disorder	Comments
Achondroplasia	An autosomal dominant genetic disorder that is a common cause of dwarfism, demonstrating a large skull with a narrow foramen magnum and relatively small skull base. Stenosis of the sigmoid sinus at the level of a narrowed jugular foramina results in an increase in intracranial venous pressure and hydrocephalus.
Alexander disease	An autosomal dominant disease with megalencephaly, seizures, spasticity, dementia, and in some cases hydrocephalus. It is caused by mutations in the gene for glial fibrillary acidic protein (GFAP) that maps to chromosome 17q21.
Canavan disease	An autosomal recessive leukodystrophy with degeneration of myelin and megalencephaly
Epidermal nevus syndrome	A neurocutaneous syndrome associated with epidermal nevus and seizures, spasticity, mental retardation, and developmental delay. Hydrocephalus may occur.
Gangliosidosis	Lipid storage disorder caused by the accumulation of lipids. Associated with megalencephaly.
Glutaric aciduria	An inherited disorder in which lysine, hydroxylysine, and tryptophan cannot be metabolized; excessive levels of their intermediate breakdown products (glutaric acid) result in neurological dysfunction. Megalencephaly is common.
Hypomelanosis of Ito	Condition with large, hypopigmented area that is whorled or streaked, seizures, mental retardation, and megalencephaly
Incontinentia pigmenti	Condition associated with swirling macular hyperpigmentation or linear hypopigmentation, mental retardation, seizures, megalencephaly
Krabbe disease	Autosomal recessive metabolic disorder due to the absence or marked reduction of galactocerebrosidase, which can lead to megalencephaly, seizures, developmental delay
Maple syrup urine disease	Autosomal recessive metabolic disorder affecting branched-chain amino acids; symptoms of the condition include poor feeding, vomiting, dehydration, lethargy, hypotonia, seizures, ketoacidosis, opisthotonus, pancreatitis, coma, and neurological decline

TABLE 16-1 *Cont.*

Metachromatic leukodystrophy	A leukodystrophy that results in abnormal myelin due to sulfatide accumulation. Megalencephaly may occur.
Neurofibromatosis	Autosomal dominant neurocutaneous syndrome with megalencephaly, mental retardation, cafÈ-au-lait spots, and seizures. Neurofibromatosis is autosomal dominant, affecting males and females equally.
Mucopoly-saccharidoses	Lysosomal disorder with impaired degradation of glycosaminoglycans. Results in cognitive impairment, megalencephaly.
Sotos syndrome	Also known as cerebral gigantism; characterized by excessive physical growth including megalencephaly during the first 2–3 years of life. Associated with mental retardation, delayed motor, cognitive, and social development, hypotonia (low muscle tone), and speech impairments.
Tuberous sclerosis	Neurocutaneous disorder with cerebral tubers, seizures, mental retardation. May be associated with megalencephaly.

Megalencephaly is defined as a head circumference >2 standard deviations above the normal distribution.
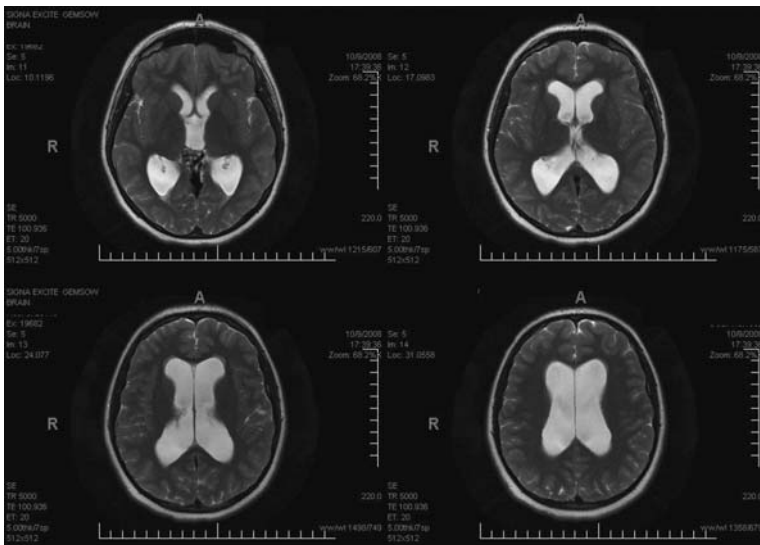
FIGURE 16-1 MRI from a 2-year-old with communicating hydrocephalus. The fourth ventricle, which is not shown here, is also enlarged, indicating that the four ventricles communicate with each other.
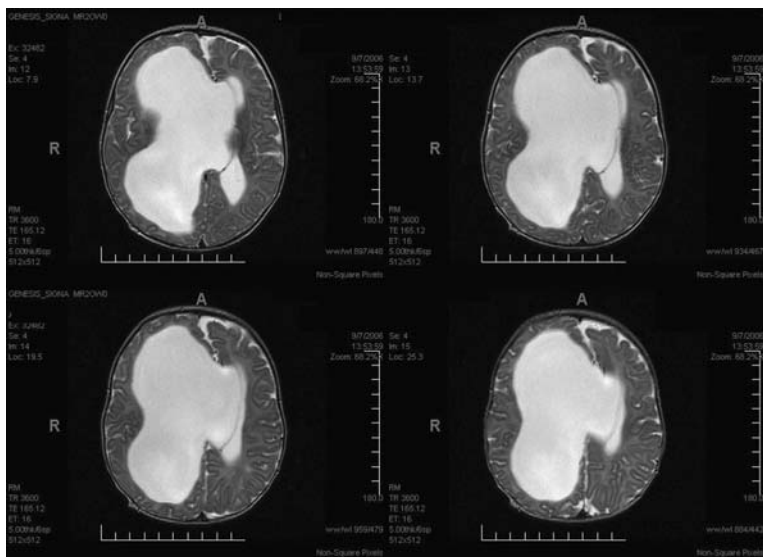
FIGURE 16-2 Unilateral left hemisphere hydrocephalus due to obstruction of the foramen of Monro.

Fig. 16.2 is an example of a patient with foramen of Monro obstruction with unilateral ventricular enlargement.

At this point the patient should be referred to neurosurgery for possible shunt placement.

KEY POINTS TO REMEMBER ABOUT HYDROCEPHALUS

- May present with vomiting, headache, weight loss.
- Sunsetting, with downward deviation of the eyes, can be a sign of hydrocephalus.
- MRI will differentiate hydrocephaly from megalencephaly of other etiologies.

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17   Infantile Spasms

You are called to the emergency room about a 9-month-old girl who was brought to the hospital because of peculiar spells characterized by sudden flexion of the trunk and extension of the arms. The family says the spells have been going on for approximately 3 weeks. They are brief, lasting less than 5 seconds, but occur in flurries, with 10 to 15 spells occurring in sequence. The parents state the episodes often occur upon awakening. Further questioning by the emergency room staff revealed that since the spells began, the girl has been less interactive and no longer smiles or follows with her eyes. The family says the pediatrician believes the child is having colic and came to the emergency room because they are concerned that she has something more ominous.

   You tell the emergency room staff to arrange for an EEG and a visit with you in your office the next day. When the girl arrives you learn that she was delivered after a normal pregnancy and labor. Birth weight and Apgar scores were normal and the child was discharged from the hospital on the second day of life.

Early developmental milestones were normal. By age 6 months the child was sitting, reaching for toys, transferring objects between hands, and rolling over and supported weight when held upright. The parents tell you she was quite sociable, squealed when happy, babbled chains of consonants, and responded to her name. However, when she began having the so-called colic spells there was a dramatic change in her alertness and activity level: she no longer showed interest in people and toys, stopped smiling and babbling, and often seemed distant. The girl also had episodes of severe irritability that would occur without provocation and sometimes would last an hour or more. The parents were quite skeptical about the diagnosis of colic and felt the girl had a serious problem.

The episodes of trunk flexion and extension of the arms occurred multiple times daily. Each episode consisted of 6 to 12 spasms. All of the events were similar in their behavioral features.

On examination you find a child who lay rather passively and did not interact with either you or the parents. She had a normal head circumference. She would not follow, but did look about the room. Funduscopic examination was normal. The tone was decreased and the reflexes were symmetrical. The child sat without support and had good head control in the sitting position.

The EEG done before the girl's clinical visit was quite abnormal, showing hypsarrhythmia. Several spasms

were recorded during the EEG. The EEG during the spasm showed a high-amplitude, sharply contoured delta wave at the vertex followed by a decremental pattern.

What do you do now?

After a review of the EEG you go back to the clinic and ask the parents to remove the child's clothes. On close examination you note that there are multiple hypopigmented macules.

The emergency room staff is describing typical infantile spasms, a unique and malignant epileptic syndrome confined to infants. The characteristic features of this syndrome are tonic or myoclonic seizures, hypsarrhythmic EEGs, and mental retardation; the triad of infantile spasms, hypsarrhythmic EEGs, and mental retardation is referred to as West's syndrome. Not all infants with infantile spasms conform strictly to this definition. The disorder is also referred to in the literature as massive spasms, salaam seizures, flexion or flexor spasms, jackknife seizures, and massive myoclonic jerks.

Infantile spasms are an age-specific disorder beginning in children during the first 2 years of life. The peak age of onset is 4 to 6 months of age. Approximately 90% of infantile spasms begin before 12 months of age. It is rare for them to begin during the first 2 weeks of life or after 18 months.

The parents were correct to be concerned that the child has something more serious than colic. The syndrome of infantile spasms is rightfully considered to be a medical emergency, not because the spasms are life-threatening but because they are frequently associated with developmental arrest or regression.

While the diagnosis can typically be made based on the history, having the parents make a videotape of the events can be very helpful in establishing the diagnosis. While gastrointestinal reflux could conceivably be confused with infantile spasms, children with reflux typically do not have repetitive episodes of tonic or myoclonic events.

If infantile spasms are suspected, the child should have an EEG. Infantile spasms are usually associated with markedly abnormal EEGs. The most commonly found EEG pattern is hypsarrhythmia (Fig. 17.1). This pattern consists of high-amplitude slow waves mixed with spikes and sharp waves whose amplitude and topography vary in an asynchronous manner between the two hemispheres. The background activity is completely disorganized and chaotic. During sleep, there are bursts of polyspike and slow waves. Somewhat surprising, in view of the marked background abnormalities, is the presence of sleep spindles in some patients. During rapid eye movement sleep there may be a marked diminution or complete disappearance of the hypsarrhythmic pattern.
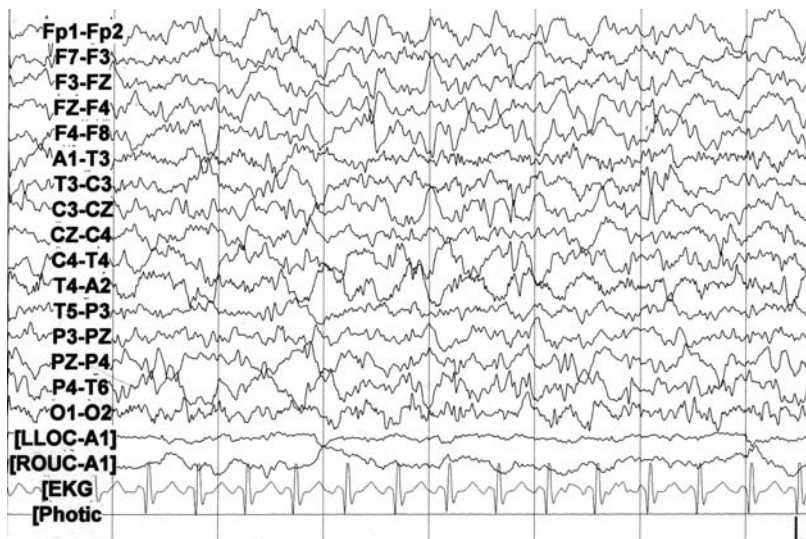
FIGURE 17-1 Hypsarrhythmia pattern in a 9-month-old with infantile spasms. Note the high-voltage chaotic pattern with multifocal spikes and sharp waves.

Once the diagnosis is established, the child needs to be evaluated for the etiology of infantile spasms and started on therapy. In this case the MRI showed periventricular and cortical tubers (Fig. 17.2). These findings, in conjunction with the hypopigmented macules on the child's skin, would establish the diagnosis of tuberous sclerosis. Infantile spasms are treated with adrenocorticotropic hormone (ACTH) or vigabatrin.

KEY POINTS TO REMEMBER ABOUT INFANTILE SPASMS

- Age-related seizures beginning in the first year of life.
- Child has flurries of flexor, extensor, or mixed tonic seizures The EEG is critical to the diagnosis, showing markedly abnormal patterns such as hypsarrhythmia.
- A normal EEG during waking and sleep would make the diagnosis unlikely.
- Determining the etiology of spasms is critical in determining the child's prognosis.
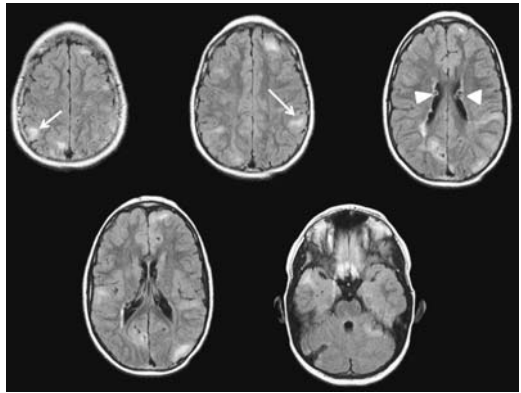
FIGURE 17-2 MRI showing subependymal nodules (*arrows*) and cortical tubers (*arrowheads*).

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18 Juvenile Myoclonic Epilepsy

You get a call from a local emergency room about a 14-year-old girl whose mother found her in bed at 6 a.m. having a generalized tonic-clonic seizure. The duration of the seizure was unknown. When seen in the ER she was postictal but had an otherwise normal neurological examination. Workup in the ER revealed a normal CT scan, CBC, electrolytes, and liver function tests. The patient and her mother denied any prior seizures.

You recommend that she make an appointment with you for an outpatient visit and suggest holding treatment at this time. She tells you that she has been under a great deal of stress recently, having broken up with a boyfriend. She does not sleep well and had difficulty falling asleep the night before the seizure. Despite the negative history given by the patient and her mother in the ER about prior seizures, you ask about possible jerks of her hands, particularly in the morning. The patient tells you that on some mornings, she is

somewhat tremulous and has had some twitching of her hands on occasion.

Her neurological examination is normal and the family history is negative.

What do you do now?

Considering the age of onset (early teenage years), timing (early morning), provoking factors (sleep deprivation), and history of probable myoclonic jerks, the most likely diagnosis is juvenile myoclonic epilepsy (JME).

You decide to do an EEG, instructing the patient to retire late at night and wake up early in the morning so that she will sleep during the recording. The EEG showed a normal background pattern for age, with 9-Hz alpha rhythm along with normal sleep features (symmetrical sleep spindles and vertex sharp waves). Intermittent bursts of generalized, fast spike-and-wave activity of 4 Hz lasting less than 3 seconds were seen. These generalized discharges were more frequent during drowsiness and sleep. Photic stimulation and hyperventilation failed to elicit any discharges.

The EEG supports the diagnosis of JME, and you decide to start the patient on levetiracetam, starting at 500 mg bid and increasing to 1,000 mg bid. You also start her on clonazepam wafers (0.5 mg), as needed, for flurries of myoclonic seizures.

JME is a familial disorder that typically begins in the second decade of life and is characterized by mild myoclonic seizures, generalized tonic-clonic or clonic-tonic-clonic seizures (a variation of generalized tonic-clonic seizures in which there is an initial clonic or myoclonic phase), and occasionally absence seizures. The myoclonic seizures are usually mild to moderate in intensity and involve the neck, shoulders, and arms. They can occur either singly or repetitively and may cause the patient to drop objects.

Rarely, the jerks may involve the legs and cause the patient to fall to the ground. There have been multiple attempts at determining the gene or genes responsible for the disorder. It now appears that there is not a single gene that accounts for all of the cases and that there is considerable genetic and locus heterogeneity in the disorder.

The interictal EEG in this disorder is distinctive and easily distinguished from other forms of generalized epilepsies. The characteristic feature of the EEG is the fast (3.5- to 6-Hz) spike-and-wave and multiple spike-and-wave complexes (Fig. 18.1). This pattern contrasts with the 3-Hz spike-and-wave complexes seen in classic absence seizures (Fig. 18.2) and the slow (1.5- to 2.5-Hz) spike-and-wave complexes of the Lennox-Gastaut syndrome (Fig. 18.3).

FIGURE 18-1 Rapid spike-wave discharge in a 14-year-old girl with juvenile myoclonic epilepsy.
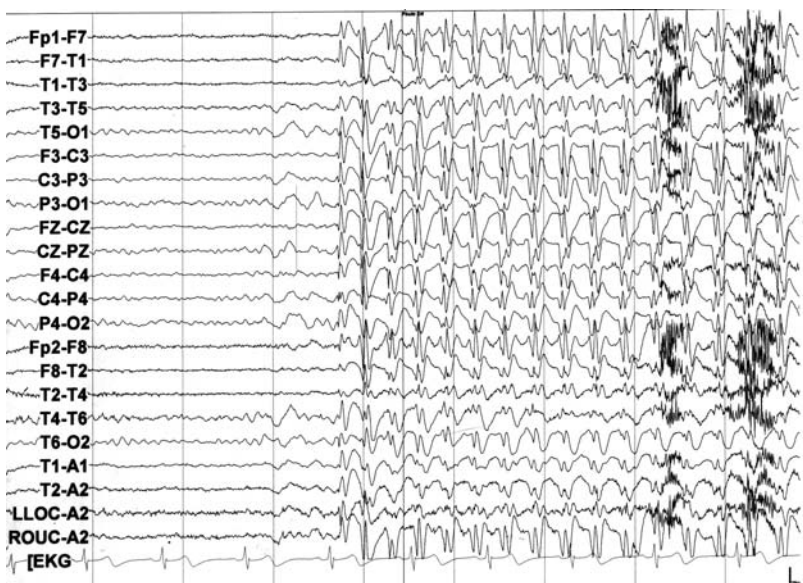
FIGURE 18-2 3-Hz spike-wave from a 6-year-old with typical absence seizure.

FIGURE 18-3 Slow spike-wave from a 12-year-old with Lennox-Gastaut syndrome.

JME falls within the category of idiopathic generalized epilepsies, which account for approximately 15% to 20% of all epilepsies. The seizure types are typical absence seizures, myoclonic jerks, and generalized tonic-clonic seizures, alone or in varying combinations and with variable severity. The seizures tend to be more frequent on awakening and with sleep deprivation. In addition to JME, other epilepsy syndromes of adolescence include juvenile absence epilepsy, idiopathic generalized epilepsy with tonic-clonic seizures, and grand mal on awakening. The classification of idiopathic generalized epilepsies follows two schools of thought; one maintains that the various types constitute different and separate syndromes, while the other suggests that the idiopathic generalized epilepsies are one biological continuum.

In a patient with a normal neurological examination and a history and EEG compatible with JME, neuroimaging (CT or MRI) is not necessary. However, most patients who have a generalized tonic-clonic seizure will have a CT or MRI in the emergency room. While from a medical stand-point such scanning is of little value, a normal neuroimaging study in a

teenager with generalized tonic-clonic seizures can be reassuring to both the family and physician.

In this case the patient was started on treatment after a single generalized tonic-clonic seizure. As a rule, patients with a single seizure are not placed on chronic antiepileptic drug therapy. However, in this case the teenager already had a history of myoclonic seizures. In addition, JME is typically a life-long disorder and recurrent seizures without therapy would be expected.

Drugs that are often effective in this condition include valproate, levetiracetam, and lamotrigine. Valproate and levetiracetam are effective in both the generalized tonic-clonic and myoclonic seizures, whereas the efficacy of lamotrigine in myoclonic seizures is more variable. Clonazepam can be quite useful for the myoclonic jerks.

As important as the drug therapy is the counseling that should occur at the first visit. It is important for the patient to be compliant with antiepileptic drug therapy and to avoid sleep deprivation and heavy alcohol consumption. Explaining to the patient that sleep deprivation is used to increase epileptiform discharges on the EEG often brings home the message that adequate sleep will reduce the likelihood of a seizure.

KEY POINTS TO REMEMBER ABOUT JUVENILE MYOCLONIC EPILEPSY

- Typically starts in adolescence.
- Patients may not be aware they are having myoclonic seizures since they can be quite mild and be considered a nuisance rather than a serious problem.
- The EEG shows rapid spike-and-wave discharges. However, the discharges can be infrequent, and a normal EEG does not rule out the condition.
- While patients typically respond well to antiepileptic therapy, the condition usually is life-long.

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19   Lissencephaly

You are asked to see a 4-month-old boy admitted to the pediatric intensive care unit because of recurrent partial seizures. The pediatric intensivist tells you the child was admitted after six tonic-clonic seizures lasting approximately 2 minutes. The parents reported that the seizures began with head deviation to the right or left, followed by rhythmic jerking of all four extremities. The boy was having a seizure when he arrived in the emergency room and he was given lorazepam (0.1 mg/kg). The child was subsequently started on phenobarbital, 5 mg/kg, after a loading dose of 20 mg/kg, and has not had any additional seizures since admission.

When you arrive in the intensive care unit you find the boy sleeping comfortably. He is afebrile. The parents tell you that this is their first child. The mother states the pregnancy went well and the delivery was uneventful. However, you learn the boy has developmental delay: he does not smile, follow, or respond to sound per the parents' report. The parents tell you when they pick up the child his head flops backward.

You examine the child. You are struck by how irritable he was when you tried to examine him. Once he settles down you note the child is hypotonic but has brisk and symmetrical reflexes. No dysmorphic features are present. No asymmetries of motor function or reflexes are present. The child has a weak Moro reflex.

What do you do now?

This is a worrisome story and it is unlikely this child has a benign cause for his seizures. The history of developmental delay and an abnormal neurological examination requires a thorough evaluation.

The history suggests this is a congenital problem rather than an acquired disorder. The most cost-effective evaluation at this point would consist of an EEG, MRI, and spinal tap. The EEG would be helpful in providing information about background activity. For example, a diffusely slow background, burst suppression pattern, or frequent multifocal or generalized epileptiform discharges would suggest a significant encephalopathic process, whereas a normal background would indicate a more benign pattern. The MRI would be useful in detecting a congenital brain malformation. While the child is afebrile and the history does not suggest an infectious process, obtaining cerebrospinal fluid would be useful in ruling out a glucose transporter defect, a condition in which the cerebrospinal fluid glucose level is low (hypoglycorrhachia) but the serum glucose level is normal.

The EEG shows a high-amplitude, slow background with multifocal spikes, sharp waves and bursts of irregular generalized spikes, and slow waves followed by periods of background suppression (Fig. 19.1). The electroencephalographer says the EEG resembles hypsarrhythmia, although it is somewhat more organized than the typical hypsarrhythmia. The spinal fluid has two lymphocytes, zero red cells, a glucose of 60 mg/dL (serum 80 mg/dL), and a protein of 40 mg/dL. The intensivists did not wish to sedate the child for a MRI and obtained a CT scan of the head. The CT is markedly abnormal, showing a thick cortex with few sulci (pachygyria) (Fig. 19.2). The radiologist tells you the child has lissencephaly.

Lissencephaly typically is a diffuse brain malformation manifested by a smooth cerebral surface, an abnormally thick cortex with four abnormal layers that includes a deep zone of diffuse neuronal heterotopia, and large, dysplastic ventricles (Fig. 19.3). It encompasses the pathologic terms agyria (no gyria) and pachygyria (broad gyri) and merges with a less severe disorder known as subcortical band heterotopia.

Children with lissencephaly or severe subcortical band heterotopia typically appear normal as newborns, although hypotonia, poor suck, and apnea may occur. Depending on the severity of the disorder the children go on to develop severe psychomotor retardation, failure to thrive, seizures, and muscle spasticity or hypotonia. The seizures can be quite severe, with
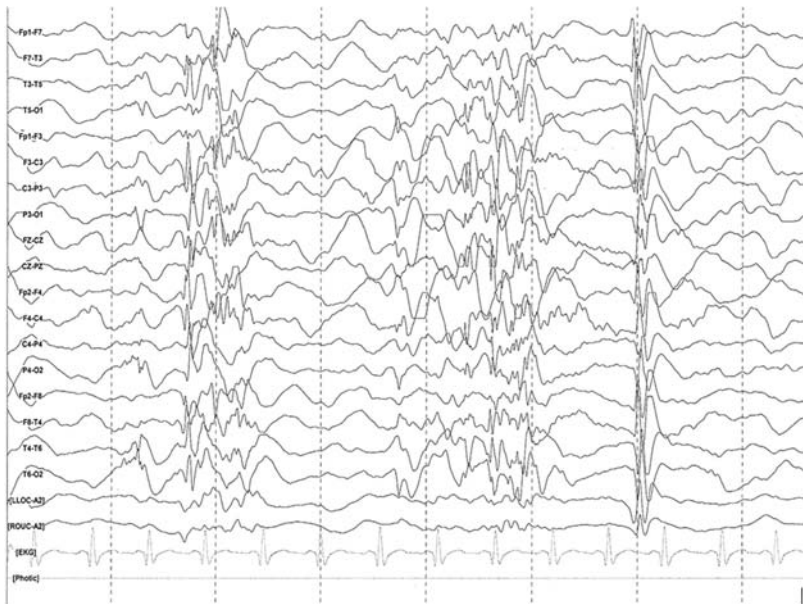
FIGURE 19-1 EEG from a child with lissencephaly. Note bursts of spikes and spike-waves with periods of background suppression following the bursts. The EEG is somewhat less chaotic than EEGs from children with hypsarrhythmia.
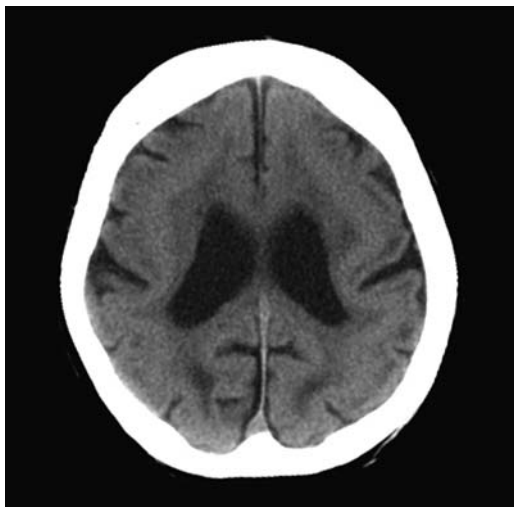
FIGURE 19-2 CT of a patient with lissencephaly. Note the flat cortex with paucity of gyri.

FIGURE 19-3   Lissencephalic brain. Note the lack of a normal gyration pattern.

some children developing infantile spasms and the Lennox-Gastaut syndrome. Children with subcortical band heterotopia or partial lissencephaly do much better in terms of development.

The Miller-Dieker syndrome consists of lissencephaly with abnormal facies. The facial features include a prominent forehead, bitemporal hollowing, short nose with upturned nares, protuberant upper lip, and a small jaw. All patients with the disorder have large deletions of chromosomal region 17p13.3 that include the lissencephaly 1 gene (*LIS1*). The isolated lissencephaly syndrome consists of classic lissencephaly with a fairly normal facial appearance except for mild bitemporal hollowing and a small jaw. Different patterns of lissencephaly have been found with mutations of two genes, doublecortin (*DCX*) occurring on Xq22.3-q23and *LIS1*. Subcortical band heterotopia occurs primarily in girls, because the most common cause is heterozygous mutations of the *DCX* gene of the X chromosome. Since boys

have only one X chromosome they have the more severe disorder of lissencephaly. Mutations of the Aristaless-related homeobox gene *ARX*, which is on Xp21.1 gene, result in X-linked lissencephaly with agenesis of the corpus callosum, abnormal basal ganglia, severe microcephaly, and abnormal genitalia that are ambiguous or hypoplastic. This disorder is referred to as X-linked lissencephaly with abnormal genitalia.

Genetic testing in this child revealed a mutation in the *DCX* gene, indicating this child has isolated lissencephaly. Unfortunately, the prognosis is quite poor, with no specific therapy available. Most children have severe epilepsy and often require gastrostomy tubes. Death typically occurs within a few years.

KEY POINTS TO REMEMBER ABOUT LISSENCEPHALY

- Despite the profound brain anomaly, clinical symptoms and signs do not usually present in the neonatal period.
- Children with the Miller-Dieker syndrome have lissencephaly and abnormal facies.
- There are multiple genetic mutations that can result in lissencephaly.
- The majority of children with lissencephaly have severe epilepsy.

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20 Moyamoya Disease

You are called about a 5-year-old girl who is being transferred to the pediatric intensive care unit (PICU) from another hospital with episodes of transient left-sided weakness involving the face and arm. The episodes would occur multiple times daily, last 4 to 5 minutes, and then clear totally. The PICU attendings tell you the neurological examination is totally normal. A CT scan of the head from the outside hospital was also apparently normal.

The PICU staff thought that these episodes were seizures and ordered an EEG. The EEG showed some right-sided slowing but no epileptiform activity. During hyperventilation the patient developed an episode of left-sided weakness that lasted approximately 5 minutes and then cleared. The child was able to talk throughout the episode. During the left-sided hemiparesis the EEG showed high-amplitude slowing that persisted for 5 minutes beyond the end of hyperventilation. The PICU staff asks for advice.

What do you do now?

This is a very worrisome story that should prompt further investigation. When you see the child, you learn from the parents that she has been having episodes for about 4 months. Since the girl seemed to improve relatively quickly after the attacks, the parents did not have any concerns until recently, when the attacks increased in frequency. They are also concerned that the child now seems to have persistent left-sided weakness. When you examine the child you concur with the PICU staff that the child has a mild left-sided weakness involving the face and arm. The examination is otherwise unremarkable, with normal visual fields, extraocular muscle movements, and cerebellar function.

Although the thought that the child was having seizures is a possibility, it is unusual for children to develop weakness as the sole manifestation of the seizures. Most seizures result in "positive" symptomatology with tonic, clonic, or myoclonic activity during the event rather than weakness. However, weakness can occur in the postictal period. When lateralized it is called a Todd's paralysis.

Another consideration would be alternating hemiparesis. Children with alternating hemiparesis typically are developmentally delayed and have abnormal neurological examinations. As indicated by the name, the hemiparesis alternates between sides. This is an unlikely diagnosis in this case, however, since the weakness has been consistently on the left side of the body. Periodic paralysis (hyperkalemic, hypokalemic, or normokalemic) may result in episodic weakness, although it is unusual to involve only one side of the body.

The persistent high-voltage slowing during the EEG and onset of symptoms during hyperventilation is highly suggestive of Moyamoya disease. This is a chronic, progressive, noninflammatory vasculopathy that results in a slow occlusion of the intracranial arteries, causing a successive ischemic event. Hemorrhagic events can also occur. The occlusion typically begins at the carotid siphon. The condition leads to irreversible blockage of the carotid arteries to the brain as they enter into the skull. It tends to affect children and adults in the third or fourth decade of life. In children it tends to cause strokes or seizures; in adults it tends to cause strokes or bleeding. The clinical features are cerebral ischemia (strokes), recurrent transient ischemic attacks, sensorimotor paralysis (numbness in the extremities), convulsions, and/or migraine-like headaches.

Because the occlusion is slowly progressive, multiple anastomoses form between the internal and external carotid arteries. On cerebral angiography these anastomoses result in an appearance of a puff of smoke. The diagnosis is initially suggested by CT, MRI, or angiogram. In fact, the name derives from its angiographic image: the "puff of smoke," which is how moyamoya loosely translates from Japanese, refers to the appearance of multiple compensatorily dilated striate vessels seen on angiography (Fig. 20.1). Contrast-enhanced T1-weighted images are better than FLAIR images for depicting the leptomeningeal ivy sign in Moyamoya disease. MRI and MRA should be performed for the diagnosis and follow-up of Moyamoya disease. Diffusion-weighted MRI can also be used to follow the clinical course of Moyamoya disease in children who develop new deficits.

Often nuclear medicine studies such as SPECT (single photon emission computed tomography) are used to demonstrate the decreased blood and oxygen supply to areas of the brain involved with Moyamoya disease. Conventional angiography provides the conclusive diagnosis of Moyamoya disease in most cases and should be performed before any surgical considerations.
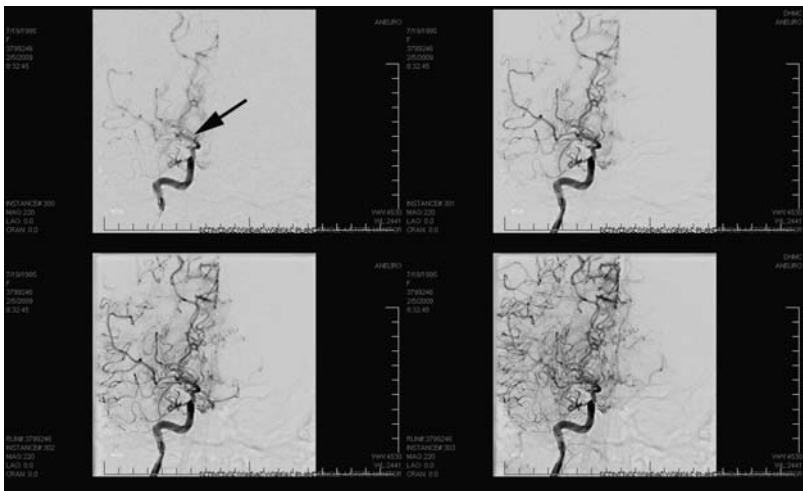
FIGURE 20-1 Arteriogram from a 10-year-old girl showing severe stenosis of the supraclinoid internal carotid artery (*arrow*). Collateral flow to the peripheral anterior and middle cerebral arteries is supplied by lenticulostriate collaterals, leptomeningeal branches from the posterior cerebral artery, and transdural anastomoses from the ophthalmic artery.

Moyamoya can be either familial or acquired. Patients with Down syndrome, neurofibromatosis, or sickle cell disease can develop Moyamoya malformations. Brain radiation therapy in children is a risk factor for the condition. The gene responsible for familial Moyamoya disease is on chromosome 17q25.

The process of blockage (vascular occlusion), once it begins, tends to continue despite any known medical management. In some people this leads to repeated strokes and severe functional impairment or even death. In others, this blockage may not cause any symptoms.

A key to the diagnosis in this patient was the onset of symptoms during hyperventilation. Hyperventilation reduces PCO_2 and cerebral blood flow, resulting in signs and symptoms due to ischemia.

Patients should be evaluated for an underlying vasculopathy or coagulopathy. A variety of treatment options are available, including surgical bypass procedures.

KEY POINTS TO REMEMBER ABOUT MOYAMOYA DISEASE

- Often presents with quick onset and offset of hemiparesis.
- Unlike alternating hemiplegia, typically involves one side of the body.
- Persistent unilateral slowing on the EEG following hyperventilation suggests the disorder.

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21 Neurofibromatosis

A pediatrician refers an 8-year-old girl to you because of concerns about development.

The child was the product of a normal labor and uneventful vaginal delivery to a 25-year-old, healthy G1P1 mother. The child weighed 3,400 grams (50th percentile), had a head circumference of 35 cm (50th percentile), and had Apgar scores of 9/10. You learn from the parents that the girl reached all motor developmental milestones on time but did not use understandable words until age 2 and phrases until age 3 (Table 21.1).

The girl was deemed to be slow in school and while in second grade had an aide and an individual education plan (IEP). She underwent psychological testing in the first grade, and the parents were told she was delayed by about a year, with her greatest difficulty in expressive and receptive speech. The parents say she is awkward and does not do well in team sports such as soccer. She prefers playing with younger children.

Her general health has been excellent, without any hospitalization or head trauma. Both parents completed

college and there is no family history of mental retardation or learning deficits.

When you observed the girl, you found that she was slow in responding and had a limited fund of knowledge for her age. For example, she could not tell time, had left–right confusion, and was unaware of the year she was born or the current date or day of the week. She had poor eye contact and had difficulty staying on task. She attempted to read a paragraph from a first-grade book but was very slow and made many errors. She could not tell you if she was right- or left-handed.

On examination you find that while her weight and height were at the 40th percentile, she has a large head (59 cm, >95th percentile). Cranial nerve examination was normal. She demonstrated dysdiadochokinesia with rapid alternating movements and had difficulty jumping on each foot. Muscle stretch reflexes, muscle strength testing, and sensory examination were normal. Her gait was awkward and she had trouble catching a bounced ball.

What do you do now?

There are numerous causes for developmental delay, and often clinicians struggle in terms of how extensively a child should be evaluated. In this case you learn that while the child has cognitive problems, there has been no developmental regression. Knowing you are dealing with a static problem is helpful in eliminating an evaluation for a degenerative problem and allows you to direct your evaluation toward static conditions.

Before embarking on a costly evaluation, you should consider possible clues from the case. The best predictor of a child's intelligence is the intelligence of the mother. Since the mother is cognitively normal, there clearly is a process occurring here that is not simply due to familial traits. The observation that the child has macrocephaly should lead you to measure both of the parents' head size, since macrocephaly may run in families and be of no clinical significance. Both of her parents have normal head circumferences.

An essential part of every examination of a child with a learning disability is an examination of the skin. When you have the child disrobe you find that she has six café-au-lait spots greater than 5 mm in diameter and axillary freckling (Fig. 21.1).

FIGURE 21-1   Café-au-lait spots in a child with neurofibromatosis.

It is likely that this child has neurofibromatosis (NF). NF is a neurocutaneous syndrome characterized by peripheral (type 1) or central (type 2) tumors. This child likely has NF1. The abnormal gene for NF1 is located on chromosome 17q and its abnormal protein product is neurofibromin. There are over 100 mutations of the gene. Almost 50% of the mutations are *de novo*. Because of the large number of mutations, commercial genetic screening for NF1 is not currently available.

Table 21.2 lists the diagnostic features of NF. In this child the café-au-lait spots and freckling in the axillary region would support the diagnosis of NF1. Macrocephaly is also common in the disorder. Although you did not note any Lisch nodules, it would be useful to have the child examined by an ophthalmologist, since in addition to Lisch nodules these children are at risk for optic gliomas.

The neurofibromatoses are genetic disorders of the nervous system that primarily affect the development and growth of neural (nerve) cell tissues. NF is associated with nerve tumors (neurofibromas). These tumors can be painful and disfiguring. Plexiform neurofibromas can be particularly difficult to manage. Children with NF are also at risk for intraspinal neurofibromas, dural ectasia, and aqueductal stenosis. As in this girl, NF is associated with learning disabilities.

In view of the large head and the risk for optic glioma, MRI screening of the head would be indicated. Although the MRI in this child was normal, NF1 may be associated with areas of increased T2 signal throughout the brain. The significance of such lesions is unclear.

NF1 is the more common type of the neurofibromatoses. NF2 is characterized by bilateral tumors on the eighth cranial nerve that cause pressure damage to neighboring nerves.

Treatment for NF1 is symptomatic. In most cases, symptoms of NF1 are mild, and patients live normal lives. In some cases, however, NF1 can be severely debilitating. Surgery can help some NF1 bone malformations and remove painful or disfiguring tumors; however, there is a chance that the tumors may grow back, and in greater numbers.

In the case presented here, having a diagnosis provides prognostic guidance for both the family and school. With speech, occupational, and physical therapy combined with a patient-specific educational plan, the child can improve.

TABLE 21-1 **Important Developmental Milestones During First 3 Years of Life**

1 Month	3 Months	6 Months	12 Months	24 Months	36 Months
Moves head from side to side while lying on stomach	Raises head and chest when lying on stomach	Reaches for object and brings to mouth	Drinks from a cup with help	Take off clothes	Drinks from a straw
Keeps hands in tight fists	Supports upper body with arms when lying on stomach	Good head control when in the sitting position	Feeds self finger foods	Scribbles with crayons	Feeds self with a spoon
Strong reflex movements	Pushes down on legs when feet are placed on a firm surface	Explores by mouthing and banging objects	Develops pincer grasp	Walks and runs without help	Washes hands
Focuses 8-12 inches away	Brings hand to mouth	Sits with minimal support	Points	Identifies an object in a picture book	Partially dresses self
Recognizes some sounds	Grasps and shakes hand toys	Rolls over	Puts small blocks in and takes them out of a container	Looks and searches for objects that are out of sight	Builds a tower of 3 or 4 blocks
	Follows moving objects	Knows familiar faces	Bangs blocksSits well without support	Follows one-step directions	Throws ballStoops and recovers
	Recognizes familiar objects and people at a distance	Laughs and squeals with delight	Crawls on hands and kneesPulls to stand	Has expressive vocabulary of 8-10 words	Walks up steps
	Begins to babble	Smiles at self in a mirror	Walks with one hand held	Looks at a person who is talking to him/her	Walks backward
	Turns head toward direction of sound		Copies sounds	Uses "hi," "bye," and "please," with reminders	Points to 5 or 6 body parts
	Begins to develop a social smile		Say first word	Recognizes self in the mirror or in pictures	Has a vocabulary of several hundred words
			Shows separation anxiety from parent		Uses 2- to 3-word sentences
			Understand simple commands		Refers to self by name and uses "me" and "mine"
					Verbalizes desires ("I want juice")

TABLE 21-2   **Diagnostic Criteria for Neurofibromatosis Type 1**

Two or more are considered diagnostic:

Six café-au-lait spots >5 mm in diameter in prepubertal individuals or >15 mm in postpubertal individuals
Two or more neurofibromas or one plexiform neurofibroma
Freckling in the axillary or inguinal region
Optic glioma
Two or more iris hamartomas (Lisch nodules)
A distinctive osseous lesion, such as sphenoid dysplasia or thinning of long bones
A first-degree relative with NF1

KEY POINTS TO REMEMBER ABOUT NEUROFIBROMATOSIS

- Part of the neurological examination is examining the skin for lesions such as café-au-lait spots and hypopigmented macules (tuberous sclerosis complex).
- Children with NF1 are at risk for optic gliomas and other tumors.
- In evaluating a child with developmental delay, do not underestimate the importance of the neurological history and examination.

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Nonketotic Hyperglycinemia

The neonatologists from the neonatal intensive care unit call and ask you to see a 2-day-old boy who is having frequent clonic jerks alternating between the left and right arm and leg.

The child was born via a normal spontaneous vaginal delivery to a healthy G1P0→1 mother; his Apgar scores were 8 at 1 minute and 9 at 5 minutes. The child was full-term and weighed 3,600 g. The mother denied any difficulties during the pregnancy and had negative cultures for group B streptococcus. While the infant seemed fine immediately after birth, he then developed jerks and became increasingly less responsive.

The neonatologists describe the child as being unresponsive. They had to intubate him because of breathing difficulties. Phenobarbital (20 mg/kg) was given without any clear response.

The neonatologists obtained a CBC, serum glucose, electrolytes, blood ammonia, and liver function tests, all of which are normal. A cerebrospinal fluid examination revealed eight white blood cells (three of which were polymorphonuclear cells and five were lymphocytes),

20 red blood cells, a protein of 90 mg/dL, and a glucose of 60 mg/dL (serum glucose was 80 mg/dL). Blood cultures were obtained and the child was started on antibiotics. Urine was sent for organic acids and serum for amino acids. A MRI of the brain was reportedly normal.

When you see the child, you find that he is flaccid and difficult to arouse. No skin lesions are seen. When vigorously stimulated he develops opisthotonus. The pupils are reactive to light and he has doll's eyes present. Reflexes are brisk with clonus at the ankles. You note myoclonic jerks that are multifocal, as well as brief generalized tonic seizures. The nurses also tell you the child is having frequent hiccups.

What do you do now?

It is clear that this child has a life-threatening disorder. The very frequent seizures and the findings on the neurological examination suggest a severe hypoxic-ischemic insult, overwhelming infection, or metabolic derangement.

The history is not compatible with hypoxic-ischemic encephalopathy since there were no prenatal difficulties and the delivery was uneventful. The mother had no risk factors for infection, the CBC was normal, and there are no signs of sepsis such as hypotension, bradycardia, or temperature instability.

It is important to get an EEG in this situation. Even though it appears obvious the child is having seizures, the EEG can provide confirmatory information that the events are epileptic as opposed to non-epileptic events. The EEG can provide clues to the diagnosis. For example, periodic discharges arising from the temporal lobe can suggest herpes simplex encephalitis, while generalized spike-wave discharges could indicate pyridoxine dependency seizures.

In this child the EEG showed a burst-suppression pattern (Fig. 22.1). Some but not all of the myoclonic jerks were linked to the generalized bursts.
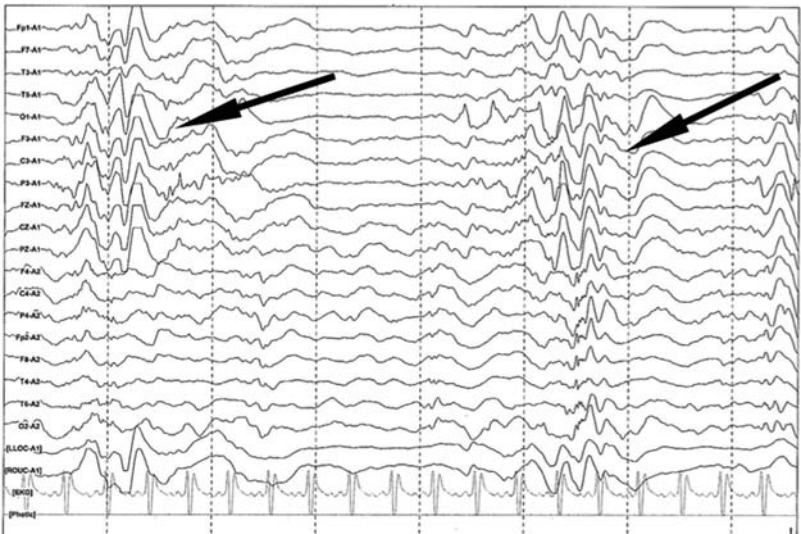
FIGURE 22-1 Burst suppression pattern in an infant with nonketotic hyperglycinemia.

The burst suppression pattern can be seen in neonates with conditions such as severe birth hypoxic-ischemic injuries, severe congenital brain anomalies, encephalitis, and trauma. However, this pattern is also consistent with a metabolic encephalopathy. Without a firm diagnosis it is recommended that a number of treatable conditions be ruled out through therapeutic trials.

The trial should consist of a pyridoxine, 100 mg, given during the EEG. If the child has pyridoxine-dependent epilepsy there should be a prompt reduction in seizures and an improvement in the EEG. Pyridoxine-dependent seizures are due to alpha-aminoadipic semialdehyde (alpha-AASA) dehydrogenase deficiency, associated with pathogenic mutations in the *ALDH7A1* (antiquitin) gene. Pyridoxal-5-phosphate is the biologically active form of pyridoxine, and some patients deficient in pyridoxamine oxidase (PNPO) cannot utilize pyridoxine. If pyridoxine-dependent seizures continue to be a concern, pyridoxal-5-phosphate (10 mg/kg) should be administered.

Severe neonatal seizures may respond to folinic acid (leucovorin), 2.5 to 5 mg given twice daily. A crossover between pyridoxine and folinic acid responsiveness has been noted in the same individuals and patients with the antiquitin mutation who have responded to folinic acid, indicating that folinic acid-responsive seizures and pyridoxine dependency appear to be allelic. Folinic acid should be given to infants with an incomplete response to pyridoxine or pyridoxal-5-phosphate.

This child did not respond to pyridoxine, pyridoxal-5-phosphate, or folinic acid, ruling out pyridoxine dependency and folinic acid-responsive seizures. At this point you should consider nonketotic hyperglycinemia. Even though the child has had a normal spinal tap, you request that the tap be repeated with analysis of amino acids and that the concentration of the cerebrospinal fluid glycine be compared to the serum concentration.

The spinal fluid examination was again normal, except for a very high level of glycine (388 μmol/L, normal range 1–15 μmol) and a ratio of cerebrospinal fluid glycine to plasma glycine of 0.2 (normal 0.01–0.03), indicating that the child has nonketotic hyperglycinemia.

Nonketotic hyperglycinemia is an inborn error of glycine degradation in which large amounts of glycine accumulate in the brain. Ketosis and abnormal organic acids in blood and urine are not present. Nonketotic

hyperglycinemia is due to a molecular defect in the glycine cleavage system (glycine decarboxylase). In the majority of cases, nonketotic hyperglycinemia presents with severe neurological dysfunction within the first 2 days of life, but sometimes later. Rapidly increasing stupor, unresponsiveness, respiratory difficulties, apnea, and seizures are characteristic. Hiccups are common in the disorder.

As in this child, the MRI is often normal. However, children may have brain abnormalities such as agenesis of the corpus callosum, progressive cerebral atrophy, hydrocephalus, and delayed myelination. Magnetic resonance spectroscopy shows increased levels of glycine, lactate, and creatine.

Unfortunately, no effective treatment of nonketotic hyperglycinemia is available. Dextromethorphan, an NMDA blocker, and benzoate, which reduce concentrations of glycine, can be helpful. While the majority of children die within days or weeks of the diagnosis, some will survive, albeit with severe neurological problems.

KEY POINTS TO REMEMBER ABOUT NONKETOTIC HYPERGLYCINEMIA

- Must be considered in any infant with severe lethargy, coma, and seizures.
- The diagnosis should be suspected if there is a burst suppression pattern on the EEG.
- The diagnosis is confirmed by examining the ratio of the cerebrospinal fluid concentration of glycine to the serum concentration.
- While waiting for the laboratory studies to return, the infant should be given trials of pyridoxine and pyridoxal-5-phosphate.

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23 Opsoclonus-Myoclonus Syndrome

You are called to the pediatric floor by the pediatric house staff to see an 18-month-old girl who presents with episodes of falling. The mother reports that over the past week the child has been unsteady and falls more than usual. At approximately the same time the girl became shaky and would sometimes drop objects. The mother also is concerned about "funny" eye movements.

The girl is the first child of this 29-year-old woman, who states that the pregnancy, labor, and delivery went well and the child was discharged home with the mother the day after delivery. Development has been normal and other than a few colds the child has been healthy. There is no family history of neurological disorder.

On examination the girl is noted to be irritable, but is consolable by the mother. The child has some subtle multifocal jerks of the arms and legs during your interview and examination. These are barely perceptible, but according to the mother they were not present a week ago. On cranial nerve examination you note that her eyes are darting about in a very quick, unpredictable manner. The eyes move conjunctively. She can follow a

toy for a few seconds before the eyes begin to jerk. It is not possible to see the fundi. The remainder of the cranial nerve examination is normal. When reaching for objects there is a tremor in the upper extremities. While strength and sensation are normal, reflexes are difficult to elicit. Upon standing there is truncal titubation and the child cannot walk without falling.

The house staff has already obtained an MRI, EEG, electrolytes, CBC, and liver function tests, all of which are normal.

What do you do now?

This is a difficult case. When faced with a patient with presumed neurological disease, the first step is to try to determine where the pathology is located. The eye movements you are seeing are referred to as opsoclonus, a condition of uncontrolled eye movements. Opsoclonus consists of rapid, involuntary, multidirectional (horizontal and vertical), unpredictable, conjugate fast eye movements. Opsoclonus is thought to be secondary to abnormalities in the midbrain. The myoclonic jerks seen are non-localizing and could be seen in cortical or subcortical, including spinal cord, pathology. The ataxia you are seeing could be related to cerebellar impairment or could be caused by the child's myoclonus.

The constellation of findings would suggest you are dealing with the opsoclonus-myoclonus syndrome, also called opsoclonus-myoclonus-ataxia, Kinsbourne syndrome, myoclonic encephalopathy of infants, and dancing eyes–dancing feet syndrome. This child had a typical presentation, with both the opsoclonus and myoclonus occurring at the onset. As the disorder progresses there is increased severity of the truncal myoclonus, which results in impaired standing and walking. The opsoclonus is usually maximal on the onset of the disorder and then subsides in intensity. The myoclonus usually disappears when the child is sleeping. In some children the myoclonus is exacerbated by intention.

The syndrome is associated with neuroblastoma, with the opsoclonus and myoclonus typically occurring before the tumor is diagnosed. It is presumed that this is a paraneoplastic syndrome in which the cancer, through a tumoral factor such as hormones or cytokines or immune-mediated activity, results in neurological dysfunction. The neurological dysfunction is not due to a direct invasion of neural tissue by tumor. The physician must undertake a careful investigation for occult neuroblastoma in all infants and children with the opsoclonus-myoclonus syndrome. The neuroblastoma may be quite difficult to detect, but if found and removed can result in a resolution of symptoms.

In about half of the children, a search for a neuroblastoma is unsuccessful. Some of the children will have a history of a prior infection, usually viral. Cerebrospinal fluid may show an elevated protein level and a mild lymphocytic pleocytosis, but this does not distinguish paraneoplastic from infectious opsoclonus-myoclonus syndrome. Likewise, serum antineuronal

antibodies have been found in patients with both postinfectious and neuroblastoma-associated opsoclonus-myoclonus syndrome.

ACTH and corticosteroids (such as prednisone or methylprednisolone) used at high dosages can improve symptoms. Intravenous immunoglobulins and immunosuppressive drugs such as cyclophosphamide, azathioprine, and rituximab may be helpful in some cases.

The prognosis is quite variable; complete or partial remission may occur and is not dependent on the etiology.

KEY POINTS TO REMEMBER ABOUT OPSOCLONUS-MYOCLONUS SYNDROME

- Opsoclonus, a key feature of this disorder, is distinguishable from nystagmus by conjugate, darting movements in all directions. The directions of the eye movements are not predictable.
- Ataxia can be secondary to truncal myoclonus or primary cerebellar involvement.
- It is necessary to undertake a thorough investigation for occult neuroblastoma in all infants and children with opsoclonus-myoclonus.
- Steroids or immune modulation therapy can by very useful.

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24 Ornithine Transcarbamylase Deficiency

You get a call from the NICU to see a 5-day-old boy admitted because of possible clonic seizures. The child was a full-term infant of a healthy 25-year-old mother. The delivery was difficult and the child was delivered with vacuum extraction. The birth weight was 3,000 g and the Apgar scores were 3 at 1 minute, 7 at 5 minutes, and 8 at 10 minutes. The infant did well the first 24 hours after birth. However, on the second day of life, the nurses noted that the child was awakening less frequently, and when awake was very irritable. Intermittent rhythmic arm jerking associated with facial twitching was observed.

The neonatologists obtained a CBC, electrolytes, and glucose level, all of which were normal, and performed a spinal tap, which revealed a protein of 70 mg/dL, glucose of 50 mg/dL, and eight white blood cells, five of which were polymorphonuclear leukocytes. The blood and spinal fluid were cultured and the child was started on broad-spectrum antibiotics and loaded with phenobarbital intravenously (20 mg/kg).

Despite phenobarbital and antibiotic treatment, the child became quite lethargic and would not feed. The child developed periods of apnea and continued to have clonic movements of both arms and legs. Temperatures fluctuated from 36° to 38°C. The neonatologists are concerned that the child suffered from birth asphyxia, and ask for your opinion.

When you examine, the infant you noted that he was very lethargic and could not be awakened. The head circumference was normal. Pupils were pinpoints and it was difficult to do a funduscopic examination. The child had full range of movements with doll's eye maneuver. The corneal reflexes were present but the child had a very weak suck. You could not elicit a Moro, grasp, or plantar response. Reflexes could not be elicited. The child was very hypotonic.

What do you do now?

The studies performed to date on the child have not yet provided a diagnosis. The history is not indicative of hypoxia-ischemia encephalopathy. The Apgar scores, while low initially, improved considerably at 10 minutes, and the child's behavior during the first 24 hours is not likely to be indicative of birth asphyxia. The cerebrospinal fluid formula is normal for a term infant. While the child was hypotonic and had no reflexes, the lethargy, possible seizures, and temperature fluctuations suggest a central rather than peripheral nervous system disorder. The onset of possible seizures after 24 hours and the progressive lethargy strongly suggest a metabolic encephalopathy (Table 24.1).

You recommend that the infant have an EEG and serum testing for organic acids, amino acids, lactate, liver function tests, and a blood ammonia.

The EEG showed an excessively discontinuous EEG pattern with frequent multifocal spikes and sharp waves. The serum ammonia level was 650 µmol/L (normal 10–40 µmol/L). Serum amino acid quantification showed elevated ornithine, glutamine, and alanine levels and relatively low citrulline levels. Urine organic acid studies showed an elevated urinary orotic acid level. Lactic acid level was normal and there was a slight elevation in the liver function tests.

TABLE 24-1 **Common Causes of Neonatal Seizures as a Function of Age**

Day 1	Day 2	Day 3 or Later
Hypoxia-ischemia	Postnatal infection	Cerebral dysgenesis
Trauma	Drug withdrawal	Cerebral venous
Stroke	(from mother)	thrombosis
Infection (bacterial or viral)	Cerebral dysgenesis	Inborn errors of
Intraventricular hemorrhage	Stroke	metabolism
Subarachnoid hemorrhage	Inborn errors of	Intracerebral
Severe metabolic disturbance:	metabolism:	hemorrhage
Non-ketotic	Urea cycle defects	Aminoacidopathies
hyperglycinemia	Glucose-transporter	Organic acidurias:
Pyridoxine dependency	defect	Methylmalonic
Sulfite oxidase		aciduria
Hypoglycemia		Propionic acidemia
Hypocalcemia		Maple syrup urine
		disease

This high blood ammonia level in the face of a normal serum glucose level and normal anion gap strongly suggests a urea cycle defect. The elevated ornithine, glutamine, alanine, and orotic acid levels, coupled with a low citrulline level, suggest that the child has ornithine transcarbamylase (OTC) deficiency (Fig. 24.1). OTC is the most common of the urea cycle disorders, yet is rare, occurring in one out of every 80,000 births. OTC is a genetic disorder resulting in a mutated and ineffective form of the enzyme ornithine transcarbamylase. As a result of this defect large levels of ammonia accumulate in the body. Mutations in the OTC gene cause ornithine transcarbamylase deficiency. A definitive diagnosis of ornithine transcarbamylase deficiency is via determination of enzyme level from a liver biopsy.

OTC deficiency is an X-linked recessive disorder caused by a number of different mutations. Since the gene is on the X chromosome, females are primarily carriers while males with non-conservative mutations are severely affected.
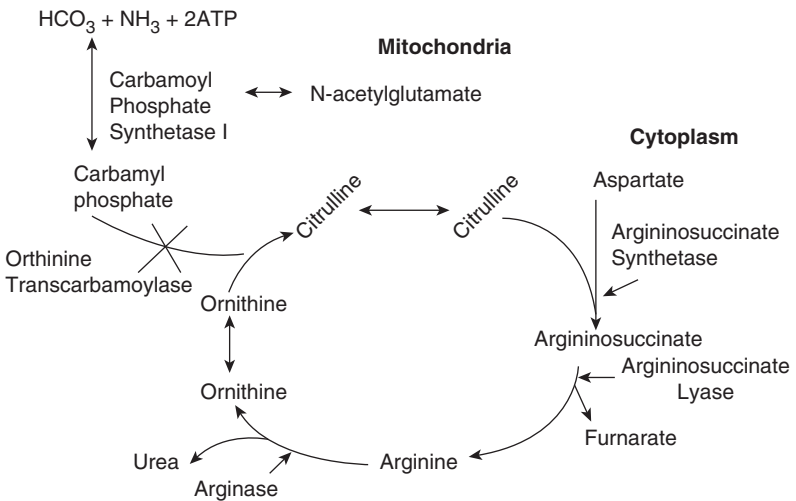
FIGURE 24-1 Amino metabolism and the urea cycle. ARG, arginase; ASL, argininosuccinate lyase; ASS, argininosuccinate synthetase; CPSI, carbamoyl phosphate synthetase I; OTC, ornithine transcarbamoylase. In this child OTC was deficient (marked by X), resulting in an increase of NH_3.

As in this case, OTC deficiency typically becomes evident within days of birth. Infants with OTC deficiency typically develop lethargy, anorexia, irregular respiratory patterns, fluctuating body temperature, and seizures. If untreated the infants typically go on to develop severe seizures, liver damage, and neurological damage, including mental retardation, or death. In some affected individuals, signs and symptoms of OTC deficiency may be less severe and may not appear until later in life. Some female carriers become symptomatic later in life, usually at the time of some form of stress, such as an illness.

With a serum blood ammonia this high, treatment must begin immediately, even before the specific diagnosis is made. Since the disease results in an inability to handle large amounts of a nitrogen load, the treatment includes strategies to decrease the intake of nitrogen (low-protein diet), prevention of excessive body protein breakdown during acute illnesses (hydration and nutrition), reducing catabolism through the introduction of calories supplied by carbohydrates and fats rather than protein, and administration of medications scavenging nitrogen (sodium benzoate and sodium phenylbutyrate). Some patients may need to have supplemental amino acids (arginine, citrulline, valine, leucine, isoleucine).

Sadly, even with meticulous monitoring of blood ammonia, episodes of hyperammonemia may occur and lead to coma and death.

KEY POINTS TO REMEMBER ABOUT ORNITHINE TRANSCARBAMYLASE DEFICIENCY

- Severe forms become symptomatic in the neonatal period.
- The infant may appear quite healthy at birth and then deteriorate over several days, with lethargy, anorexia, apnea, temperature fluctuations, seizures, and abnormal movements.
- A high blood ammonia level in the face of a normal serum glucose level and normal anion gap strongly suggests a urea cycle defect.
- Early recognition and treatment is critical to prevent severe brain damage and death.

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25 Rett Syndrome

You are asked by concerned parents to evaluate their 2-year-old daughter. They state that the girl was fine until approximately age 12 months, when they noted that she had a decreased interest in her toys, reduced eye contact, and a "fogginess." Recently she began some self-abusive behavior, including hitting her face with her hands.

You learn this is the third daughter of a 33-year-old woman. The pregnancy, labor, and delivery were without incident. Her birth weight was 3,200 g and the Apgar scores were normal. A normal head circumference of 35 cm was obtained. Early developmental milestones were met on time, including smiling, rolling over, sitting up, and walking. The parents have been told she is autistic. The child no longer makes eye contact and ignores both her parents and sisters.

At the appointment to see you, your nurse notes that obtaining a respiratory rate was difficult since the child had frequent respiratory pauses. The nurse found a weight and height around the 20th percentile but a head circumference at the 5th percentile (43 cm).

When you see the child you note she has no dysmorphic features, but you are concerned about her lack of interest in the surroundings. The child looked blankly ahead and showed little interest in what you were doing. Her cranial nerves were normal. You noted diffuse hypotonia with depressed but present tendon reflexes. The child would not cooperate with muscle testing. She would not reach for objects or grasp objects placed in her hands. Her gait was wide-based and unsteady.

What do you do now?

There are multiple clues to the diagnosis here. The rapid developmental decline, deceleration in head circumference, abnormal breathing pattern, and loss of purposeful movements of the hands in a girl makes it almost certain that she has Rett syndrome.

The first step in this case would be to obtain genetic testing for deletions in the *MECP2* gene (methyl cytosine binding protein 2), which is found on the X chromosome. The *MECP2* gene protein acts as a biochemical switch that causes other genes to stop producing their own unique proteins. The genetic defect appears to result in a loss of function of the *MECP2* protein, although the exact mechanism by which the abnormal protein leads to the constellation of findings in Rett syndrome is unknown. Seventy to eighty percent of girls given a diagnosis of Rett syndrome have the MECP2 genetic mutation detected. The other 20% to 30% of cases may be caused by partial gene deletions, by mutations in other parts of the gene, or by genes that have not yet been identified.

Rett syndrome is a childhood neurodevelopmental disorder character-ized by normal early development followed by loss of purposeful use of the hands, slowed brain and head growth, gait abnormalities, seizures, and mental retardation. It affects females almost exclusively.

The course of Rett syndrome, including the age of onset and the severity of symptoms, varies from child to child. Before the symptoms begin, however, the child appears to grow and develop normally. Then, gradually, mental and physical symptoms appear. Hypotonia (loss of muscle tone) is usually the first symptom. As the syndrome progresses, the child loses purposeful use of her hands and the ability to speak. Early symptoms may include problems crawling or walking and diminished eye contact. The loss of functional use of the hands is followed by compulsive hand movements such as wringing and washing. The onset of this period of regression is sometimes sudden. Another symptom, apraxia (the inability to perform motor functions), is perhaps the most severely disabling feature of Rett syndrome, interfering with every body movement, including eye gaze and speech.

Individuals with Rett syndrome often exhibit autistic-like behaviors in the early stages. Many girls with Rett syndrome show intense visual fixation which is puzzling in terms of their low communication levels.

Other symptoms may include toe walking; sleep problems; wide-based gait; teeth grinding and difficulty chewing; slowed growth; seizures; cognitive disabilities; and breathing difficulties while awake, such as hyperventilation, apnea (breath-holding), and air swallowing. The table lists essential, supportive but not required, and exclusionary features of Rett syndrome.

There are four stages of Rett syndrome. Stage I (*early onset*), typically begins between 6 and 18 months of age. Reduced eye contact and interest in toys and the surroundings become apparent to the family. A slowing in early milestones such as crawling, sitting, standing, and walking is observed. This stage usually lasts for a few months but can persist for more than a year. Stage II (*rapid destructive* stage) occurs between ages 1 and 4. This stage may have either a rapid or a gradual onset as purposeful hand skills and spoken language are lost. The characteristic hand movements begin to emerge during this stage and often include wringing, rubbing, clapping, or tapping. The child often puts her hands in her mouth during this stage. Breathing irregularities such as episodes of apnea and hyperventilation may occur. Loss of social interaction and communication may occur. The gait is unsteady, and initiating motor movements can be difficult. Slowing of head growth is usually noticed during this stage. Stage III (*plateau* or *pseudostationary*) typically begins between ages 2 and 10 and can last for years. Apraxia, motor problems, and seizures are prominent during this stage. However, this stage is usually associated with reductions in irritability, crying, and autistic-like features. Many girls remain in this stage for most of their lives. Stage IV (*late motor deterioration*) can last for years or decades and is characterized by reduced mobility, weakness, rigidity (stiffness), spasticity, and dystonia. Girls ambulating before this stage may become wheelchair-bound. Usually there is no decline in cognition or communication skills during this phase. Repetitive hand movements may decrease, and eye gaze usually improves.

There is no cure for Rett syndrome, and treatment is symptomatic. Seizures are not infrequent in Rett syndrome, and antiepileptic drug therapy may be indicated. The EEG is almost always abnormal in patients with Rett syndrome. Rhythmical slowing and focal and generalized spike and spike-wave discharges are common.

TABLE 25-1 **Criteria Used in the Diagnosis and Exclusion of Rett Syndrome**

Essential	Supportive but Not Required	Exclusion
Normal development until age 6–18 months Normal head circumference at birth followed by a slowing of the rate of head growth with age (between 3 months and 4 years) Severely impaired expressive language Repetitive hand movements Toe-walking or an unsteady, wide-based, stiff-legged gait	Breathing difficulties EEG abnormalities Seizures Muscle rigidity, spasticity, and/or joint contracture that worsen with age Decreased mobility with age Scoliosis Teeth-grinding Small feet in relation to height Growth retardation Decreased body fat and muscle mass Abnormal sleep patterns Irritability or agitation Chewing and/or swallowing difficulties Poor circulation of the lower extremities, with cold and bluish-red feet and legs Constipation	Enlargement of body organs or other signs of storage disease Vision loss due to retinal disorder or optic atrophy Microcephaly at birth An identifiable metabolic disorder or other inherited degenerative disorder An acquired neurological disorder resulting from severe infection or head trauma Evidence of growth retardation in utero or evidence of brain damage acquired after birth

Some of these clinical features may be age-related.

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26 Spinal Muscular Atrophy (SMA)

You are asked by a pediatrician to see a 3-month-old boy with "floppiness." The child was the product of a difficult delivery that ended in a cesarean section because of failure to progress. The mother, who had two other children who were in good health, noted that there were decreased fetal movements compared to her other pregnancies. The full-term infant had moderate respiratory distress at birth but responded to bagging and was sent to the well-baby nursery.

The mother said the child has been floppy since birth and she has struggled to feed him because of a poorly sustained suck. Over the past month the parents have become concerned about his poor head control and muscle tone.

When you see the child you find he has a head circumference (41 cm) and length (62 cm) at the 50th percentile but a weight (4.8 kg) that is below the 3rd percentile. You find the child to be alert, and no dysmorphic features are present. The child follows a toy with his eyes in all directions. No nystagmus is noted. There appears to be mild bilateral facial weakness.

Fasciculations of the tongue (worm-like movements) are noted and the gag is weak. The child has some movements of the hands and feet but has little movement of the arms and legs. Reflexes cannot be elicited. The tone is remarkably decreased and there is no head control when the child is pulled from the supine to the sitting position. A Moro reflex is absent.

What do you do now?

This is obviously a very severe condition. The observation that the boy is alert and follows well would make it unlikely you are dealing with a central nervous system cause for the hypotonia. Disorders of the motor unit are not associated with malformations of other organs, although joint deformities may occur. The decreased tone and areflexia would indicate anterior horn, peripheral nerve, or muscle disease. The tongue fasciculations would suggest anterior horn cell disease. The age of presentation and the findings on the neurological examination, taken together, would best fit the diagnosis of spinal muscular atrophy (SMA).

The differential diagnosis would include a number of other disorders of the motor unit. Polyneuropathies are an unusual cause of hypotonia in infants. However, congenital hypomyelinating neuropathy can be indistinguishable from infantile SMA. These children typically have EMG findings consistent with denervation and motor nerve conduction velocities that are less than 10 m/sec.

Infantile botulism is caused from eating food contaminated by an exotoxin of *Clostridium botulinum*. The infants can present with profound hypotonia, ptosis, facial and pharyngeal weakness, dilated pupils, and respiratory failure. Typically there is a prodromal syndrome of constipation and poor feeding. In this case the decreased fetal movements and poor tone present from birth would indicate a congenital rather than an acquired disorder.

Congenital and familial myasthenia gravis may present with hypotonia. Children of a healthy mother can, very rarely, develop myasthenic symptoms beginning at birth. Familial infantile myasthenia presents with prominent respiratory and feeding difficulties at birth, whereas congenital myasthenia gravis has ophthalmoplegia as the primary clinical picture. Unlike myasthenia gravis seen in older children and adults, the neonatal form is not caused by an autoimmune process but is due to synaptic malformation, which in turn is caused by genetic mutations. Multiple mutations have been identified and the inheritance pattern is typically autosomal recessive. A decremental EMG response on low-frequency stimulation of the compound muscle action potential can be seen. Mothers with myasthenia gravis may deliver a baby with transient weakness due to passive transfer of acetylcholine receptor antibodies to the fetus.

A number of congenital myopathies can present with neonatal hypotonia and weakness. Congenital myotonic dystrophy presents with pronounced

facial diplegia with a tent-shaped mouth, arthrogryposis, hypotonia, and weakness. The clinical features of congenital myotonic dystrophy are typically more severe than SMA. Other congenital myopathies such as central core disease, multiminicore disease, myotubular myopathy and nemaline myopathy typically have only mild hypotonia at birth and are usually diagnosed at a later age.

SMA is one of the most common autosomal recessive diseases, affecting approximately one in 10,000 live births. The disorder is characterized by symmetrical proximal muscle weakness and is caused by a degeneration of the anterior horn cells of the spinal cord. SMA is classically divided into three types based on age of onset and clinical manifestations, although the subtypes are actually a continuum. The severe type (SMA I, also called Werdnig-Hoffman disease) always begins before 6 months of age, the intermediate type (SMA II) begins between 6 and 18 months, and the juvenile type (SMA III) begins after 18 months.

SMA is associated with homozygous mutations in the survival motor neuron 1 gene (SMN1) and its centromeric homolog, SMN2. The genes lie within the telomeric and centromeric halves of a large inverted repeat in chromosome 5q13. It is an autosomal recessive condition, and in most cases affected individuals have inherited a gene deletion from each parent. The parents each have one normal (or wild-type) copy of the gene and one mutant copy. Approximately one in 50 to one in 200 people worldwide carry a mutation of the SMN1 gene. Because the disease is autosomal recessive, there is usually not a prior history of SMA.

In this case, since the child is not critically ill, the first step is to obtain genetic testing for mutations of *SMN1* gene. While EMG and nerve conduction studies would be useful in differentiating SMA from botulism, myotonic dystrophy, and a polyneuropathy, there is little reason to do these studies until the genetic studies return. Unfortunately, in this child, there were zero copies of the *SMN1* gene and only two copies of the *SMN2* gene; an increased number (at least three copies) of *SMN2* has been associated with a less severe phenotype of SMA.

Because there is no effective therapy for SMA, management consists of preventing or treating the complications of severe weakness, such as restrictive lung disease, poor nutrition, orthopedic deformities, immobility, and psychosocial problems.

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Status Epilepticus

You are called to the emergency room to see a 6-year-old boy who is in status epilepticus. The child has epilepsy likely due to a hypoxic-ischemic injury at birth. He has been having one or two generalized tonic-clonic seizures per month and is taking carbamazepine and valproic acid. On the day of admission he apparently was doing well until he had a generalized tonic-clonic seizure that persisted despite rectal diazepam (7.5 mg). He was taken to the emergency room and continued to have the seizure despite another dose of diazepam (7.5 mg/kg) intravenously. The emergency room staff says the seizure has lasted approximately 45 minutes. He was estimated to weigh 22 kg.

What do you do now?

Status epilepticus is a condition in which the seizure lasts 30 minutes or more without any period during which the child regains consciousness. Refractory status epilepticus refers to status that lasts over an hour. Status epilepticus is a medical emergency that requires prompt intervention. It is important that the child have an open airway and adequate oxygenation. Reliable intravenous access is necessary. The blood pressure should be monitored and adequate glucose levels maintained. If the child is not ventilated well, he or she should be intubated.

There should be aggressive management of the status with intravenous medication. The longer the seizure continues, the more difficult it is to stop. There is evidence that reduced surface expression of GABA(A) receptors, due to intracellular accumulation of the receptors, contributes to the reduced effectiveness of benzodiazepines. In addition, changes in the microenvironment, with accumulation of extracellular potassium and intracellular calcium, contribute to the heightened excitability. The child has received only two doses of diazepam, and at this point the physicians need to be more aggressive in stopping the seizures.

While diazepam is widely used for status epilepticus, the child did not respond to two doses. Lorazepam (0.1–0.15 mg/kg) is a first-line drug for status due to its longer distribution half-life than diazepam, which results in a lower incidence of status epilepticus recurrence. In clinical trials lorazepam appears to be superior to other drugs.

If lorazepam was not effective, you could give another dose of lorazepam or treat with fosphenytoin (15–20 mg/kg of phenytoin equivalents). Fosphenytoin is a pro-drug of phenytoin and 1 mmol of phenytoin is produced for every mmol of fosphenytoin administered. Using fosphenytoin is less likely to produce venous sclerosis or the "purple glove" syndrome due to extravasation of the drug.

If fosphenytoin was not effective, intravenous phenobarbital (15–20 mg/kg) could be used. At this point the child should be intubated and should be in the intensive care unit (if he had not been already admitted), since phenobarbital in combination with a benzodiazepine could lead to respiratory depression. Phenobarbital produces considerable sedation, making it difficult to monitor neurological function after the status epilepticus

has ceased. Valproic acid (20–25 mg/kg) has been used for status epilepticus, although there are concerns about valproic acid–induced liver toxicity.

If the status continues, one could try a continuous drip of midazolam, a benzodiazepine (a 0.15-mg/kg bolus followed by a 1- to 5-μg/kg/min infusion), or pentobarbital, a barbiturate (a 5-mg/kg loading dose, then a1- to 3-mg/kg/hr continuous infusion). The goal of midazolam or pento-barbital is to put the EEG into burst suppression in order to disrupt the continuous seizure activity, allowing the brain to recover. The table provides a summary of antiepileptic drugs used to treat status epilepticus.

Children with status epilepticus should have EEG monitoring. This is critical if the child is given a paralytic agent, since ongoing brain status epilepticus can be detrimental even when there is no obvious clinical seizure activity due to the paralysis. In refractory status epilepticus EEG monitoring is necessary to assess the effectiveness of the midazolam or pentobarbital.

While trying to stop the status epilepticus is the primarily goal, the physician should also be evaluating the child for precipitating factors for the status epilepticus. The etiologies of status epilepticus are as varied as those of epilepsy in general. Most cases have a symptomatic etiology, although idiopathic cases can occur. Causes include nonspecific febrile illness, hypoxic-ischemic encephalopathy, infection, rapid drug withdrawal, trauma, and toxins. The etiology of the status epilepticus is the major determinant of the outcome.

KEY POINTS TO REMEMBER ABOUT STATUS EPILEPTICUS

- The longer status epilepticus persists, the more difficult it will be to stop.
- The airway must be protected and venous access must be achieved.
- Lorazepam is a first-line therapy for status epilepticus.
- The etiology of the status epilepticus is critical, since it is the primary factor in determining the outcome.

TABLE 27-1 **Drugs Used to Treat Status Epilepticus**

Drug	Intravenous Dosage
Diazepam	0.3–0.5 mg/kg (rectal or intravenous)
Lorazepam	0.1–0.15 mg/kg
Fosphenytoin	15–20 mg/kg phenytoin equivalents
Phenobarbital	15–20 mg/kg
Valproate	20–25 mg/kg
Midazolam	0.15-mg/kg bolus followed by a 1- to 5-µg/kg/min infusion
Pentobarbital	5-mg/kg loading dose, then a 1- to 3-mg/kg/hr continuous infusion

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28 Tethered Cord

You see a 6-year-old boy who is brought to your office by his parents, who are concerned about his gait. There are five other children in the family, and the parents have always noticed that this child's gait was more awkward than his siblings. The family says they were told by their pediatrician that the boy probably had a mild form of cerebral palsy.

In reviewing the history, you learn that the child had a normal birth and had normal early developmental milestones except for a delay in walking. He did not walk until age 18 months and did not run until 36 months. The parents noted that his legs were often stiff, as though he had Parkinson's disease. He was not able to compete in sports where running was required. Despite these problems, the parents felt he had been improving until the past few months, when they observed that he was having more difficulty walking and running. He began walking on his toes and complained of discomfort in his legs. On further questioning you learn that while he had previously been dry in the morning, recently he has been having accidents with enuresis.

On examination you find a delightful, bright 6-year-old child who volunteers that he has been having pain in his legs, pointing to his calves. The neurological examination reveals that he has normal cranial nerve function. His upper extremities were strong, with symmetrical deep tendon reflexes. Cerebellar function was measured by finger-to-nose and rapid alternating movements. In the lower extremities you find increased tone and 3+ reflexes. He had extensor plantar reflexes bilaterally. He walked on his toes and could not stand on his heels. Sensory examination revealed some patchy loss of pinprick sensation in his calves. Position and vibration sensation was normal.

What do you do now?

All the signs and symptoms in this child point to a spinal cord problem. The upper extremities demonstrate normal function and it would be difficult to place a lesion in the brain that would account for these neurological findings. It is always important to do a full examination when faced with this problem. When you examine the child's back you discover a dermal sinus in the sacral region surrounded by a small tuft of hair. You probe the sinus with a sterile Q-tip and find it extends approximately 5 mm. You immediately order a MRI of the lumbar spine.

A change in gait associated with pain and enuresis is concerning and requires prompt investigation. The fact that this child never walked normally suggests that this is a developmental abnormality. Further support for a spinal dysraphism abnormality of the spinal cord is the discovery of the dermal sinus.

A spinal cord tumor in the lumbar sacral region could account for the findings. The lack of a sensory level would argue against a tumor but would not rule it out totally. The history and constellation of findings would indicate that the child has a tethered spinal cord.

The spinal cord is said to be "tethered" when it is abnormally attached within the spinal canal. This can occur in spina bifida, when the cord attaches to scar tissue at the time of surgical closure of the spine, or in spina bifida occulta, where an outward defect is not readily apparent. A thickened filum terminale, a lipoma, a dermal sinus, or diastematomyelia (a bifid spinal cord) may anchor the conus medullaris to the base of the vertebrae (Figs. 28.1 and 28.2).

Dermal sinuses are often marked by a tuft of hair or skin discoloration. An abnormal invagination of ectoderm into the posterior closure site of the neural is responsible. As in this case, most sinuses terminate subcutaneously as a blind pouch or dermoid cyst. The cyst may extend into the dura of the spinal through the spina bifida.

Signs and symptoms of a tethered cord include changes in bowel control, incomplete emptying of the bladder, urinary tract infections, persistent back pain, increasing scoliosis, decreased sensation in the legs or feet, stumbling, toe-walking, and lower extremity weakness. A common presentation is of asymmetric talipes with a small foot, deficiency of specific muscles below the knees, loss of ankle jerks and sensory loss in the leg.

FIGURE 28-1 MRI of cord tethered to the lower sacral region. This 4-year-old had lower extremity spasticity and toe-walking.

FIGURE 28-2 MRI of spinal cord demonstrating a lipoma (hyperdense signal, *arrow*) that does not allow movement of the conus medullaris as the child matures. This MRI is from a 6-year-old with lower extremity weakness and back pain.

The neurological examination is somewhat variable. Children with only a clumsy gait or urinary control dysfunction typically have normal or exaggerated reflexes and extensor plantar responses. Children with more severe deficits have loss of reflexes and foot deformities. A neuropathic bladder is common.

The MRI is the appropriate diagnostic test and is very helpful in defining the anatomical abnormalities. Surgical correction of the tethering prevents further deterioration of neurological function and often reverses some of the deficits.

KEY POINTS TO REMEMBER ABOUT TETHERED CORD

- A progressive deterioration in gait requires an immediate investigation; cerebral palsy is a static condition and should not lead to increasing neurological impairment.
- Consider a tethered cord in children with deterioration in gait who have a dermal sinus.
- When evaluating the spinal cord for tumors or dysraphism, MRI is the imaging test of choice.
- Bladder function should be evaluated in all children with tethered cord.

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29 The Worster-Drought Syndrome

A four year old boy is taken to the emergency room with a series of episodes involving jerking and stiffening of the face, mouth and right arm. When you are called by the emergency room staff you are told that the history was complex and the child had numerous other problems.

Feeding was very slow from birth and nasogastric tube feeding was required for the first 4 months. Although slowly improving, at 4 years he was still taking a soft diet, not coping with solid food, and using his fingers to push food to the back of his mouth. He would often choke particularly on drinking. Weight gain was not adequate. He has persistent dribbling and jaw malocclusion. He had suffered recurrent otitis media and recurrent ear tubes. He had one-in patient admission because of pneumonia.

In the first year, he had unexplained excessive crying and his sleeping was poor. Gastro-oesophageal reflux was proven, but medical treatment was only partially effective. Speech was severely delayed and only a few rudimentary sounds had appeared. Comprehension,

however, was much better with the ability to respond to two simple, single-step instructions. Attempts at using signing were going slowly because of difficulties with motor organization and attention control.

Gross motor development was slow; walking at 2 years of age but still not having an effective run. The neurologist had found mild pyramidal signs and the MRI scan was normal but no unifying diagnosis was made. The parents said that they were exhausted and concerned by doctors' inability to give them adequate prediction of future progress. The appearance of epilepsy was for them the lowest point in their lives, they were now quite desperate.

What do you do now?

The seizures had stopped, but having had a cluster of unprovoked attacks it would be appropriate to start anti-epilepsy drug treatment. A review of the history taking the family through each of the elements of their child's disease indicates slow, but steady improvement to all areas affected. It is important to go through a typical day to understand the problems of sleep, self care and feeding. The best method of assessing feeding and drinking is to watch it–parents may under report what is a daily nightmare of force-feeding and choking.

The history is typical of the Worster-Drought Syndrome (WDS) otherwise known as bulbar cerebral palsy. Physical examination reveals an alert, irritable boy who was thin and small for his age. His mouth was open and tongue movements were restricted. The jaw jerk was brisk. The mild pyramidal signs in the limbs were confirmed.

WDS is a mild spastic tetraplegia in which the major motor burden falls upon the bulbar muscles. The cerebral cortical localization of the disorder is emphasized by the high rate of cognitive/psychiatric impairments (attention deficit/hyperactive disorder, autistic spectrum disorder, and non-specific problems with compliance) and epilepsy. The cardinal assessment finding is of speech being significantly poorer than comprehension and non verbal skills even in the context of a degree of global cognitive impairment. This requires careful assessment, but parents are usually fully aware of this development profile.

The differential diagnosis is of a progressive degenerative disease (e.g. peroxisomal disease) which may be uncertain in the first year of life, but the history eventually indicates slow improvement. Conditions with peripheral neuromuscular involvement have appropriate examination findings of pure weakness and absence of spasticity. They also usually lack central nervous system impairments. However, a subgroup of children with WDS has focal non-progressive loss of muscle and talipes. This patient illustrates the more severe end of the range of consequences of an upper motor neuron bulbar palsy (otherwise known as suprabulbar paresis or even 'pseudo bulbar palsy'). Early feeding difficulties predominate and may persist for years. The safety and adequacy of oral feedings needs to be regularly reviewed. Middle ear disease, secondary to Eustachian tube dysfunction and gastro-oesophageal reflux, is very common likely due to the loss of normal swallowing. Drooling is common and medical and surgical (salivary duct transposition) treatments

are used. However, drying the mouth is unwise because of the high rate of dental caries. Gastro-oesophageal reflux and incomplete protection of the airway increase the risk of lower respiratory infection.

The relatively specific speech delay or dysarthria in milder forms is critically important and early multi-disciplinary assessment should identify that the child has better skills than are represented by speech. Because of the additional motor and behavioural problems (often fulfilling criteria for attention deficit hyperactivity disorder or autism spectrum disorder) parents, care givers and child need a great deal of support to develop a communication system that suits the child's needs. This may involve specific behavioural treatments. The child may never develop effective speech. The MRI in this condition is usually normal.

This form of cerebral palsy has been markedly under-diagnosed and it seems likely that paediatric departments see such multiply impaired children. Work in the United Kingdom indicates that it is not a rare disorder but it is one of the most challenging to manage. The appearance of epilepsy after a few years is common and this has indicated a very close relationship to bilateral perisylvian polymicrogyria (BPPMG). The phenotypes of WDS and BPPMG seem identical although only about 20% of those clinically identified as WDS have BPPMG as acknowledged on MRI. There are families with more than one affected member who are discordant for identifiable MRI changes. This, with the cognitive, behavioral and Rolandic type seizures suggests a perisylvian localisation in those with currently normal MRI changes.

The likely timing of damage is around 12-16 weeks gestation. A number of patterns of inheritance have been described and after one affected child the recurrence rate is about 10%. Seizures can be associated with regression which usually includes worsening of the bulbar features of the phenotype.

The parental predicament and concern relate to the high rate of illness, the multiple types of illness and the threat to the child's quality of life and survival. The appearance of bulbar seizures may be what finally convinces the family that they are going to lose their child. A confident diagnosis, some literature, a support group and a comprehensive service can make a big impact despite the continuing problems with management.

Further Reading

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Index