FP Essentials™

523

December 2022

Childhood Neurologic Conditions

www.aafp.org/fpe

AAFP

FP Essentials™

ISSN# 2159-3000

FP Essentials is indexed in MEDLINE and PubMed.

Subscription Information

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Childhood Neurologic Conditions

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Fine A, Nickels K, Youssef P, Schupack KM. Childhood Neurologic Conditions. FP Essent. *2022;523:1-50.*

Foreword

When my youngest son was in high school, he was on the swim team. He told us that whenever he dived off the starting block at the beginning of a race, one hand and one leg would involuntarily spasm, slowing him down for the first few strokes. Since he was in the water by then, this was difficult to observe. However, he began to report that this involuntary movement was happening more frequently. He would get up from the dinner table and say, "There, it just happened again!" but I never had seen it clearly.

We consulted a pediatric neurologist, and the movements occurred when he was asked to move from a chair to the examination table. That was the first time I clearly observed his movement disorder, which turned out to be paroxysmal kinesigenic dyskinesia. This is a rare disorder with brief involuntary attacks that are triggered by voluntary movement.[1] Fortunately, his dystonia remains well-controlled with a low dose of carbamazepine (and he gave me permission to share his story with you).

This edition of *FP Essentials* provides updates on a range of childhood neurologic issues. I hope you find it useful in your practice. Section One provides guidance on the evaluation of a patient with a first childhood seizure. Key elements include determining whether the event was a seizure, and whether it was provoked or unprovoked.

Section Two focuses on management of epilepsy in children, including an overview of epilepsy types and a review of important antiseizure drugs. I particularly was interested to read about the benefits of a ketogenic diet in patients with pharmacoresistant epilepsy. The authors also provide helpful information on how to counsel family members and caregivers about seizure safety, first aid, and drugs for status epilepticus.

Section Three addresses movement disorders in children, with useful sections on the diagnosis and management of tic disorders (including Tourette syndrome), chorea, dystonia, ataxia, and others. Section Four covers neuroanatomic abnormalities that lead to abnormal head shape and size, including craniosynostosis, plagiocephaly, microcephaly, macrocephaly, and hydrocephalus.

When you have finished studying this edition of *FP Essentials* and are ready to submit your posttest answers, please tell us what was most useful and what we can do to improve. We look forward to hearing your ideas for topics you would like covered in future editions.

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University of Michigan Medical School, Ann Arbor

1. Manca D, Liyanaarachchi R, Starreveld E. Diagnosis and treatment of paroxysmal kinesigenic dyskinesia in a 15-year-old boy. *Can Fam Physician.* 2014;60(5):445-447.

Learning Objectives

- Determine whether an electroencephalogram or magnetic resonance imaging study is needed for a child with a first seizure.
- Discuss the diagnostic criteria for epilepsy in children.
- Describe seizure safety, use of rescue drugs, and anticipatory guidance for caregivers and family members of children with epilepsy.
- Screen for the associated conditions commonly found in children with tics and Tourette syndrome.
- Distinguish between craniosynostosis and positional plagiocephaly.
- Summarize the initial evaluation and diagnosis of microcephaly and macrocephaly in infants and children.
- Describe the signs of increased intracranial pressure in newborns, infants, and children with hydrocephalus that indicate the need for emergent referral to a neurosurgeon.

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Peer Reviewers

All manuscripts published in *FP Essentials* undergo peer review by subject matter experts and our editorial board members, a process that helps ensure the quality and clinical usefulness of our content. Below we acknowledge the individuals who performed those reviews for editions published in 2022. We offer our sincere thanks for the time and effort they devoted to the peer review process.

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Pretest Questions

To assess your current knowledge of this *FP Essentials* topic, complete the pretest below and check your answers against the explanations provided at the end. Use the results to inform your study of this edition and prepare to complete the posttest, which appears later in the edition and online for CME credit. Each question has only one correct answer.

1. Which one of the following statements about childhood seizures is correct?

- ☐ A. A seizure is considered status epilepticus if it is a generalized tonic-clonic (ie, convulsive) seizure lasting 5 minutes or longer.
- ☐ B. A seizure that occurs in an afebrile patient with hypoglycemia is considered an unprovoked seizure.
- ☐ C. Multiple provoked seizures are considered epilepsy.
- ☐ D. Febrile seizures occur in 8% to 10% of children between ages 6 months and 5 to 6 years.

2. Which one of the following seizure types in children is considered a neurologic emergency?

- ☐ A. Childhood absence epilepsy.
- ☐ B. Epileptic (infantile) spasms.
- ☐ C. Focal to bilateral tonic-clonic seizures.
- ☐ D. Juvenile myoclonic epilepsy.
- ☐ E. Temporal lobe epilepsy.

3. Which one of the following statements is true of antiseizure drugs?

- ☐ A. Carbamazepine primarily is used to manage absence seizures.
- ☐ B. Lamotrigine primarily is used to manage myoclonic seizures.
- ☐ C. Levetiracetam can cause mood or behavioral changes.
- ☐ D. Valproic acid is preferred for its safety during pregnancy.

4. Rescue drugs (eg, benzodiazepines) typically are not prescribed for out-of-hospital management of status epilepticus.

- ☐ A. True.
- ☐ B. False.

5. Hypokinetic movement disorders are relatively uncommon in childhood. Which one of the following is a type of hypokinetic movement disorder?

- ☐ A. Akinesia.
- ☐ B. Ataxia.
- ☐ C. Chorea.
- ☐ D. Dystonia.

6. Repetitive, nonpurposeful, rhythmic movements that demonstrate some degree of volitional control, such as flapping of the hands and arms, are categorized as which one of the following?

- ☐ A. Benign neonatal sleep myoclonus.
- ☐ B. Jitteriness.
- ☐ C. Shuddering.
- ☐ D. Stereotypies.

7. Which one of the following statements about craniosynostosis and positional plagiocephaly is correct?

- ☐ A. Approximately 50% of craniosynostosis cases are associated with an underlying genetic disorder (syndromic).
- ☐ B. The incidence of craniosynostosis is estimated to be approximately 1 case in 1,000 live births.
- ☐ C. Positional plagiocephaly is estimated to occur in 5% to 10% of infants age 6 months.
- ☐ D. Positional plagiocephaly can be confused with unilateral lambdoid craniosynostosis.

8. Which one of the following is true of microcephaly?

- ☐ A. It typically is identified when the head circumference measures 3 or more SDs below the mean.
- ☐ B. Symptomatic cytomegalovirus infection is associated with a 50% risk of microcephaly.
- ☐ C. It typically does not increase the risk of vision and hearing deficits.
- ☐ D. The most likely causes include rubella, varicella, and cytomegalovirus infection.

Pretest Answers

Question 1: The correct answer is A.
A seizure is considered status epilepticus if it is a generalized tonic-clonic (ie, convulsive) seizure lasting 5 minutes or longer, a focal seizure lasting 10 minutes or longer, or recurrent seizures without a return to baseline function in between. See page 8.

Question 2: The correct answer is B.
Epileptic (infantile) spasms constitute a neurologic emergency. See *Table 1*.

Question 3: The correct answer is C.
Adverse effects of levetiracetam include sedation, dizziness, and mood changes. Severe changes in behavior can occur, such as aggression, irritability, worsening of suicidal thoughts, and psychotic symptoms. See page 16.

Question 4: The correct answer is B.
Rescue drugs often are prescribed for out-of-hospital management. These are benzodiazepines, including lorazepam, diazepam, clonazepam, and midazolam, which are available in a variety of formulations. See page 18.

Question 5: The correct answer is A.
Hypokinetic movement disorders include akinesia, bradykinesia, and rigidity. See page 20.

Question 6: The correct answer is D.
Stereotypies are movements that are repetitive, nonpurposeful, rhythmic, and demonstrate some degree of volitional control. Common examples include head banging, rocking, jumping, or flapping of the hands and arms, often occurring when the child is excited or bored. See page 26.

Question 7: The correct answer is D.
Positional plagiocephaly is asymmetric deformation of the skull often caused by infant positioning or torticollis. This can be confused with unilateral lambdoid craniosynostosis. See page 27.

Question 8: The correct answer is D.
The infections most likely to cause microcephaly include rubella, toxoplasmosis, varicella, and cytomegalovirus and Zika virus infections. See page 32.

Key Practice Recommendations

These key learning points summarize the consensus- and evidence-based recommendations included in this edition. The sources listed here for each statement recommend that physicians perform or implement these actions directly in a clinical setting.

1. Perform an electroencephalogram during wakefulness and sleep as part of the evaluation of a child with a first unprovoked seizure.
   Evidence rating: SORT C
   Source: American Academy of Neurology, reference 6
   Website: https://n.neurology.org/content/55/5/616.long

2. Diagnose epilepsy in a child after at least two unprovoked seizures occur more than 24 hours apart, after one unprovoked seizure with a high likelihood of recurrence, or when criteria for an epilepsy syndrome are met.
   Evidence rating: SORT C
   Source: International League Against Epilepsy, reference 52
   Website: https://onlinelibrary.wiley.com/doi/10.1111/epi.12550

3. Children with epilepsy should undergo screening for associated conditions (eg, intellectual disability, learning disabilities, autism spectrum disorder, attention-deficit/hyperactivity disorder, depression, anxiety) as part of routine care.
   Evidence rating: SORT C
   Sources: *Epilepsy Behav*, *Nat Rev Neurol*, references 62 and 88
   Websites: https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S1525505020309173; https://www.nature.com/articles/nrneurol.2016.98

4. Urgently evaluate newborns, infants, and children with hydrocephalus who are symptomatic and show signs of increased intracranial pressure.
   Evidence rating: SORT C
   Source: *Pediatr Rev*, reference 202
   Website: https://publications.aap.org/pediatricsinreview/article/37/11/478/34935/

Strength of Recommendation Taxonomy (SORT)

Evidence Rating	Definition
A	▪ Recommendation based on consistent and good-quality patient-oriented evidence.[a]
B	▪ Recommendation based on inconsistent or limited-quality patient-oriented evidence.[a]
C	▪ Recommendation based on consensus, usual practice, opinion, disease-oriented evidence,[a] or case series for studies of diagnosis, treatment, prevention, or screening.

[a]*Patient-oriented evidence measures outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life. Disease-oriented evidence measures intermediate, physiologic, or surrogate end points that may or may not reflect improvement in patient outcomes (eg, blood pressure, blood chemistry, physiologic function, pathologic findings).*

(From Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy [SORT]: a patient-centered approach to grading evidence in the medical literature. Am Fam Physician. *2004;69:548-556.)*

SECTION ONE

Evaluation of a First Seizure

Seizure is one of the most common neurologic conditions in children, occurring most often in the first year of life. Identification of provoking factors, such as fever, illness, head trauma, electrolyte disturbance, or central nervous system infection, is important for determining prognosis and likelihood of recurrence. In patients presenting with a suspected first seizure, a history should be taken and a neurologic examination performed to determine whether the event was a seizure. If seizure is confirmed, it should be determined whether it was a first seizure and was provoked or unprovoked. The final step is to determine the cause. For children who present with simple febrile seizures, no additional evaluation typically is needed. An electroencephalogram performed during wakefulness and sleep is recommended for children with a first unprovoked seizure. For children with new-onset seizures, particularly focal seizures or status epilepticus, neuroimaging with magnetic resonance imaging study is recommended. Most children will have only a single seizure, whereas a small number will develop epilepsy. Risk factors for epilepsy development include a history of febrile seizures, status epilepticus, a family history of epilepsy, developmental delay, and abnormal neurologic examination results.

Case 1. CR is a 2-year-old boy with a history of recurrent otitis media who is brought to the emergency department after a seizure. His parents say he was not feeling well before the seizure. They report having heard a strange gurgling sound on the baby monitor, and when they checked, CR was having a convulsion that affected his whole body and lasted 2 minutes. CR currently is tired and fussy. The physical examination is notable for otitis media of the right ear and a fever of 102°F (38.9°C).

Epidemiology

The incidence of new-onset seizures in children ranges from 30 to 204 cases per 100,000 children per year, depending on the population examined.[1,2,3] The highest rates typically are seen during the first year of life, particularly during the neonatal period. The risk of seizures declines through childhood and adolescence until it reaches a nadir at approximately age 18 years. Boys are slightly more likely to have seizures than girls.[2,3]

Status epilepticus is a neurologic emergency that occurs in approximately 20 cases per 100,000 children per year.[4] It occurs when there is a failure of the mechanisms responsible for seizure termination, or the initiation of mechanisms that lead to abnormally prolonged seizures. A seizure is considered status epilepticus if it is a generalized tonic-clonic (ie, convulsive) seizure lasting 5 minutes or longer, a focal seizure lasting 10 minutes or longer, or recurrent seizures without a return to baseline function in between.[5]

Provoked Versus Unprovoked Seizures

Provoked seizures are those with an identifiable cause. One of the most common provoking factors in young children is fever. Other provoking factors can include intracranial infection, electrolyte disturbance, gastrointestinal illness, hypoglycemia, and traumatic brain injury.[6] Children who experience multiple provoked seizures, such as those who have recurrent febrile seizures, are not considered to have epilepsy unless they begin to experience unprovoked seizures.

In some children, provoked seizures may be the initial manifestation of an underlying epilepsy syndrome. One example would be an infant with prolonged febrile seizures in the setting of vaccination or illness, who shortly after seizure onset experiences developmental regression. This is concerning for a diagnosis of Dravet syndrome (ie, severe myoclonic epilepsy of infancy), which is a developmental and epileptic encephalopathy associated with intractable epilepsy with fever/illness-induced seizures and afebrile seizures, developmental regression, and significant morbidity and mortality.[7,8]

Febrile Seizures

Febrile seizures are the most common type of seizure that occurs in childhood, and occur in 2% to 5% of children between ages 6 months and 5 to 6 years.[9,10,11] Some children may experience only one febrile seizure, while others may have many. No additional evaluation typically is needed for children who present with simple febrile seizures.[12]

Several features qualify an event as a complex febrile seizure and indicate that a patient will require additional evaluation. These include signs of a focal seizure (ie, a seizure affecting one side or part of the body or starting in one limb and then spreading), longer duration (lasting

more than 10-15 minutes or febrile status epilepticus), or more than one febrile seizure in a 24-hour period.[13] Some children have an increased risk of febrile seizures due to a familial febrile seizure syndrome called genetic epilepsy with febrile seizures plus (GEFS+). This most commonly is attributable to a sodium channelopathy (*SCN1A*, *SCN2A*, *SCN1B*).[14]

Case 1, cont'd. The neurologic examination results are normal, with no postictal deficits. CR's father had recurrent febrile seizures in early childhood, which resolved with age. CR has had normal development without concerns about delays. His parents want to know if CR will ever experience another seizure.

Risk Factors for a First Seizure

Risk factors for a first unprovoked seizure include a history of perinatal complications, previous neonatal seizures, central nervous system infection, head trauma, febrile seizures, developmental delay, and a family history of epilepsy.[15,16,17] Specific risk factors for febrile seizures, based on the results of a matched case-control study, include a history of febrile seizure in a first-degree relative and the height of the fever temperature.[17]

Classification

There have been multiple iterations of classifications of seizures and epilepsies, with the most recent classification created by the International League Against Epilepsy (ILAE) in 2017.[18,19] Seizure classification is based on the clinical presentation (*Table 1*) and electroencephalographic features. In most instances, it is helpful to describe the main features of the seizures rather than rely on older terms, such as grand mal or petit mal, which can have different definitions.

Nonepileptic Events and Seizure Mimics

It can be challenging for clinicians and caregivers to distinguish between epileptic seizures and nonepileptic events. Some events tend to occur at specific ages, such as breath-holding spells in infants and young children or vasovagal syncope in adolescents (*Table 2*).[20] Accurate seizure classification is critical for next diagnostic steps and

TABLE 1
Common Seizure Features in Children

Features	Classification and Potential Syndromes	Distinguishing Factors
Staring spells, behavioral arrest	Generalized absence Childhood absence epilepsy Juvenile absence epilepsy	Brief (seconds), very frequent (many per hour), no postictal period
	Focal impaired awareness Temporal lobe epilepsy	Seconds to minutes, no recollection, may have automatisms, has a postictal period
Clonic jerking of face, arm, trunk, and/or leg	Focal motor seizures (with retained or impaired awareness)	Repeated, rhythmic jerks that can affect one or more areas, can progress with a jacksonian march
Generalized convulsion	Generalized tonic-clonic	Generalized stiffening at onset with rhythmic jerking of the extremities
	Focal to bilateral tonic-clonic	Starts at onset as focal seizure with evolution to bilateral tonic-clonic seizure, often asymmetric
Rapid muscle jerks affecting one or more areas	Myoclonic seizures Juvenile myoclonic epilepsy	Involuntary rapid jerks of the body or extremities without impaired awareness
Rapid flexor or extensor spasms of the trunk	Epileptic (infantile) spasms	Repeated clusters of spasms, can occur hundreds of times per day, developmental regression with continued spasms, constitute a neurologic emergency

Information from Fine A, Wirrell EC. Seizures in children. Pediatr Rev. *2020;41(7):321-347; Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology.* Epilepsia. *2017;58(4):512-521.*

TABLE 2
Select Conditions That Can Mimic Seizures in Children

Neonatal onset	
Benign neonatal sleep myoclonus	Rapid jerks of one or more limbs or the face, lasting several seconds with variable pause in between
	Occurs in sleep
	Can continue into infancy and early childhood
Infant onset	
Shuddering attacks	Brief stiffening and shivering with retained awareness
	Can occur more often when excited or frustrated
	Can occur in neurotypical infants
Breath-holding spells	Can start with crying or immediate breath-holding with stiffening
	Occur in setting of pain, minor injury, frustration, crying
	Color change typically seen (pallid or cyanotic)
Sandifer syndrome	Episodes of back arching, posturing of the limbs, with head turn or retroflexion
	Temporal relationship to feeding
	Often provoked by laying the infant flat
Infantile gratification syndrome (benign idiopathic infantile dyskinesia, infantile masturbation)	Repeated episodes of stiffening, posturing, rocking, grunting, flushing, sweating
	Interruptible
	Variable frequency and duration
	Child may be referred for seizure evaluation
Stereotypies	Rocking, head banging, or complex finger and hand movements
	Occur when the child is excited or anxious
	Interruptible, no loss of awareness
	Can be seen in neurotypical children
	More common in children with autism spectrum disorder
Childhood onset	
Parasomnias	Behaviors occurring in sleep (eg, sleepwalking, sleep talking, night terrors, confusional arousals)
	Can last 10-15 min
	Child may be unresponsive or partially responsive
Tics	Sudden, repetitive movements or sounds
	Occur multiple times per day
	Interruptible and partially suppressible
	Premonitory urge
Childhood and adolescent onset	
Panic attacks	Sudden, brief episodes with feeling of impending doom, shortness of breath, globus sensation, chest pain, paresthesia, dizziness, lightheadedness
	Immediate return to baseline
Vasovagal syncope	Sudden loss of tone or tonic posturing with pallor
	Prodrome of lightheadedness, sweating, tinnitus, blurred vision followed by loss of tone
	Induced by prolonged standing, dehydration, hair-combing, rapid position change, blood draws
Psychogenic nonepileptic spells	Recurrent, refractory, and often prolonged
	Variable semiology
	Minimal postictal period
	Do not respond to antiseizure drugs

Note: Seizure semiology is the clinically observed behavioral, motor, sensory, or other signs that occur in a pattern or sequence as a seizure begins and evolves, reflecting the activation or dysfunction of areas of the brain.

Information from Stephenson JBP, Zuberi S. Nonepileptic seizures and similar phenomena in children and adolescents. In: Kaplan PW, Fisher RS, eds. Imitators of Epilepsy. *2nd ed. New York: Demos Medical Publishing Inc; 2005:89-110; DiMario FJ Jr. Paroxysmal nonepileptic events of childhood.* Semin Pediatr Neurol. *2006;13(4):208-221; Fine A, Wirrell EC. Seizures in children.* Pediatr Rev. *2020;41(7):321-347.*

in guiding management. It often is helpful if caregivers can record video of these events.[6,21,22]

Psychogenic Nonepileptic Seizures

Psychogenic nonepileptic seizure (PNES) is a type of seizure that should be identified early to prevent delays in care. These seizures are not due to abnormal electrical signals from the brain but still can result in significant disability. Other terms for these seizures include dissociative seizures, functional seizures, pseudoseizures, or stress-induced seizures.[23]

Some terms commonly used to describe these seizures, such as conversion disorder, hysterical spells, or psychosomatic spells, can be offensive to patients and families.[24,25] However, it is important that clinicians use a descriptive term for what is occurring, whether they refer to these as spells, events, or episodes. The author uses the terms *functional spells* and *functional neurologic disorder* when discussing this condition with patients and families.[23]

Making an accurate and timely diagnosis is critical to prevent unnecessary drug trials and testing.[26,27] This can be challenging but specific features can help distinguish between epileptic seizures and nonepileptic events (*Table 3*).[28,29] Cognitive behavioral therapy is recommended for management of PNES.[30]

Evaluation

Most children with a suspected first seizure are taken to an emergency department, urgent care, or primary care office. The American Academy of Neurology (AAN) Practice Parameter: Evaluating a First Nonfebrile Seizure in Children recommends that in all settings a detailed history be taken and a neurologic examination performed to help determine whether the event was a seizure. If an event is found to be a seizure, the physician should determine whether it was a first seizure and was provoked or unprovoked. The final step in evaluation is to determine the cause.[6]

HISTORY

Depending on the information available, it may be challenging to confirm whether an event was a seizure. If the event was witnessed, it can be beneficial to have the witness recount the event and physically act out what occurred. According to the AAN practice parameter, key features to assess include preceding symptoms or auras, level of awareness and responsiveness, loss of tone, eye movements, motor activity (including the rhythmicity and progression of activity), bowel and bladder incontinence, oral injury, and postictal

Table 3
Differentiating Features of Epileptic Seizures and Psychogenic Nonepileptic Seizures

Feature	Epileptic Seizure	Nonepileptic Seizure
Frequency	Rare to frequent	Tend to be frequent
Location and timing	Any setting	School or home
	Diurnal, nocturnal	Diurnal
Triggers	Stress, sleep deprivation, illness	Stress
Duration	Brief	Prolonged
Stop and start quality	Absent	Present
Eyes	Open	Closed
Semiology:		
Hip thrusting	Absent	Present
Side-to-side head movements	Absent	Present
Odd movements or behaviors	Absent[a]	Present
Variability in semiology	Absent	Present
Postictal period	Present	Absent
Other features:		
Tongue biting	Lateral	Frontal or absent
Loss of bowel or bladder control	Present or absent	Present or absent
Severe injury	Can occur	Usually absent or minor
Witnesses	Present or absent	Nearly always present

Note: Seizure semiology is the clinically observed behavioral, motor, sensory, or other signs that occur in a pattern or sequence as a seizure begins and evolves, reflecting the activation or dysfunction of areas of the brain.

[a]If there is a history of stereotyped arousals from sleep with hypermotor activity or odd behavior, consider nocturnal frontal lobe seizures.

Information from Mostacci B, Bisulli F, Alvisi L, Licchetta L, Baruzzi A, Tinuper P. Ictal characteristics of psychogenic nonepileptic seizures: what we have learned from video/EEG recordings—a literature review. Epilepsy Behav. *2011;22(2):144-153; Devinsky O, Gazzola, D, LaFrance WC Jr. Differentiating between nonepileptic and epileptic seizures.* Nat Rev Neurol. *2011;7(4):210-220.*

state. Postictal deficits, such as hemiparesis (Todd paralysis), are a sign of focal seizure and may aid in localization.[6]

As much information as possible should be obtained from the patient about what they can recall of the event. Young children, even as young as age 3 years, often can provide important details when asked, such as what they remember before the seizure, whether they saw, felt, or heard anything abnormal, and whether they have experienced this before. For children who are nonverbal or too young to provide much information, it is helpful to ask the witness about behavior changes before the seizure, such as sudden fear or distress.

EMERGENCY DEPARTMENT

Patients presenting to the emergency department are likely to have more severe manifestations. The AAN practice parameter recommends that the first steps for these patients be stabilization and confirmation that the event has ceased before proceeding with the rest of the evaluation.[6]

Depending on the individual clinical circumstances, it may be reasonable to obtain blood glucose and electrolyte levels, including sodium, calcium, and magnesium, particularly if the patient has had a recent gastrointestinal illness.[6] There is some evidence to suggest that sodium levels should be obtained in children younger than 6 months, as hyponatremia is common in this age group.[31]

If the event occurred in the setting of head injury, then emergent imaging with computed tomography (CT) scan to assess for intracranial bleeding is indicated. Other clinical situations in which CT scan can be helpful include suspected stroke and brain tumor. Additional investigations should be tailored to the clinical scenario, such as lumbar puncture in a patient with new seizures and meningism or toxicology if there is concern about ingestion of a toxic substance.[6]

OUTPATIENT SETTING

For patients presenting to outpatient settings, such as a primary care office, the evaluation should start with a detailed history and neurologic examination.[6] If a child presents for evaluation of staring spells and absence seizures are suspected, then an in-office trial of 3 to 5 minutes of hyperventilation could induce an absence seizure.[32,33,34] Some methods to induce hyperventilation include asking children to repeatedly blow on a pinwheel or pretend to blow bubbles.

Advanced Diagnostics

ELECTROENCEPHALOGRAM

The AAN practice parameter recommends that an electroencephalogram (EEG) be performed during wakefulness and sleep for a child with a first unprovoked seizure.[6] An EEG performed shortly after a seizure can identify epileptiform abnormalities, which can be helpful in guiding management.[35]

Because up to 3% of healthy children can have epileptiform abnormalities on EEG and approximately 10% of patients with epilepsy can have a normal interictal EEG, correlation with the patient history is critical for clinical interpretation.[36,37] The incidence of abnormalities on EEG is higher in children with a history of autism spectrum disorder and attention-deficit/hyperactivity disorder.[38,39]

Hyperventilation and photic stimulation (ie, use of a repeated series of light flashes delivered via strobe) can be useful in identifying an underlying epilepsy syndrome. Examples include hyperventilation-induced absence seizures in childhood absence epilepsy, and a photoparoxysmal response and myoclonic seizures during photic stimulation in an adolescent with juvenile myoclonic epilepsy.[40]

NEUROIMAGING

For children with new-onset seizures, particularly focal seizures or status epilepticus, the AAN practice parameter and American College of Radiology (ACR) Appropriateness Criteria for child seizures recommend that neuroimaging with magnetic resonance imaging (MRI) study be obtained.[6,41] MRI study is more effective than CT scan for identification of cortical malformations.[41] However, CT scan is appropriate if concerns exist about an acute intracranial process, such as tumor, stroke, hemorrhage, or abscess or other infection.[6,41]

The ACR Appropriateness Criteria for child seizures include more detailed guidelines that can help determine whether neuroimaging is needed, and, if so, which type of imaging is appropriate.[41] Imaging may not be needed for children with a clinical history and EEG findings suggestive of a self-limited focal epilepsy of childhood, such as self-limited epilepsy with centrotemporal spikes (SeLECTS).[6,42]

Referral

In some areas, access to consultation with a pediatric neurologist can be limited, so appropriate identification and triage are important in determining which patients need referral. Children with recurrent unprovoked seizures, prolonged seizures, recurrent focal seizures, complex febrile seizures, or abnormal neuroimaging findings should be referred to a pediatric neurologist. Such referral also may be warranted for children with unexplained developmental delays, seizures, or physical examination findings concerning for an underlying genetic etiology (*Table 4*).

Vaccinations and Seizures

The safety of vaccinations in children who have had seizures is a frequent concern. Several vaccines and vaccine combinations have been associated with a small increased risk of febrile seizures, but there is no evidence that vaccination increases the risk of subsequent seizures or the development of epilepsy.[43,44,45]

In a study that used data from the Centers for Disease Control and Prevention (CDC) Vaccine Safety Datalink (VSD) project, the diphtheria-tetanus-pertussis (DTP) vaccine was found to be associated with an increased risk of febrile seizures on the day of administration, with approximately 6 to 9 additional febrile seizures per 100,000 children vaccinated. The measles-mumps-rubella (MMR) vaccine was associated with an increased risk of febrile seizures at 8 to 14 days postvaccination, with approximately 25 to 34 additional febrile seizures per 100,000 children vaccinated.[45]

One study compared infants who received the quadrivalent measles, mumps, rubella, and varicella (MMRV) vaccine with those who received separate MMR plus varicella vaccines. It showed an additional risk of febrile seizures at 7 to 10 days after MMRV administration of 4.3 seizures per 10,000 doses.[46]

In some children, vaccine-associated seizures may be the first manifestation of an underlying epilepsy syndrome. In retrospective series evaluating the relationship between postvaccination febrile seizures and underlying epilepsy, 52% to 58% of vaccine-associated seizures were found to represent the initial manifestation of a severe childhood epilepsy.[47,48]

Children with seizures and epilepsy should receive recommended vaccinations,[49] including influenza and COVID-19 vaccinations. The harms of vaccine-preventable illnesses outweigh the potential risks of vaccination.

TABLE 4
Physical Examination Findings Suggestive of Underlying Genetic Disorders

Body Area	Findings	Potentially Associated Conditions
Skin	Port-wine stain	Sturge-Weber syndrome
	Hypopigmented macules (ash leaf spots)	Tuberous sclerosis complex
	Facial angiofibromas (often malar distribution)	Tuberous sclerosis complex
	Café au lait macules (hyperpigmented macules)	Neurofibromatosis (*NF1* > *NF2*)
Eye	Optic nerve pallor	Septo-optic dysplasia (multiple potential causes)
	Iris coloboma	Multiple genetic disorders
	Glaucoma	Sturge-Weber syndrome
		Multiple disorders
Head/face	Macrocephaly	Multiple genetic disorders (eg, tuberous sclerosis complex, neurofibromatosis)
	Microcephaly	Multiple genetic disorders (eg, Angelman syndrome, Williams syndrome)
	Coarse facial features	Multiple genetic and metabolic disorders (eg, mucopolysaccharidoses, gangliosidoses)
Abdomen	Hepatosplenomegaly	Multiple metabolic disorders

Information from Rosser T. Neurocutaneous Disorders. Continuum (Minneap Minn). *2018;24(1, Child Neurology):96-129; Swaiman KF, Phillips J. Neurologic examination after the newborn period until 2 years of age. In: Swaiman KF, Ashwal S, Ferreiro DM, et al, eds.* Swaiman's Pediatric Neurology: Principles and Practice. *6th ed. Elsevier: 2017:e21-e38.*

Risk of Recurrence and Evolution to Epilepsy

AFEBRILE SEIZURES

Most unprovoked seizures are isolated events. The likelihood of recurrence is highest within the first 1 to 2 years after the initial seizure. Approximately 90% of recurrences happen within 2 years of the initial seizure,[15] and many reoccurrences happen within 6 months of the initial seizure.[50,51] After a second unprovoked or afebrile seizure, the likelihood of additional seizures continues to increase.

In one long-term prospective study, the risk of a second seizure was found to be approximately 29% at 1 year, 37% at 2 years, and 43% at 5 years. The cumulative risk increased with each subsequent seizure, with a risk of a third seizure of 71% at 5 years. This study showed

that among children who had multiple seizure recurrences, 10% experienced 10 seizures or more.[16]

Risk factors associated with an increased risk of subsequent seizures include a symptomatic etiology, such as a previous traumatic brain injury or neonatal stroke; abnormal neurologic examination results; or epileptiform abnormalities on EEG. Epilepsy may be diagnosed after at least two unprovoked seizures occur more than 24 hours apart, after one unprovoked seizure with a high likelihood of recurrence, or when epilepsy syndrome criteria are met.[52]

FEBRILE SEIZURES

Approximately one-third of children who experience a febrile seizure will have a second febrile seizure, with most recurrences within 1 year. A smaller number will have a third febrile seizure, and so on.[53,54]

Risk factors for recurrence include earlier age at onset (ie, younger than 12-18 months), a family history of febrile seizures, associated low-grade fever, or febrile seizure heralding the illness.[53,54] The risk of recurrence is not affected by the first febrile seizure duration or whether it was complex versus simple. However, if the initial seizure was prolonged, there is a greater likelihood that subsequent seizures will be prolonged.[55]

Among children with febrile seizures, the risk of developing epilepsy is estimated at 2% to 5%, compared with a 1% risk in the general population.[56] The most significant risk factors for epilepsy development are developmental delay, abnormal neurologic examination results, a history of complex febrile seizures (particularly febrile status epilepticus), and a family history of epilepsy.[57] Febrile status epilepticus can be associated with hippocampal injury resulting in mesial temporal sclerosis, which can provide an epileptogenic focus for future seizures.[58,59]

For children with previous prolonged febrile seizures, caregivers may be provided with a prescription for a rescue drug, such as a buccal, nasal, or rectal benzodiazepine (*Table 5*).[60,61] This particularly should be considered if the patient and family live a significant distance from medical care.[60]

Case 1, cont'd. You tell CR's parents that approximately one-third of children with a febrile seizure will have a second febrile seizure. You advise them that CR does not require antiseizure drugs, and that treatment does not alter the possibility of later development of epilepsy. You review seizure safety and discuss the natural history of febrile seizures. You tell his parents that fever reducers such as aspirin will not reduce the risk of recurrent febrile seizures, but should be used to manage fever. You advise them that if febrile seizures appear to start or occur on one side of the body, or if CR is not able to move one side of the body after a seizure, then he will need additional evaluation and referral to a pediatric neurologist.

TABLE 5
Drugs Commonly Used to Manage Acute Seizures or Status Epilepticus in Children

Drug	Formulation	Adverse Effects
Clonazepam	Tablet, oral disintegrating tablets	Dizziness, drowsiness, unsteadiness, impaired attention and memory, irritability, hyperactivity, drooling, depression, nausea Serious adverse effects: hypersensitivity reactions
Diazepam	Rectal gel, oral solution, intranasal spray	Dizziness, headache, unsteady gait, behavior change, poor coordination Serious adverse effects: breathing problems, central nervous system depression, suicidality
Lorazepam[a]	Tablet, oral solution	Dizziness, poor coordination, fatigue, blurred vision, behavior change Serious adverse effects: hypersensitivity reactions, shortness of breath, hallucinations, suicidality
Midazolam[b]	Intranasal spray	Sedation, headache, nasal discomfort Serious adverse effects: heart and breathing problems, central nervous system depression, suicidality

[a]*Use of this drug in children is off-label.*

[b]*Use of this drug in children younger than 12 years is off-label.*

Information from Epilepsy Foundation. Seizure medication list. https://www.epilepsy.com/tools-resources/seizure-medication-list

SECTION TWO

Epilepsy Management

Epilepsy is the most common neurologic condition in children and is characterized by recurrent unprovoked seizures. Epilepsy can be diagnosed after a first unprovoked seizure if characteristic clinical and electroencephalographic features suggest a high risk of future seizures. Epilepsy is classified based on seizure type, underlying causes, and potential electroclinical syndromes. This classification guides management and predicts its effectiveness. Some epilepsy syndromes resolve spontaneously (ie, are self-limited) or improve with management (ie, are pharmacoresponsive). Syndromes that contribute to intellectual disability, referred to as developmental and epileptic encephalopathies, are not self-limited, are unlikely to improve with management (ie, are pharmacoresistent), and are associated with poor long-term outcomes. Antiseizure drugs are the mainstay of epilepsy management. Some broad-spectrum drugs are used to manage multiple seizure types, and others have indications for specific seizure types or epilepsy syndromes. Dietary therapy, surgical resection, and neuromodulation may be options if drugs do not control seizures. Neurodevelopmental and mental conditions are common in children with epilepsy. These include intellectual disability, learning disabilities, autism spectrum disorder, attention-deficit/hyperactivity disorder, depression, and anxiety. Patients with epilepsy should undergo screening for these associated conditions as part of routine care. Physicians should instruct caregivers and family members on how to manage seizures, including use of rescue drugs.

Case 2. JH is a 3-year-old girl who is brought to the emergency department by her parents after she has a 2-minute generalized tonic-clonic seizure. JH has a history of two simple febrile seizures but currently has no symptoms of illness and is afebrile. Her father and older brother had febrile seizures that resolved before age 2 years; a paternal aunt takes a drug to manage generalized epilepsy. JH is otherwise healthy, with normal growth and development. Neurologic examination results are normal.

Epilepsy is the most common neurologic condition in children, and affects approximately 1% of children in the United States.[62] It is characterized by recurrent unprovoked seizures.[52]

Most often, a diagnosis of epilepsy is not made after a first unprovoked seizure because less than half of children have seizure recurrence.[52,15] However, a diagnosis of epilepsy can be made after a first unprovoked seizure if other features suggest that the patient is at high risk of additional seizures.[52] Electroencephalogram (EEG) results are the most important predictor of outcome. Epileptiform abnormalities on EEG are significantly associated with seizure recurrence.[15,52]

Case 2, cont'd. This is JH's first unprovoked seizure; the previous two were febrile seizures. A routine electroencephalogram performed during wakefulness and sleep shows generalized epileptiform discharges. Therefore, a diagnosis of epilepsy can be made with this seizure. The family history of seizures and the history of febrile seizures are factors that increase the risk of seizure recurrence for JH.

Epilepsy Types

Epilepsy is classified on multiple levels. Seizure onset can be focal, generalized, or unknown.[63] Similarly, seizures are classified as focal seizures, generalized seizures, combined generalized and focal seizures, or unknown.[18,19] The underlying cause can be structural, genetic, metabolic, infectious, autoimmune, or unknown.[19] Approximately one-third of epilepsies can be classified further as specific electroclinical syndromes, which is helpful to determine management and anticipate possible associated conditions and outcomes.[2]

Some epilepsy syndromes resolve spontaneously (ie, are self-limited) or improve with management (ie, are pharmacoresponsive). These syndromes are less likely to significantly affect long-term child development. In contrast, electroclinical syndromes typically significantly affect development, and are referred to as developmental and epileptic encephalopathies. These syndromes are not self-limited and are unlikely to improve with antiseizure drugs (ie, are pharmacoresistant).[19]

Management

Antiseizure drugs are the mainstay of epilepsy management. It is important to recognize that epilepsy is a chronic neurologic condition. Pharmacotherapy helps to control seizures but does not resolve epilepsy.

Antiseizure drugs are classified as drugs that are useful in management of focal seizures, broad-spectrum drugs for management of multiple seizure types, and drugs with indications for specific seizure types or epilepsy syndromes.

Although broad-spectrum drugs can be used to manage all seizure types, drugs indicated only for management of focal seizures have the potential to exacerbate generalized seizures. For example, carbamazepine is indicated for management of focal seizures and generalized tonic-clonic seizures but can exacerbate absence seizures.[64]

The first antiseizure drug is effective in controlling seizures in approximately 60% of children. Among children who have not benefited from three antiseizure drug regimens, only 10% will experience seizure control for more than 1 year.[65]

Pharmacotherapy

Table 6 lists select drugs used to manage seizures in children. It includes indications and adverse effects. Some of these drugs are discussed in greater detail here.

ETHOSUXIMIDE

Ethosuximide is Food and Drug Administration (FDA)-approved only for management of absence seizures in children 3 years and older.[66] Therefore, ethosuximide typically is insufficient for patients with other seizure types in addition to absence seizures. Possible adverse effects include rash, dizziness, lethargy, fatigue, sleep disturbance, mood disturbance, gastrointestinal upset, agranulocytosis, pancytopenia, and Stevens-Johnson syndrome.[66]

VALPROIC ACID

Valproic acid is FDA-approved for management of multiple types of focal and generalized seizures.[67] It is as effective as ethosuximide for controlling absence seizures and is a preferred drug for management of generalized tonic-clonic and myoclonic seizures.[68,69] Adverse effects include gastrointestinal upset, somnolence, tremor, weight gain, alopecia, and psychiatric disturbance.[67] (Valproic acid is not approved for use in children younger than 10 years.)

There are multiple safety warnings for valproic acid, including warnings about hepatoxicity, pancreatitis, and teratogenicity. Use of valproic acid is contraindicated in patients with some metabolic disorders, such as urea cycle disorders, and in patients with significant hepatic dysfunction.[67]

Major congenital malformations have been reported in 31% of infants with prenatal exposure to valproic acid, including cardiac defects, neural tube defects, hypospadias, and oral clefts, even when used in low doses (ie, less than 700 mg/day). Cognitive issues have been shown to occur in children born to women taking valproic acid during pregnancy.[70] Because more than 50% of pregnancies in women with epilepsy are unplanned,[71] use of valproic acid should be avoided in patients who could become pregnant.[70]

LAMOTRIGINE

Lamotrigine is a first-line drug for management of absence seizures and generalized tonic-clonic seizures, and is a preferred drug for focal seizures.[68,69,72,73] However, it may worsen myoclonic seizures.[74] It typically is well-tolerated but potential adverse effects include headache, dizziness, blurred vision, and nausea.[75] There is a risk of serious rash and Stevens-Johnson syndrome but a slow dosage titration schedule (ie, over 8-12 weeks) decreases this risk.[76]

Concurrent use of valproic acid more than doubles the elimination half-life of lamotrigine and increases the risk of Stevens-Johnson syndrome. Some hormonal contraceptives significantly increase the metabolism of lamotrigine, which decreases serum levels.[74,77]

LEVETIRACETAM

Levetiracetam is approved for management of myoclonic, generalized tonic-clonic, and focal seizures, and is a preferred drug for focal seizures.[69,78] Adverse effects include sedation, dizziness, and mood changes. Severe changes in behavior can occur, such as aggression, irritability, worsening of suicidal thoughts, and psychotic symptoms. Drug interactions are rare.[78]

OXCARBAZEPINE

Oxcarbazepine is approved for management of focal epilepsy and is a preferred drug in children.[79] It typically is well tolerated. However, oxcarbazepine can worsen absence seizures.[69] Hyponatremia has been reported, with sodium levels as low as less than 125 mEq/L, which often is asymptomatic. Other adverse effects include dizziness, double vision, headache, fatigue, tremor, and nausea.[79] (The safety and efficacy of oxcarbazepine have not been established in children younger than 2 years)

Severe dermatologic reactions can occur, including Stevens-Johnson syndrome and drug reaction with eosinophilia and systemic symptoms (DRESS)/multiorgan hypersensitivity.[79] There is rash cross-sensitivity among certain antiseizure drugs. Patients who developed rashes with other antiseizure drugs developed rashes with oxcarbazepine as well.[80]

CARBAMAZEPINE

Carbamazepine is similar to oxcarbazepine and is FDA-approved to manage focal and generalized convulsive (ie, tonic-clonic) seizures.[64] However, carbamazepine can worsen absence seizures.[69] Adverse effects include blurred vision, dizziness, headache, nausea, fatigue, hypersensitivity reactions, blood disorders, and liver problems.[64]

Carbamazepine can be associated with Stevens-Johnson syndrome, as well as toxic epidermal necrolysis. Patients

Table 6
Select Drugs Used to Manage Seizures in Children

Drug	Indications/Conditions	Adverse Effects/Comments
Cannabidiol	Seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, tuberous sclerosis complex	Fatigue, decreased appetite, diarrhea, sleep disturbance Serious adverse effects: hypersensitivity reactions, liver problems, somnolence, suicidality
Carbamazepine	Focal, generalized tonic-clonic	Blurred vision, dizziness, headache, nausea, fatigue, hypersensitivity reactions, blood disorders, liver problems Serious adverse effects: Stevens-Johnson syndrome, toxic epidermal necrolysis, suicidality Can exacerbate absence seizures
Divalproex sodium-valproic acid[a]	Focal, generalized	Fatigue, slowed thinking, dizziness, gastrointestinal upset, tremor, alopecia, weight gain, psychiatric disturbance Serious adverse effects: hypersensitivity reactions, liver failure, blood clotting disorder
Ethosuximide[b]	Absence, atypical absence	Gastrointestinal upset, dizziness, lethargy, rash Serious adverse effects: Stevens-Johnson syndrome, agranulocytosis, pancytopenia, hallucinations, suicidality
Lacosamide	Focal, generalized convulsive	Fatigue, dizziness, double vision, nausea, headache, arrhythmias Serious adverse effects: hypersensitivity reactions, low white blood cell count, suicidality
Lamotrigine	Focal, generalized (absence)	Dizziness, nausea, headache, double vision, allergic rash Serious adverse effects: Stevens-Johnson syndrome, hemophagocytic lymphohistiocytosis, suicidality Can exacerbate myoclonic seizures
Levetiracetam	Focal, generalized (myoclonic)	Dizziness, headache, irritability, fatigue, sedation, hypersensitivity reactions Serious adverse effects: changes in behavior, mood, or thoughts; suicidality
Oxcarbazepine[c]	Focal	Dizziness, double vision, headache, hyponatremia, fatigue, tremor, nausea Serious adverse effects: hypersensitivity reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis; hyponatremia; suicidality
Topiramate[c]	Focal, generalized	Fatigue, decreased concentration, word retrieval problems, dizziness, decreased appetite Serious adverse effects: glaucoma, kidney stones, metabolic acidosis, inadequate sweating
Zonisamide[d]	Focal, generalized	Fatigue, dizziness, decreased appetite, nausea, poor concentration, headache, irritability Serious adverse effects: hypersensitivity reactions, kidney stones, insufficient sweating, depression, psychosis

[a]Use of this drug in children younger than 10 years is off-label.

[b]The safety and efficacy of this drug have not been established in children younger than 3 years.

[c]The safety and efficacy of this drug have not been established in children younger than 2 years.

[d]Use of this drug in children and adolescents ages 1 to 15 years is off-label.

Information from Epilepsy Foundation. Seizure medication list. https://www.epilepsy.com/tools-resources/seizure-medication-list

with the *HLA-B*1502* allele are more likely to develop these, and should not take carbamazepine.[64]

LACOSAMIDE

Lacosamide is approved for management of focal seizures and generalized tonic-clonic seizures. Adverse effects include fatigue, dizziness, double vision, nausea, headache, and heart rhythm problems.[81]

Case 2, cont'd. You recommend daily antiseizure drugs for JH. You review drug options and potential adverse effects with her family members and counsel them on seizure safety.

Seizure Safety, Rescue Drugs, and Anticipatory Guidance

Seizures are frightening for parents and are responsible for 1% to 2% of all emergency department visits.[82] Many parents fear their children will die as a result of a seizure. Although sudden unexpected death in epilepsy and other epilepsy-related deaths occur, the risk of this in children is low — approximately 43 deaths per 100,000 person-years.[83]

It is essential for caregivers and family members to know how to manage a seizure and a prolonged seizure. Most children with seizures will need a seizure action plan for school that outlines actions to be taken during a seizure and during status epilepticus, and defines what constitutes a seizure emergency.

Physicians should review with caregivers and family members steps to take during a seizure, such as placing the child on their side during convulsive seizures.

Physicians should review with caregivers and family members steps to take during a seizure, such as placing the child on their side during convulsive seizures to help prevent aspiration during vomiting or excessive salivation. The child should not be restrained, and nothing should be placed in the child's mouth. Caregivers should stay calm during the seizure and time the duration. They should call emergency medical services if the seizure lasts more than 5 minutes, if the child is not breathing, if the child remains unresponsive for an unusual length of time, or if there are other concerns.[84]

Up to 10% of children with epilepsy will experience status epilepticus.[85] Rescue drugs often are prescribed for out-of-hospital management. These are benzodiazepines, including lorazepam, diazepam, clonazepam, and midazolam, which are available in a variety of formulations.[86] (Status epilepticus in children and adolescents is an off-label use of lorazepam. Status epilepticus in neonates is an off-label use of diazepam. Status epilepticus is an off-label use of clonazepam, midazolam, and some other benzodiazepines.)

Rectal diazepam and intranasal midazolam are the only nonintravenous rescue drugs that are FDA-approved for management of acute repetitive seizures. For management of status epilepticus, the most cost-effective options available in the United States are buccal and intranasal midazolam.[86]

Patients with epilepsy are at increased risk of injury, and it is important to discuss anticipatory guidance with their caregivers and family members. For example, to help reduce the risk of drowning, children with epilepsy should take showers instead of baths and always be supervised by a responsible adult when they are in or around water, including bathing and swimming.[87] These children should not sleep in a top bunk bed, and parents should consider placing a baby monitor in their bedroom.

Associated Conditions

Neurodevelopmental and mental conditions are common in children and adults with epilepsy, affecting up to 50%.[62] These include intellectual disability, learning disabilities, autism spectrum disorder, attention-deficit/hyperactivity disorder, depression, and anxiety. Associated conditions can occur in children with normal development.[62,88] Although these conditions are more likely to occur in patients with more severe epilepsy, the underlying cause is not always clear.[88] Patients with epilepsy should undergo screening for associated conditions as part of routine care. These conditions can have a greater effect on quality of life than epilepsy.[62,88]

Refractory Epilepsy

Pharmacotherapy for epilepsy is not always effective. Referral to a comprehensive epilepsy center is warranted if two appropriately chosen drugs have not managed seizures. Referral also is warranted for children experiencing developmental plateaus or regressions, and for children with complex medical histories.[89]

At these centers, pediatric epileptologists perform comprehensive evaluations to determine the underlying cause of epilepsy. They also identify which treatments, if any, may be effective for each patient, including drugs, dietary therapies, surgery, and neuromodulation. Comprehensive epilepsy centers also can assist in identification and management of associated conditions.

Surgery should be considered for patients with refractory focal-onset epilepsy, particularly those with epilepsy due

to a structural cause.[90] For patients who are not surgical candidates, nonpharmacologic treatments include ketogenic, modified Atkins, and low-glycemic index therapy (ie, high-fat, low-carbohydrate) diets. These medical nutritional therapies are used to manage drug-resistant epilepsy. A ketogenic diet has been shown to result in an overall reduction of seizure frequency of approximately 65%.[91] It appears to be most effective in children with epilepsy due to unknown or genetic etiologies.[92]

For some patients, vagal nerve stimulation is an option. This treatment is associated with a greater than 50% reduction in seizures in 55% of children with focal or generalized epilepsy, including Lennox-Gastaut syndrome.[93]

Other Management

Integrative medicine (IM) therapies are used in 24% to 78% of pediatric neurology practices, and in patients with a variety of neurologic conditions, including epilepsy.[94] None of these therapies are FDA-approved for epilepsy management.

One study on the use of IM therapies in an outpatient pediatric neurology clinic found that these therapies are used more often in children with multiple neurologic conditions whose parents have higher levels of education. In this study, half of respondents surveyed reported that their physician did not ask about use of IM therapies.[94]

Some of these therapies can interact with drugs, so physicians should inquire about their use. For example, St. John's wort (*Hypericum perforatum*) can reduce the plasma concentration of several antiseizure drugs, and concurrent use of ginseng (*Panax ginseng*) and lamotrigine increases the risk of DRESS.[95,96]

Case 2, cont'd. You prescribe levetiracetam for JH. She initially experiences mild fussiness and fatigue, but these improve after a few weeks without changing the dosage. JH remains seizure-free with levetiracetam monotherapy.

SECTION THREE

Movement Disorders

Most movement disorders in children are hyperkinetic. The most common type is tic disorders, which can involve motor and phonic tics and are classified as simple or complex. Motor or phonic tics that persist for more than 1 year are defined as persistent (chronic) tic disorder. Tourette syndrome can be diagnosed if a child has multiple motor tics and at least one phonic tic for more than 1 year with onset before age 18 years. Children with Tourette syndrome may have symptoms of attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, depression, or behavioral disorders. Chorea can be seen as a symptom of rheumatic fever (Sydenham chorea), in children with a history of kernicterus, and in dyskinetic cerebral palsy. Chorea also may be part of an underlying metabolic or genetic condition. Dystonia is characterized by repetitive contortions and posturing of the limbs and body. It can be isolated or part of an underlying neurologic condition. Tremor can occur as a manifestation of essential tremor or can be an enhanced physiologic tremor exacerbated by drugs, illness, or stimulants. Ataxia most often is seen as a postinfectious or postvaccination acute cerebellar ataxia. Progressive ataxias are consistent with an underlying metabolic or genetic condition. Transient and developmental movement disorders include benign neonatal sleep myoclonus, jitteriness in neonates, shuddering, and stereotypies.

Case 3. SA is an 8-year-old boy with attention-deficit/hyperactivity disorder who is brought to your office for a well-child visit. When discussing school, his parents mention that SA has been told to leave the classroom because of disruptive behaviors several times. On further questioning, his parents say SA has been making frequent whistling noises in class, particularly during tests. As SA discusses these noises, he begins making whistling sounds and has repetitive facial twitching. His parents note that SA has had episodes of face twitching and repeated eye blinking since age 6 years.

Movement disorders are divided into two major categories. The first is hyperkinetic movement disorders (also referred to as dyskinesias), which are excessive, repetitive, involuntary movements that intrude into normal motor activity. This category includes most of the childhood movement disorders: tics; chorea; dystonia; tremor; ataxia; myoclonus; and stereotypies.[97,98] The second category is hypokinetic movement disorders, which include akinesia, bradykinesia, and rigidity.[98] In childhood, hypokinetic movement disorders are relatively uncommon.

Tic Disorders and Tourette Syndrome

TIC DISORDERS

Tics, the most common movement disorder in children, are repetitive, brief, nonrhythmic, involuntary movements or sounds. Simple motor tics involve a single muscle group and can include nose twitching, facial grimacing, neck jerking, shoulder elevation, bruxism, or abdominal tensing. Complex motor tics involve a more coordinated sequence of movements that appear purposeful but serve no purpose, such as head shaking, scratching, finger tapping, hitting, jumping, kicking, and gestures.[99]

Simple phonic tics involve various sounds and noises (eg, sniffing, coughing). Complex phonic tics involve spoken syllables, words, or phrases and can include repetition of the words of others (echolalia); repetition of the final syllable, word, or phrase of one's own words (palilalia); or shouting of obscenities or profanities (coprolalia).[100,101]

Tics have a waxing and waning course, with exacerbations provoked by stress, fear, anxiety, excitement, or illness.[102,103] They characteristically are suppressible, and are reduced when the child is intensely focus or engaged. Tics can occur during sleep.[104] Most patients report a premonitory urge or sensory phenomenon that resolves after the tic is permitted to occur.[105]

Tic disorders are diagnosed based on the clinical history and physical examination.[99] According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* (*DSM-5-TR*), provisional tic disorder is defined as tics occurring for less than 1 year. Motor or phonic tics that persist for more than 1 year are defined as persistent (chronic) tic disorder.[106] Most tics do not require management. For patients without functional impairment related to tics who are motivated to attempt treatment, the initial recommended therapy is the Comprehensive Behavioral Intervention for Tics (CBIT).[107]

TOURETTE SYNDROME

The *DSM-5-TR* defines Tourette syndrome as multiple motor tics and at least one phonic tic occurring for more

than 1 year, with onset before age 18 years.[106] Tics typically begin during the preschool or early grade school years, with an average age of onset of 6 years. Tic severity often increases during childhood, reaching a peak at age 10 to 12 years. Tourette syndrome can be highly variable. Many patients have fewer tics or a complete disappearance of tics by late adolescence or early adulthood.[108,109,110]

Although there is evidence to suggest a strong genetic contribution, nongenetic factors (eg, history of prematurity, anxiety, head injury, infections, use of dopaminergic agonist drugs) also may play a role.[100,111]

More than half of children with Tourette syndrome have symptoms of attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder, depression, or behavioral disorders.[103,112,113] Attention problems typically are evident before tic onset, and use of stimulants to manage ADHD may coincide with the first appearance of tics.[114] This does not indicate causality. Recent randomized, double-blind, controlled trials have shown a positive effect of stimulants on attention and tics.[115]

Symptoms of anxiety or obsessive-compulsive behaviors may improve with selective serotonin reuptake inhibitors (SSRIs) or cognitive behavioral therapy.[116,117] (These are off-label uses of some SSRIs.)

MANAGEMENT

A therapeutic plan for bothersome Tourette syndrome or tic disorders includes education of the patient and family members, behavioral approaches (eg, CBIT), and pharmacotherapy.[99] A 2014 meta-analysis of behavioral therapy for Tourette syndrome showed moderate treatment benefit.[118]

Pharmacotherapy can be used to reduce the frequency or severity of tics to minimize physical or psychosocial disturbances but it does not alter the clinical course. For milder tics in Tourette syndrome, alpha$_2$-adrenergic agonists, such as guanfacine or clonidine, commonly are used and may help manage associated ADHD.[99,107,119] For refractory cases, baclofen, topiramate, and clonazepam have been used with variable response rates.[99] (Tourette syndrome is an off-label use of all of these drugs.) For more severe tics in Tourette syndrome, typical and atypical antipsychotics may be effective, but adverse effects frequently limit their usefulness.[99,107,120] (Tourette syndrome is an off-label use of some typical and atypical antipsychotics.)

Case 3, cont'd. SA says he knows when the whistling and facial movements are about to happen, and that sometimes it is possible to suppress them. He says these tics happen more often when he is stressed, such as during test taking. Based on this history of chronic motor and phonic tics for more than 1 year, SA meets criteria for a diagnosis of Tourette syndrome. You provide education on the natural history of tics, and after discussing drug options, you prescribe guanfacine. (This is an off-label use of guanfacine.)

Chorea

Chorea consists of hyperkinetic, jerky movements that can seem to flow into the writhing snakelike movements of athetosis. All body parts may be involved, but the face and upper limbs more commonly are affected.[97]

Chorea can be seen as a symptom of rheumatic fever (Sydenham chorea), in children with a history of kernicterus, and in dyskinetic cerebral palsy. However, many genetic and neurodegenerative conditions can affect the basal ganglia and result in chorea, athetosis, or ballism.

Because chorea in children may be associated with various chronic, progressive metabolic, or neurodegenerative conditions (*Table 7*), the evaluation should include the clinical and family histories and a thorough neurologic examination. Magnetic resonance imaging (MRI) study of the brain and metabolic or genetic testing may be needed to help determine the etiology.[97,121]

SYDENHAM CHOREA

Sydenham chorea is the most common form of acute, isolated chorea in children.[122] It is considered a manifestation of rheumatic fever secondary to group A beta-hemolytic streptococcal infection.[123] Chorea typically begins 1 to 6 months after the inciting infection, in contrast to carditis and arthritis, which typically develop 1 to 5 weeks after the infection. Chorea onset is subacute, developing over hours to days, beginning with clumsiness, restlessness, and fatigue.[121]

The chorea is quick, often with unilateral uncoordinated motions, whereas the athetosis is writhing.[97] Dysarthric speech and adventitious facial movements are seen. Personality changes, inattention, anxiety, emotional lability, and obsessive compulsiveness may occur around the onset of motor dysfunction.[123,124]

Uncomplicated Sydenham chorea typically is a benign, self-limited condition. Chorea typically resolves in 2 to 6 months and rarely persists past 1 year.[125] Approximately 20% of patients have recurrent episodes within the first 2 years after onset. Up to 70% of patients may develop rheumatic heart disease, so an electrocardiogram and echocardiogram are recommended to assess for carditis.[126]

Management of Sydenham chorea includes prophylaxis with a 10-day course of oral penicillin or monthly intramuscular penicillin injections until age 21 years.[122] The goal is to prevent group A streptococcal reinfection that can result in rheumatic heart disease. Suppression of chorea symptoms may not be needed in mild cases.

Case series have reported benefits of valproic acid, carbamazepine, haloperidol, and dopamine receptor blockers (ie, pimozide, fluphenazine).[122,123] Management with steroids or intravenous immunoglobulin (IVIG) also can be considered in severe cases.[127,128,129] (Chorea is an off-label use of these drugs.)

KERNICTERUS

Chorea due to kernicterus (ie, bilirubin encephalopathy) typically is caused by exposure to toxic levels of unconjugated bilirubin from hemolytic diseases of the newborn.[130,131] Symptom severity depends on the amount and duration of elevated bilirubin exposure, gestational age, and other factors that increase transport of bilirubin to the brain, including acidosis and hypoalbuminemia.[130]

The three classic neurologic sequelae of kernicterus include: choreoathetosis or dystonia involving all limbs (mainly upper); sensorineural hearing loss; and oculomotor impairments.[130,132] Cognitive impairment is variable. Results of brain MRI study may appear normal initially or may show subtle hyperintensity in the basal ganglia.[130]

TABLE 7
Etiologies of and Diagnostic Tests for Childhood Movement Disorders by Category

Category	Specific Etiologies	Diagnostic History, Tests, Imaging
Vascular	Stroke	Brain or blood vessel imaging (or both)
	Moyamoya disease	
	Vascular malformation	
Autoimmune	Sydenham chorea	Brain imaging, antistreptolysin O and antideoxyribonuclease B titers
	Systemic lupus erythematosus, antiphospholipid syndrome	Antinuclear antibody test
		Lupus anticoagulant or anticardiolipin antibodies (or both)
Neoplastic or paraneoplastic	Basal ganglia or subthalamic nuclear mass	Brain imaging
Metabolic or endocrine	Bilirubin encephalopathy	Clinical history and imaging
	Hyperthyroidism	Thyrotropin level
	Hypernatremia	Electrolyte panel
	Hypocalcemia	Serum calcium level
	Hypoparathyroidism	Serum calcium, parathyroid hormone levels
	Vitamin B_{12} deficiency	Vitamin B_{12} level
Drugs	Antiseizure drugs	History of use, drug and toxin screening, drug levels
	Psychotropic drugs	
	Stimulants	

continues

MRI = magnetic resonance imaging.

DYSKINETIC CEREBRAL PALSY

Cerebral palsy is a static motor impairment due to insults acquired before, at, or immediately after birth. It has four major types based on the predominant motor disability: spastic (approximately 50%); dyskinetic (approximately 20%); ataxic (approximately 10%); and mixed (approximately 20%).[133,134] Approximately 20% of children with cerebral palsy develop movement disorders. Extrapyramidal symptoms include dystonia, akathisia, rigidity, and parkinsonism.[135]

Dyskinetic cerebral palsy tends to occur in term newborns with severe perinatal asphyxia, but the etiology is heterogeneous and can include metabolic or genetic conditions.[98,134] It is characterized by choreoathetoid and dystonic movements of the limbs, typically beginning after age 2 years.[98]

Management is individualized and focuses on the dyskinetic symptom that causes the greatest difficulty. Benzodiazepines, tetrabenazine, valproic acid, carbamazepine, and gabapentin often are prescribed when choreoathetosis is prominent. Anticholinergics (eg, trihexyphenidyl), baclofen, levodopa-carbidopa, and botulinum toxin are used when dystonia is more prominent.[136] (These are off-label uses of these drugs.)

Dystonia

Dystonia is characterized by slow, sustained contortions of axial and appendicular muscles with nonsuppressible twisting, repetitive movements or abnormal postures. In childhood, it may be isolated or part of an underlying genetic, metabolic, or neurodegenerative condition (*Table 8*).[97]

TABLE 7
Etiologies of and Diagnostic Tests for Childhood Movement Disorders by Category *(continued)*

Category	Specific Etiologies	Diagnostic History, Tests, Imaging
Genetic disorders	Benign hereditary chorea	Genetic testing
	Wilson disease	Serum copper and ceruloplasmin levels, slit lamp examination
	Neurodegeneration with brain iron accumulation	*Eye of the tiger* sign on brain MRI study
	Huntington disease	CAG repeats in Huntington gene
	Neuroacanthocytosis	Peripheral blood smear
	Phenylketonuria	Serum amino acid levels
	Glutaric aciduria	Urine organic acid levels
	Lesch-Nyhan syndrome	Urine purine and pyrimidine levels
	Mitochondrial encephalopathies (eg, Leigh disease)	Brain imaging, elevated arterial or cerebrospinal fluid lactate to pyruvate ratio
		Genetic or histologic testing
	Neuronal ceroid lipofuscinosis	Genetic testing
	Friedreich ataxia	Alpha fetoprotein level, genetic testing
	Ataxia telangiectasia	Genetic testing
	Spinocerebellar ataxias	
Other	Cardiopulmonary surgery with bypass	Clinical history and imaging
	Burn encephalopathy	Clinical history
	Pregnancy	Clinical history, beta human chorionic gonadotropin level
	Dyskinetic (athetotic) cerebral palsy	Clinical history and imaging

MRI = magnetic resonance imaging.

Information from Mink JW, Zinner SH. Movement disorders ii: chorea, dystonia, myoclonus, and tremor. Pediatr Rev. *2010;31(7):287-295; Pearson TS, Pons R. Movement disorders in children.* Continuum (Minneap Minn). *2019;25(4):1099-1120.*

Early-onset primary torsion dystonia is an autosomal dominant condition with incomplete penetrance, caused by deletions in the *TOR1A* gene.[137] This is estimated to account for early-onset dystonia in 50% of non-Jewish populations, and 80% to 90% of cases in Ashkenazi Jewish patients.[137,138] The average age of onset is 10 years.[139]

The initial major symptom typically is dystonic posturing of a lower extremity, with variable progression to the other limbs, neck muscles, trunk, pelvis, and, rarely, cranial muscles. Symptoms typically generalize within 5 years but may remain multifocal, segmental, or focal.[140] Diagnosis is based on clinical findings and genetic test results.

Goals of management are to minimize and control symptoms. Carbidopa-levodopa, trihexyphenidyl, benzodiazepines, phenytoin, carbamazepine, or baclofen can be helpful in some patients.[141,142] For children with isolated focal or generalized dystonia, an initial trial of carbidopa-levodopa should be considered as a first step in identifying patients with dopa-responsive dystonia. Second-line drugs include anticholinergics, such as trihexyphenidyl, followed by baclofen, benzodiazepines, or botulinum toxin injections.[141] Deep brain stimulation has shown promising results.[143,144,145]

Dopa-responsive dystonia (Segawa syndrome) is an autosomal dominant condition with variable penetrance, caused by a sequence variation in the *GCH1* gene.[146] Symptoms typically begin before age 10 years with progressive dystonia, and there is sustained marked response to low doses of levodopa.[98,147] Females are affected more than males in a 2:1 ratio.[146]

Patients with dopa-responsive dystonia typically present with a gait disturbance due to dystonia of a lower extremity. The dystonia progresses and becomes more generalized, and features of parkinsonism may appear. Symptoms are diurnal, worsening by the end of the day and improving after sleep, although not all patients experience these fluctuations. In addition to clinical assessment, diagnosis may require cerebrospinal fluid examination and genetic tests.[147,148,149]

Tremor

Tremor is an involuntary, rhythmic oscillation of a body part about a fixed point or axis. Tremor can be categorized

by features of the tremor and its relationship to purposeful movement.[97]

Rest tremor is uncommon in children; it occurs more commonly in hypokinetic syndromes, such as Parkinson disease. Action tremor is more common in children and includes postural and kinetic tremor. Postural tremor worsens with sustained posture against gravity and may improve with movement or rest. Kinetic tremor occurs during directed voluntary movement or with simple movements of the extremities. Intention tremor is a kinetic tremor that worsens as the arm approaches a target.[97,150,151]

PRIMARY

Essential tremor (benign familial tremor) is the most common form of tremor in children. It can be inherited in an autosomal dominant pattern, with variable penetrance and severity, and a family history is present in approximately 70% of cases.[151] Essential tremor is monosymptomatic, characterized by isolated tremor with normal brain imaging results in the absence of other etiologies. Mean age of onset in children is 9 years.[152] The incidence increases with age, and it is seen more commonly in adults.[150]

Essential tremor is an action tremor that primarily involves the arms, with tremor observed during voluntary movement. The characteristic tremor is rapid and exacerbated by stress, anxiety, caffeine, and antigravity posture.[150,151] Slow progression with prolonged plateaus may occur. When activities of daily living are affected, management with propranolol or primidone may be effective. Benzodiazepines, gabapentin, and topiramate may be helpful in select patients.[150,151] (Benign familial tremor is an off-label use of these drugs.)

Physiologic tremor is a primary tremor that is present in many neurotypical individuals but typically is not visually apparent. Transient stressors, such as increased emotion, fatigue, hunger, or drugs can induce noticeable tremor caused by increased adrenergic activity (ie, enhanced physiologic tremor).[150,151] Management is not needed and progression is rare.

SECONDARY

Secondary tremor can be caused by many conditions, including structural lesions

TABLE 8
Differential Diagnosis of Secondary Generalized Dystonias in Newborns, Infants, and Children

Category	Conditions
Vascular	Ischemic stroke
	Perinatal cerebral injury
Infectious	Postinfectious
Inflammatory	Autoimmune
Neoplastic or paraneoplastic	Tumor (basal ganglia)
Metabolic or endocrine	Bilirubin encephalopathy
Drugs or toxins	Dopamine receptor blockers (eg, typical antipsychotics)
Genetic, autosomal dominant	Dentatorubral-pallidoluysian atrophy
	Huntington disease
	Lesch-Nyhan syndrome
	Pelizaeus-Merzbacher disease
	Spinocerebellar ataxias
Genetic, autosomal recessive	Ataxia telangiectasia
	Glutaric aciduria
	G_{M1} and G_{M2} gangliosidoses
	Hartnup disease
	Juvenile Parkinson disease
	Metachromatic leukodystrophy
	Methylmalonic aciduria
	NBIA (most often PKAN)
	Neuronal ceroid lipofuscinosis
	Niemann-Pick disease type C
	Wilson disease
Mitochondrial	Leber disease
	Leigh disease
	MELAS
	MERRF
Other	Cerebral palsy
	Psychogenic
	Trauma

MELAS = mitochondrial encephalomyopathy, lactic acidosis, and strokelike symptoms; MERRF = myoclonus epilepsy with ragged red fibers; NBIA = neurodegeneration with brain iron accumulation; PKAN = pantothenate kinase-associated neurodegeneration.

Information from Mink JW, Zinner SH. Movement disorders ii: chorea, dystonia, myoclonus, and tremor. Pediatr Rev. *2010;31(7):287-295; Pearson TS, Pons R. Movement disorders in children.* Continuum (Minneap Minn). *2019;25(4):1099-1120.*

(eg, infarctions, tumors, cysts), metabolic and genetic conditions (eg, Wilson disease), drugs, toxins, and trauma.[97,147,151] Hyperthyroidism is important to exclude because it can be a cause of tremor or can worsen a preexisting tremor.[97,147] Hyperadrenergic states can cause tremor and may occur in the presence of epinephrine-secreting tumors, such as pheochromocytoma or neuroblastoma, or in the context of severe anxiety disorders.[153]

Drugs such as valproic acid and lithium, as well as heavy metals, alcohol, and stimulants (eg, caffeine) can produce tremor.[146,151] Tremor has been found to develop in approximately 45% of children with severe traumatic brain injury within the first 18 months after injury.[151]

Ataxia

Ataxia refers to lack of coordination of voluntary muscle movements. This may result from impaired spatial pattern or timing of muscle activity.[98] Cerebellar ataxia is the most common type.[154]

Children with ataxia may have generalized or localized coordination difficulties. Abnormalities of eye movements may occur, notably oscillatory nystagmus or eye movement difficulties (ie, oculomotor apraxia). Titubation, or bobbing of the head and trunk, is common. Limb movements may be imprecise or show significant tremor when the child is performing a task. Speech may be dysarthric, with slow, irregularly emphasized speech. The gait may be broad-based and clumsy.[98]

Causes of cerebellar ataxia include acquired and congenital lesions, such as Dandy-Walker malformation or perinatal cerebellar hemorrhage in premature children, resulting in chronic, nonprogressive ataxia. Acute ataxia can be caused by infection, drug intoxication, and vascular or traumatic insults.[154,155] Recurrence of acute ataxia may occur in patients with inborn errors of metabolism, episodic ataxias, migraine, and functional or psychogenic movement disorders.[154,156,157]

Subacute ataxias should raise concerns about posterior fossa neoplasms, particularly in the setting of new headaches, vomiting, or papilledema. Rarer causes of subacute ataxia could include immune-mediated or parainfectious conditions, such as opsoclonus-myoclonus syndrome or acute disseminated encephalomyelitis.[154,155] Finally, many genetic and degenerative conditions can cause chronic progressive ataxia in children.[155]

ACUTE CEREBELLAR ATAXIA

Acute cerebellar ataxia (ACA) typically occurs between ages 2 to 5 years and develops days to weeks after a clinical or subclinical infection or vaccination. Numerous infectious agents have been implicated in the pathogenesis of ACA, with varicella infection being one of the most common postinfectious causes, though this has diminished because of vaccination. Rates of ACA after vaccination are much lower than those after infection.[154,157]

This condition often manifests as a sudden disturbance of gait and balance. Although gait ataxia is the most prominent sign, appendicular (limb) ataxia and nystagmus also can occur.[156] Finger dysmetria is seen in two-thirds of children with ACA. Transient behavioral alterations and school difficulties occur in at least one-third of children with ACA.[158]

The pathophysiology of ACA is not entirely understood but it is thought to be immune-mediated. Laboratory test results may show a mildly elevated white blood cell count in the cerebrospinal fluid (pleocytosis). Neuroimaging study results typically are normal, although abnormal signal can be seen in the cerebellum.[156,159]

Management is supportive because approximately 90% of cases resolve within 30 days of onset. Case reports of management with steroids or IVIG in refractory cases have shown some beneficial response.[160] (This is an off-label use of these drugs.) Some children may experience behavioral problems or speech impairment for weeks to months after ACA onset.[158]

Transient and Developmental Movement Disorders

The immature nervous system can produce motor patterns that appear pathologic but are benign. Recognition of these transient and developmental movement disorders is important in order to distinguish them from more serious underlying conditions and prevent unnecessary evaluation.

BENIGN NEONATAL SLEEP MYOCLONUS

Benign neonatal sleep myoclonus is characterized by repetitive myoclonic jerks occurring during sleep and is akin to hypnic jerks in older children and adults. The myoclonic jerks may be rhythmic or nonrhythmic, and typically occur more commonly in the distal limbs than in the proximal limbs. The movements are most likely to occur during non-REM sleep and cease when the newborn is awakened.[98,161]

Benign neonatal sleep myoclonus typically begins during the first week of life and gradually diminishes by age 6 months but can persist until age 3 years. Electroencephalogram (EEG) results are normal.[162] Management is not necessary and neurologic outcomes are normal.[161]

JITTERINESS

Jitteriness commonly is observed in the first week of life and is present in approximately 45% of healthy term

newborns. It also can accompany hypoxic-ischemic injury, electrolyte derangements, or drug withdrawal in neonates. Jitteriness includes generalized, symmetric, rhythmic oscillatory movements that are stimulus-sensitive, triggered by startlement or crying, and suppressed by passive flexion of the limb. Unlike with seizures, there are no associated abnormal eye movements or autonomic changes.[163]

It typically is recommended to evaluate newborns with jitteriness for seizures. However, additional diagnostic tests usually are not needed unless abnormalities are identified on neurologic examination or in neurodevelopment. Jitteriness typically resolves shortly after birth but may persist until age 6 months.[163]

SHUDDERING

Shuddering episodes occur in infancy or early childhood and are characterized by periods of rapid tremor of the head, shoulders, and arms that resembles shivering. Consciousness is preserved during the episodes. They typically last several seconds, may occur up to 100 times per day, and often are incited by excitement or surprise.[164,165]

Shuddering often is confused with epileptic seizures, but preserved consciousness and normal EEG results distinguish these episodes from seizures.[164,165] Shuddering episodes typically resolve over time and neurodevelopment is normal. Only reassurance is needed.[164]

STEREOTYPIES

Stereotypies typically occur in children with developmental delays or autism spectrum disorder, but can occur in children with normal development.[97] These movements are repetitive, nonpurposeful, rhythmic, and demonstrate some degree of volitional control. Common examples include head banging, rocking, jumping, or flapping of the hands and arms, often occurring when the child is excited or bored.[97,166] In children with normal development, stereotypies may be associated with anxiety and obsessive-compulsive behaviors.

These movements can be transient or may persist for years, even into adulthood. Pharmacotherapy is ineffective.[166] No intervention is needed beyond reassurance.[97]

Case 3, cont'd. At a follow-up visit after 1 month of treatment with guanfacine, SA reports that the severity and frequency of the tics have decreased. His parents say they have seen improvement in the tics and in SA's mental focus over the past month. They bring comments from SA's teacher, who also has noticed his improved focus and attention.

SECTION FOUR

Neuroanatomic Abnormalities

Abnormal head shape and size often are apparent in infancy and typically are noted by caregivers or by clinicians on physical examination. Positional plagiocephaly consists of deformation of the skull not associated with an underlying skull fusion abnormality. This should be differentiated from craniosynostosis, which is the premature fusion of one or more skull sutures. For patients with craniosynostosis, early referral to a pediatric neurosurgeon or craniofacial specialist is important to prevent continued skull deformity and decrease the risk of increased intracranial pressure due to reduced skull adherence and obstruction of cerebrospinal fluid flow. Microcephaly is defined as a head circumference measuring 2 or more SDs below the mean for age and sex, and macrocephaly is defined as a head circumference measuring 2 or more SDs above the mean for age and sex. Etiologies of micro- and macrocephaly include perinatal factors, inherited head size, structural factors, and metabolic and genetic disorders. Brain imaging may be recommended. A rapid increase in head size should raise concerns about accumulation of cerebrospinal fluid and hydrocephalus, which may require emergent evaluation. A detailed history should be taken and a physical examination performed to identify any signs or symptoms of increased intracranial pressure.

Case 4. TT is a 4-month-old girl who was born at term via spontaneous vaginal delivery to a 30-year-old woman (gravida 1, para 1). Her parents bring TT to your office for a well-child visit with concerns that her head appears abnormal. All serial measurements appear to be following growth curves from previous visits. Length is at the 25th percentile, weight at the 40th percentile, and head circumference at the 7th percentile for age and sex. On physical examination, the head shape is symmetric but appears long, with a prominent forehead and occiput. The anterior fontanelle is open and flat. TT's development has been normal.

Craniosynostosis

EPIDEMIOLOGY

Cerebral volume quadruples within the first year of life, so accommodation of the cranial vault to cerebral growth is a critical component in the development of normal skull shape. Craniosynostosis is the premature closure of one or more cranial sutures before the brain has finished growing.[167]

The incidence of craniosynostosis is estimated to be approximately 1 case in 2,000 to 2,500 live births. Approximately 8% of craniosynostosis cases are associated with an underlying genetic disorder (syndromic) (*Table 9*), with the majority of remaining cases being isolated (nonsyndromic).[167] Most nonsyndromic cases are considered multifactorial.[168]

Intrauterine and perinatal factors have been associated with craniosynostosis, including prematurity, low birth weight, nulliparity, maternal smoking, and maternal thyroid disease (hyperthyroidism more commonly than hypothyroidism).[168,169,170] More than 180 syndromes associated with craniosynostosis have been described, with autosomal dominant or sporadic pathogenic variants in fibroblast growth factor receptors and other cellular signaling genes being the most common.[171,172]

COMMON MANIFESTATIONS AND ASSOCIATED CONDITIONS

Premature closure of the cranial sutures results in cranial deformity, with the potential for increased intracranial pressure due to growth restriction from skull noncompliance. Closed sutures do not allow for perpendicular growth of the cranium, which results in compensatory growth parallel to the closed sutures.[167] Skull deformation patterns can be predicted based on the fused sutures involved (*Figure 1*, *Table 10*).

Positional plagiocephaly is asymmetric deformation of the skull often caused by infant positioning or torticollis. This can be confused with unilateral lambdoid craniosynostosis, but no premature suture closure occurs in positional plagiocephaly.[167] It is estimated to occur in 20% to 50% of infants age 6 months.[172]

Positional plagiocephaly manifests as unilateral occipital flattening, and the ipsilateral ear and forehead are displaced anteriorly, resulting in a parallelogram skull shape when viewed from above. This differs from unilateral lambdoid craniosynostosis, in which the ipsilateral ear and forehead are displaced posteriorly, resulting in a trapezoidal skull shape (*Figure 1*).[172] Since the start of the successful 1994 Back to Sleep (now known as Safe to Sleep) campaign to reduce the incidence of sudden infant death

syndrome (SIDS), the reported incidence of positional plagiocephaly has increased.[173,174] The risk can be reduced by increasing the time an infant spends prone (ie, tummy time) and frequent repositioning of the head when an infant is supine.[172,174]

If positional plagiocephaly is the result of (or has resulted in) torticollis, then physical therapy can be helpful.[172,175,176] Use of cranial molding orthoses (ie, helmet therapy) has been shown to result in better cosmetic outcomes compared with head repositioning for infants with deformational brachycephaly or positional plagiocephaly.[177]

SCREENING AND SIGNS

As part of routine newborn and well-child visits, a complete physical examination, including assessment of head shape, fontanelles, and head circumference (occipitofrontal circumference), is essential. For newborns, infants, and children younger than 2 years, the World Health Organization (WHO) child growth standards are used. For children ages 2 to 3 years, the Centers for Disease Control and Prevention (CDC) growth charts are used.[178] For children and adolescents older than 3 years to age 18 years, the Nellhaus charts commonly are used.[179]

Clinicians should consider craniosynostosis in patients with the following features: a head that is not round and symmetric; bulging fontanelles; overriding or ridged skull sutures; and a lack of movement when cranial bones are gently pressed in infants and children younger than 12 to 18 months. In addition, although it is not uncommon for neonates to be born with asymmetric heads due to expected cranial accommodation from childbirth, if the asymmetry persists beyond the first few weeks, craniosynostosis should be considered.[180]

EVALUATION

A diagnosis of craniosynostosis typically is made based on clinical examination followed by confirmatory imaging.[180] Low-dose computed tomography (CT) scan commonly is obtained as first-line imaging in suspected craniosynostosis because of its availability and the lack of need for anesthesia. Other advantages of CT scan are that it can detect intracranial pathology and 3-dimensional reconstruction can be obtained for surgical planning (*Figure 2*). Skull x-rays historically have been used as a rapid, cost-effective method for identification of fused sutures, but plain x-rays have poor sensitivity for detection of complex or subtle synostoses.[181]

Cranial ultrasound (US) can be used for assessment of suture patency when suspicion of additional intracranial anomalies is low.[181] US is inexpensive, quick, and does not involve exposure to radiation or anesthesia, but it requires expertise in performance and interpretation that may not be available.[181,182] Magnetic resonance imaging (MRI) study protocols are being explored, but access, cost, and the potential need for sedation remain barriers.[182]

After craniosynostosis is diagnosed, patients should undergo assessment for an underlying genetic disorder (ie, syndromic etiology) and evaluation for possible multiorgan

TABLE 9
Select Craniosynostoses and Associated Genes and Features

Syndrome	Inheritance/Associated Gene(s)	Affected Sutures	Associated Features
Apert	Autosomal dominant or sporadic/*FGFR2*	Bicoronal	Cleft palate, midface hypoplasia, hypertelorism (increased distance between the eyes), hydrocephalus, syndactyly, hearing loss, developmental delay, cognitive impairment
Crouzon	Autosomal dominant or sporadic/*FGFR2*, *FGFR3*	Bicoronal	Midface hypoplasia, hypertelorism, proptosis, normal intelligence, patent ductus arteriosus, aortic coarctation
Pfeiffer	Autosomal dominant or sporadic/*FGFR1*, *FGFR2*	Bicoronal-lambdoid-sagittal	Cleft palate, broad toes and thumbs, hearing loss, hydrocephalus, pulmonary artery stenosis, tetralogy of Fallot, atrial septal defect
Muenke	Autosomal dominant or sporadic/*FGFR3*	Bicoronal or unicoronal	Hearing loss (sensorineural > conductive), mild intellectual disability, speech delay, ADHD, epilepsy

ADHD = attention-deficit/hyperactivity disorder; FGFR = fibroblast growth factor receptor.

Information from Governale LS. Craniosynostosis. Pediatr Neurol. *2015;53(5):394-401; Ko JM. Genetic syndromes associated with craniosynostosis.* J Korean Neurosurg Soc. *2016;59(3):187-191; Johnson D, Wilkie AOM. Craniosynostosis.* Eur J Hum Genet. *2011;19(4)369-376.*

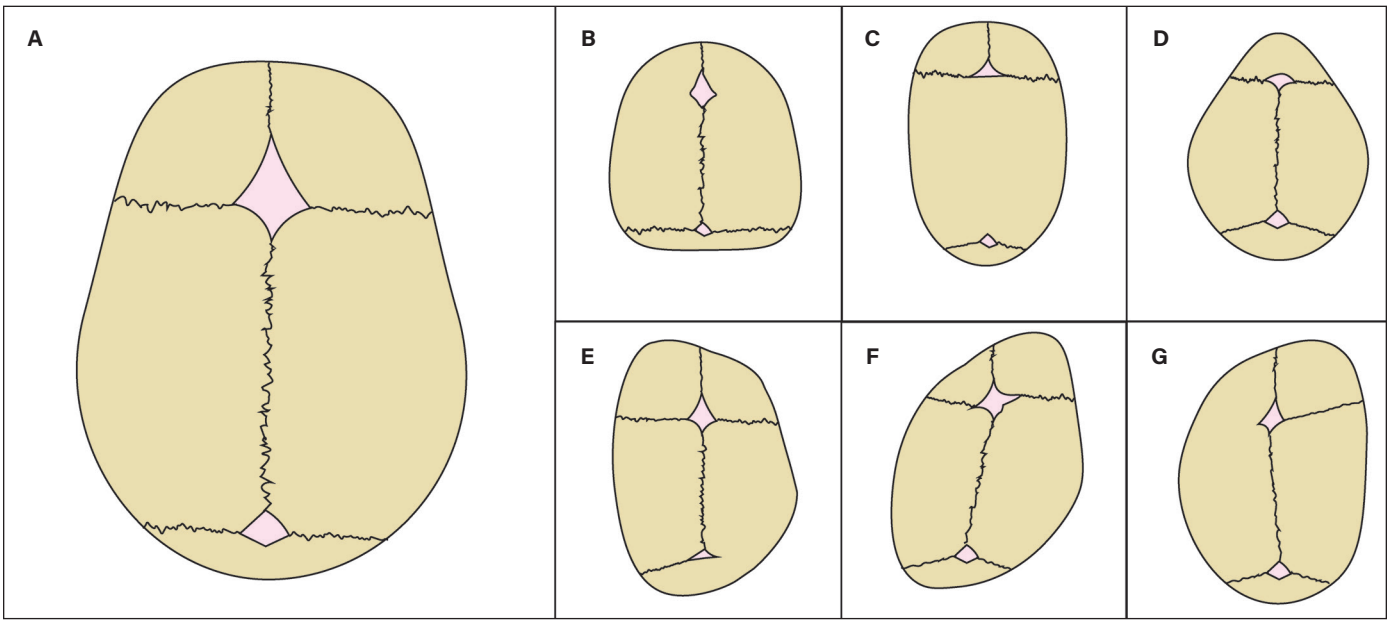

Figure 1. Skull Shapes

A. Normocephaly.

B. Brachycephaly, which could be positional in origin but also is seen in bicoronal synostosis. Note fusion of the bilateral coronal sutures and flattening of the occiput.

C. Dolichocephaly, also known as scaphocephaly, refers to an elongated skull with flattening on the sides. This can be seen with sagittal synostosis. It is seen more commonly in infants with a history of prematurity and a neonatal intensive care unit stay.

D. Trigonocephaly, or metopic synostosis, refers to the premature fusion of the metopic suture. This results in a triangular shape of the front of the head.

E. and F. Unilateral lambdoid synostosis is due to premature fusion of one of the lambdoid sutures. This can be mistaken for positional posterior plagiocephaly (F.) due to the unilateral posterior flattening seen with both. However, note that the contralateral forehead is displaced anteriorly in unilateral lambdoid synostosis, compared with the ipsilateral anterior displacement seen in positional plagiocephaly.

G. Unilateral coronal synostosis is shown here with premature fusion of one of the coronal sutures, resulting in more prominent anterior asymmetry.

Illustration courtesy of Anthony Fine, MD, with information from Sanchez P, Graham JM Jr. Congenital Anomalies of the Skull. In: Swaiman KF, Ashwal S, Ferreiro DM, et al, eds. Swaiman's Pediatric Neurology: Principles and Practice*. 6th ed. Elsevier: 2017:233-241.*

system involvement, such as cardiac, renal, and other skeletal abnormalities.[167,172]

COMPLICATIONS AND ASSOCIATED RISKS

One major complication of craniosynostosis is development of increased intracranial pressure due to reduced adherence of the skull with premature suture fusion. Elevated intracranial pressure occurs in 4% to 42% of single-suture craniosynostosis cases and 50% to 68% of multisuture cases.[172] The risk is significantly higher in syndromic cases.[172,180] Symptoms of elevated intracranial pressure can vary depending on patient age and rapidity of progression, but may include irritability, behavioral change, headaches, vomiting, sleep disturbances, ophthalmoparesis, lethargy, seizures, and coma.[180]

Patients with nonsyndromic or isolated craniosynostoses have a higher incidence of learning disabilities and vision problems than people in the general population.[183,184] Ongoing developmental screening and surveillance are recommended for patients with syndromic and nonsyndromic causes of craniosynostosis, with a low threshold for referral to a developmental specialist.[171,183]

MANAGEMENT AND REFERRAL

Patients with craniosynostosis should be referred to a multidisciplinary craniofacial practice for surgical consultation soon after diagnosis. Surgery to release the sutures and reconstruct the synostotic skull typically is performed by a pediatric neurosurgeon and/or plastic surgeon.[167,180]

Surgery is not urgent unless concerns exist about increased intracranial pressure. Factors that can influence the timing and type of surgery include patient age, severity of the condition, and the number of sutures involved. Surgical correction typically is not initiated until the patient is

TABLE 10
Suture Fusion Patterns and Skull Shapes in Craniosynostosis

Skull Shape	Suture(s) Involved	Features	Prevalence/Comments
Scaphocephaly	Sagittal	Long and narrow skull, prominent forehead	Most common type (>50% of cases)
Brachycephaly	Bilateral coronal	Short and wide skull, flat and wide forehead, bilateral recessed eyes	Second most common type (approximately 25% of cases)
Anterior plagiocephaly (trapezoid shape)	Unilateral coronal	Ipsilateral (to side of suture) forehead flattening, orbit and lateral sphenoid wing elevation, ear anterior	More likely to have genetic etiology or associated syndrome More common in females than in males
Trigonocephaly	Metopic	Narrow and pointed forehead with triangle shape when viewed from above	Third most common type Typically isolated
Brachycephaly	Bi-lambdoid	Short and wide skull, flat occiput	Rare
Posterior plagiocephaly (trapezoid shape)	Unilateral lambdoid	Ipsilateral occipital and forehead flattening, posterior ear displacement, prominent contralateral occiput	Rare Important to differentiate from positional plagiocephaly

Information from Governale LS. Craniosynostosis. Pediatr Neurol*. 2015;53(5):394-401; Lajeunie E, Crimmins DW, Arnaud E, Renier D. Genetic considerations in nonsyndromic midline craniosynostoses: a study of twins and their families.* J Neurosurg*. 2005;103(4 Suppl):353-356.*

at least age 3 to 6 months.[167,180] Multiple staged procedures often are required.[180]

Team members at multidisciplinary craniofacial clinics may include geneticists, pediatric neurologists, physiatrists, occupational, physical and speech therapists, and dietitians.[180]

Microcephaly

EPIDEMIOLOGY

Microcephaly is defined as a head circumference more than 2 SDs below the mean for age and sex.[185] The prevalence in the United States is approximately 7 cases in 10,000 children.[186] Microcephaly often is multifactorial and is affected by genetic and in utero environmental factors, including maternal infection or exposures. It often indicates arrest of brain development, but can be a nonspecific finding, whether isolated or as part of a larger disease complex.[187,188]

COMMON MANIFESTATIONS AND ASSOCIATED CONDITIONS

Microcephaly may be identified prenatally, at delivery, or during well-child visits. The presence of extracranial findings on physical examination is associated with a genetic etiology and earlier presentation (*Table 11*). Some forms of microcephaly are familial.[187]

In the neonatal period, a potential infectious etiology may be indicated by clinical clues, such as hepatosplenomegaly, elevated transaminase levels, rash, hearing loss, and intracranial calcifications (*Table 12*).[189] In other cases, microcephaly may develop over time. In children with brain injuries from trauma, meningitis, anoxic injury, or massive stroke, brain growth may plateau, leading to reduced skull growth.[188] Systemic conditions that can result in acquired microcephaly include congenital heart disease, untreated hypothyroidism, and lead poisoning.[185]

Microcephaly may not be identified until infants or children are seen for other concerns, such as developmental delay, seizures, or cerebral palsy.[185,188]

SIGNS

Microcephaly typically is identified during well-child visits when the head circumference measures 2 or more SDs below the mean or is below the third percentile on growth charts.[185,188] Some patients may have earlier manifestations due to perinatal or congenital onset (eg, in utero infarction, brain malformations), whereas others may have postnatal arrest of head growth in cases of acquired microcephaly (eg, severe hypoxic-ischemic encephalopathy, traumatic brain injury, Rett syndrome).[190]

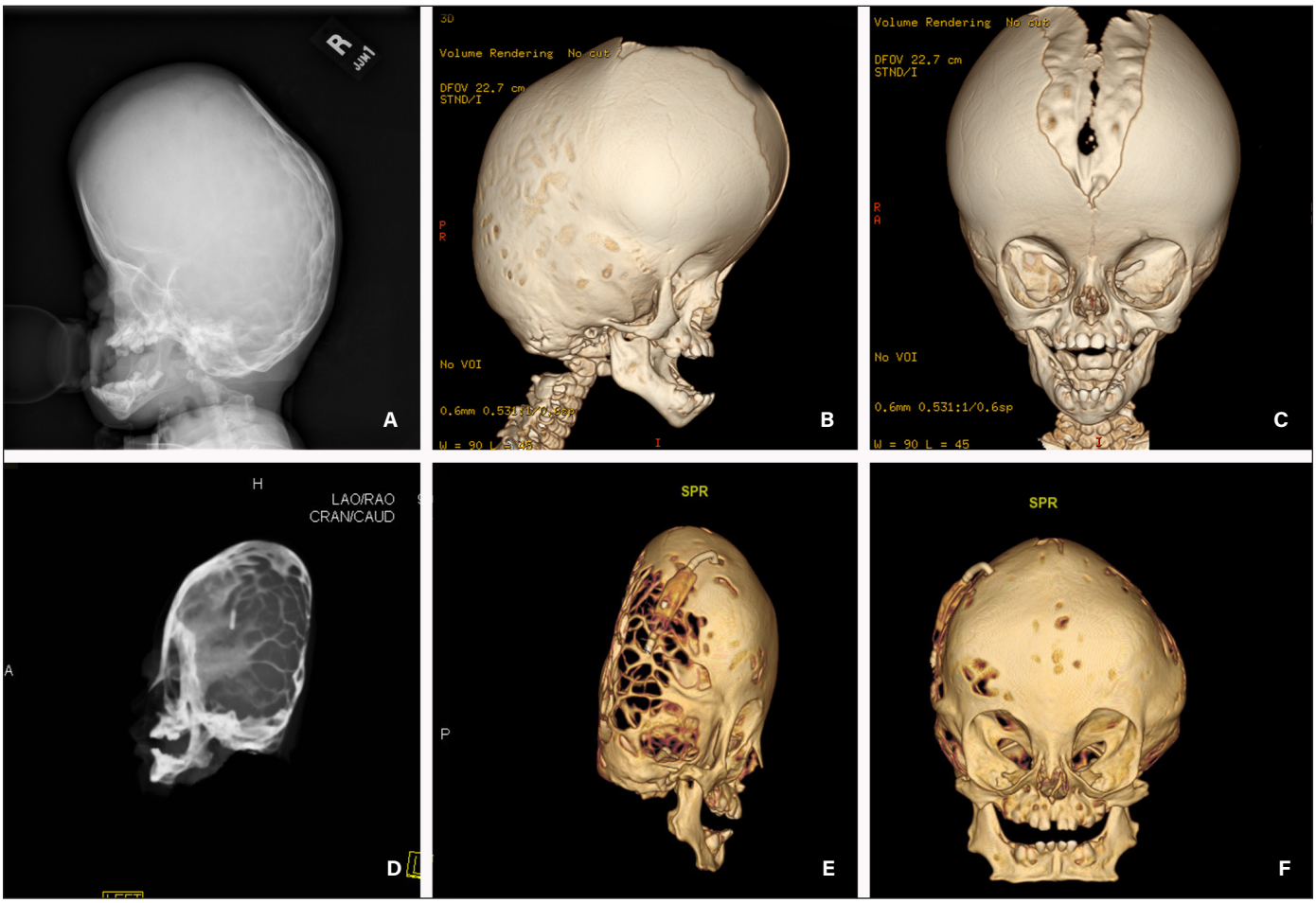

Figure 2. Examples of Craniosynostosis on Imaging

A.-C. Images of an 8-year-old girl with craniosynostosis and Pfeiffer syndrome.

A. Skull x-ray demonstrating brachycephaly with elongation of the skull. Note that the posterior skull demonstrates a copper beaten appearance caused by increased intracranial pressure.

B.-C. 3-dimensional reconstruction computed tomography (CT) scans. Note the enlarged, widely patent anterior fontanelle.

D.-F. Images of a 10-month-old girl with Schinzel-Giedion syndrome and complex multisuture synostoses.

D. Sagittal skull view on CT scan showing extreme brachycephaly.

E. and F. 3-dimensional reconstruction CT scan. Ventricular shunt present on the right. Note trabeculations in posterior skull, corresponding with multiple bony defects.

Images courtesy of Anthony Fine, MD.

EVALUATION

After a diagnosis of microcephaly has been made, additional history should be obtained, including information about the pregnancy, labor, and delivery, as well as growth patterns of family members.[185,190]

Neuroimaging is beneficial in most cases, with abnormalities detected in 43% to 80% of CT scans or MRI studies. Findings may include neuronal migration abnormalities, callosal dysgenesis, cerebral infarction, or hydranencephaly. A diagnosis of severe microcephaly (ie, head circumference more than 3 SDs below the mean) is more likely to be associated with abnormalities on imaging.[185]

Genetic testing may be considered if features are concerning for syndromic microcephaly.[185] Initial tests might include karyotyping and chromosomal microarray.[185,187] Further evaluation should be guided by a geneticist.

In a newborn with microcephaly plus other findings in the history or on physical examination that are concerning for an in utero infection, urine and serum tests for TORCH (toxoplasmosis, other [congenital syphilis and viruses], rubella, cytomegalovirus, herpes simplex virus) syndrome should be considered.[189,191] The category of "other" may include enteroviruses, hepatitis B virus, HIV, parvovirus B19, and Zika virus. The infections most likely

Table 11
Select Congenital and Postnatal-Onset Microcephalic Conditions

Etiologies and Classifications	Features and Findings
Congenital-genetic	
Seckel syndrome (autosomal recessive, *ATR* gene on 3q23)	Also called microcephalic primordial dwarfism type 1
	Growth retardation, birdlike features (eg, sloping forehead, prominent nose, small chin)
Williams syndrome (7q11.23 microdeletion)	Long narrow face, upturned nose, intellectual disability, cardiovascular disease
	Overly friendly and sociable, lack stranger anxiety
Wolf-Hirschhorn syndrome (4p deletion syndrome)	Poor growth, feeding difficulties, congenital heart disease, hearing loss, severe developmental delays, epilepsy
	Broad forehead, prominent glabella, hypertelorism (described as appearing similar to a Greek warrior helmet)
Postnatal-genetic	
Angelman syndrome	Loss of expression of maternal *UBE3A* on 15q11q13
	Absent expressive language, hypopigmentation, hyperactivity, happy demeanor, ataxia, epilepsy, sleep difficulties
CDKL5-related disorders	Previously called atypical Rett syndrome but is a distinct entity
	Can affect males and females
	Early onset epileptic encephalopathy often with epileptic spasms
	Early developmental stagnation (lacks regression seen in Rett syndrome)
MECP2-related disorder (Rett syndrome)	X-linked due to loss of function sequence variant in *MECP2*
	Developmental regression in females (majority) between 6 to 30 mo
	Loss of language, stereotyped hand movements, slowing of head growth
	Epilepsy, abnormal breathing patterns, scoliosis, spasticity
Postnatal-metabolic	
Glucose transporter type 1 deficiency (GLUT1)	Autosomal dominant, sequence variant in *SLC2A1* gene
	Variant results in reduced transport of glucose to the central nervous system (diagnosed by comparing cerebrospinal fluid glucose with blood glucose)
	Early onset epilepsy (often atypical absence), developmental delay, spasticity, ataxia, family history of paroxysmal kinesigenic dyskinesia
	Managed with ketogenic diet
Phenylketonuria	Poorly controlled maternal phenylketonuria results in an embryopathy
	Intrauterine growth restriction, intellectual disability, cardiac defects
	Preventable with dietary restriction of maternal phenylalanine

Information from Abuelo D. Microcephaly syndromes. Semin Pediatr Neurol. *2007;14(3):118-127; Seltzer LE, Paciorkowski AR. Genetic disorders associated with postnatal microcephaly.* Am J Med Genet C Semin Med Genet. *2014;166C(2):140-155.*

to cause microcephaly include rubella, toxoplasmosis, varicella, and cytomegalovirus and Zika virus infections. Symptomatic cytomegalovirus has a 20% risk of causing microcephaly.[190]

ASSOCIATED RISKS

Children with microcephaly are at increased risk of intellectual disability, developmental delays, epilepsy, cerebral palsy, and vision and hearing deficits.[185,190,192,193] Children

with microcephaly and epilepsy tend to have worse outcomes.[192] Other conditions or issues may be present, depending on the underlying etiology.

MANAGEMENT AND REFERRAL

Neurodevelopmental monitoring through well-child visits and early childhood screening is important, given the high rates of developmental delays and intellectual disabilities associated with microcephaly. Early referral for physical, occupational, and speech therapy should be considered. Referral to a pediatric neurologist or geneticist can be helpful when the etiology of microcephaly is not clear.

Macrocephaly

EPIDEMIOLOGY

Macrocephaly is defined as an occipitofrontal circumference that is at least 2 SDs above the mean for age and sex. It occurs in 2% to 5% of the population.[194] The pathogenesis depends on the etiology. Macrocephaly can result from abnormal cerebrospinal fluid dynamics, structural abnormalities, or genetic causes (*Table 13*). The majority of cases are due to a benign etiology.[195]

COMMON MANIFESTATIONS AND ASSOCIATED CONDITIONS

The two causes of benign macrocephaly are benign familial macrocephaly and benign enlargement of the subarachnoid space (BESS) in infancy. Benign familial macrocephaly is inherited, and the diagnosis often is made in an otherwise healthy child with isolated macrocephaly whose parent has macrocephaly.[194]

Benign enlargement of the subarachnoid space in infancy is thought to be due to reduced cerebrospinal fluid absorption from immature arachnoid villi, resulting in enlarged subarachnoid spaces and increased head circumference. Infants typically present with increasing head circumference (often crossing major growth curve percentile lines), but have no other abnormalities or significant findings on physical examination.[194]

There are numerous pathologic causes of macrocephaly, including perinatal insults, developmental disorders, and metabolic and genetic disorders.[194]

Table 12
Select Acquired Microcephalic Conditions

Etiologies and Classifications	Features and Findings
Acquired-infectious (TORCH infections)	
Cytomegalovirus infection	Petechiae, hearing loss, hepatosplenomegaly, thrombocytopenia, seizures, chorioretinitis, intracranial calcifications
Herpes	Vesicular or ulcerated lesions (can be absent), keratoconjunctivitis, seizures, poor feeding, irritability, hydrocephalus, multiorgan failure
Rubella	Purpura (*blueberry muffin rash*), hearing loss, cataracts, cardiac malformations, hepatosplenomegaly, jaundice, thrombocytopenia
Toxoplasmosis	Maculopapular rash, hepatosplenomegaly, jaundice, thrombocytopenia, seizures, chorioretinitis, hydrocephalus, intracranial calcifications
Varicella virus infection	Cortical atrophy, seizures, hyperpigmented or depressed scarring, chorioretinitis, cataracts
Zika virus infection	Hypertonia, spasticity, seizures, arthrogryposis (multiple joint contractures), irritability, hearing loss, intracranial calcifications, hydrocephalus
Acquired-structural	
Hypoxic-ischemic encephalopathy	Neonatal depression at birth History, laboratory test results, and imaging results consistent with hypoxic/anoxic event
Perinatal stroke	Often present with seizures Imaging reveals infarction or hemorrhage
Hydranencephaly	Absence of majority of cerebral hemispheres with preservation of basal ganglia and brainstem Thought to be due to a severe infectious or ischemic insult in the second trimester

TORCH = toxoplasmosis, other [congenital syphilis and viruses], rubella, cytomegalovirus, herpes simplex virus.

Information from Abuelo D. Microcephaly syndromes. Semin Pediatr Neurol. *2007;14(3):118-127; de Vries LS. Viral infections and the neonatal brain.* Semin Pediatr Neurol. *2019;32:100769.*

SIGNS

Macrocephaly should be suspected if the head circumference is greater than 2 SDs above the mean, serial measurements cross two or more major growth curve percentile lines over time, or head circumference increases rapidly (ie, more than 2 cm/month in the first 6 months of life).[194]

EVALUATION

In patients with suspected or known macrocephaly, the initial evaluation should include a detailed developmental

Table 13
Select Macrocephalic Conditions

Classification	Conditions	Features
Macrocrania	Benign familial macrocephaly	Increased HC growth velocity in first 6 mo of life then stabilization Family history of macrocephaly
	Benign enlargement of the subarachnoid space in infancy	Common finding Normal or near normal development Normal physical examination results Confirmed by imaging
Megalencephaly	ASD	15%-35% of children with ASD
	Achondroplasia	Can be seen in multiple skeletal dysplasia
	Sotos syndrome	Also called cerebral gigantism Overgrowth syndrome ID, brain malformations, and seizures possible
	PTEN-related overgrowth syndromes	Group of overgrowth disorders Hamartomatous overgrowth and benign growths Increased cancer risk
	Fragile X syndrome	One of the most common causes of inherited ID Developmental delays, learning disabilities, ADHD, ASD, seizures
	Neurocutaneous disorders	Tuberous sclerosis complex Neurofibromatosis
	Leukodystrophies	Metabolic disorders that primarily affect the white matter (eg, Alexander disease, Canavan disease, adrenoleukodystrophy, leukoencephalopathy with vanishing white matter)
Impaired CSF dynamics	Hydrocephalus due to reduced CSF flow	Congenital aqueductal stenosis (eg, sporadic, X-linked [*L1CAM*], autosomal recessive)
	Hydrocephalus due to reduced CSF absorption or flow	Postinfectious (in utero infection, meningitis) Posthemorrhagic (perinatal intraventricular hemorrhage, trauma) Tumor (can cause obstruction or increase CSF production [eg, choroid plexus papillomas])
Vascular	Galen vein malformation	Manifests in the neonatal period Can auscultate bruit over anterior fontanelle Can rapidly decompensate due to high-output cardiac failure

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; CSF = cerebrospinal fluid; HC = head circumference; ID = intellectual disability; PTEN = phosphatase and tensin homolog deleted on chromosome 10.

Information from Bryant JP, Hernandez NE, Niazi TN. Macrocephaly in the primary care provider's office. Pediatr Clin North Am. *2021;68(4):759-773; Williams CA, Dagli A, Battaglia A. Genetic disorders associated with macrocephaly.* Am J Med Genet A. *2008;146A(15):2023-2037.*

history and physical and neurologic examinations.[194] This should include a skin examination for neurocutaneous stigmata, such as hyper- and hypopigmented macules, neurofibromas, shagreen patches (associated with tuberous sclerosis complex), and other findings.[196] Asking about parental macrocephaly and plotting the head circumferences of the parents on a Weaver curve can be helpful to assess for familial macrocephaly (*Figure 3*).[197,198] Assessment of parental head circumference percentiles compared with height also can be useful.[198]

Ultrasound can be obtained if the anterior fontanelle is still patent.[194] It can be useful if there are concerns about

BESS or the infant has a history of a complicated neonatal course and assessment of ventricle size is needed. When detailed assessment of the brain parenchyma and ventricles is needed, MRI study is the imaging modality of choice.[196,199] MRI study is recommended when the concern is an etiology other than benign familial macrocephaly or BESS.[200]

ASSOCIATED RISKS

Benign macrocephaly traditionally has been thought to be associated with few risks. However, patients may have attention, learning, and behavioral difficulties.[195] In patients with BESS, dilation of the subarachnoid space stretches the bridging veins, increasing the risk of nontraumatic subdural hematoma, which can be mistaken for signs of nonaccidental trauma.[201] In patients with genetic and metabolic causes of macrocephaly, complications are varied and often related to the underlying etiology.

MANAGEMENT AND REFERRAL

Management is dependent on the etiology. For patients with benign macrocephaly, no additional management is needed, and referral is not required. Referral to a pediatric neurologist is recommended if an etiology other than benign macrocephaly is suspected.[194]

Hydrocephalus

EPIDEMIOLOGY

Hydrocephalus is the result of increased pressure within the cerebral ventricular system due to abnormal cerebrospinal fluid dynamics.[202] It is typically seen in infancy, with an incidence of approximately 0.9 cases per 1,000 births in the United States and a global prevalence of 88 cases per 100,000 children.[203,204] It is the most common condition managed by pediatric neurosurgeons.[202]

Hydrocephalus is associated with significant mortality (13% during initial neonatal hospitalization) and long-term morbidity.[202] It is associated with annual expenditures of $2 billion in the United States.[205]

COMMON MANIFESTATIONS AND ASSOCIATED CONDITIONS

Hydrocephalus is first classified as congenital or acquired, and subsequently as communicating or noncommunicating (ie, obstructive).[202] Causes of acquired obstructive hydrocephalus include neonatal intraventricular hemorrhage, tumor, and intrauterine infection.[206]

Acquired obstructive hydrocephalus may be identified before delivery or may manifest in the neonatal period as bradycardic and apneic events or rapidly increasing head circumference. Infants and older children may have symptoms of increased intracranial pressure, such as severe headaches, seizures, focal neurologic deficits, vision changes, vomiting, and irritability.[204]

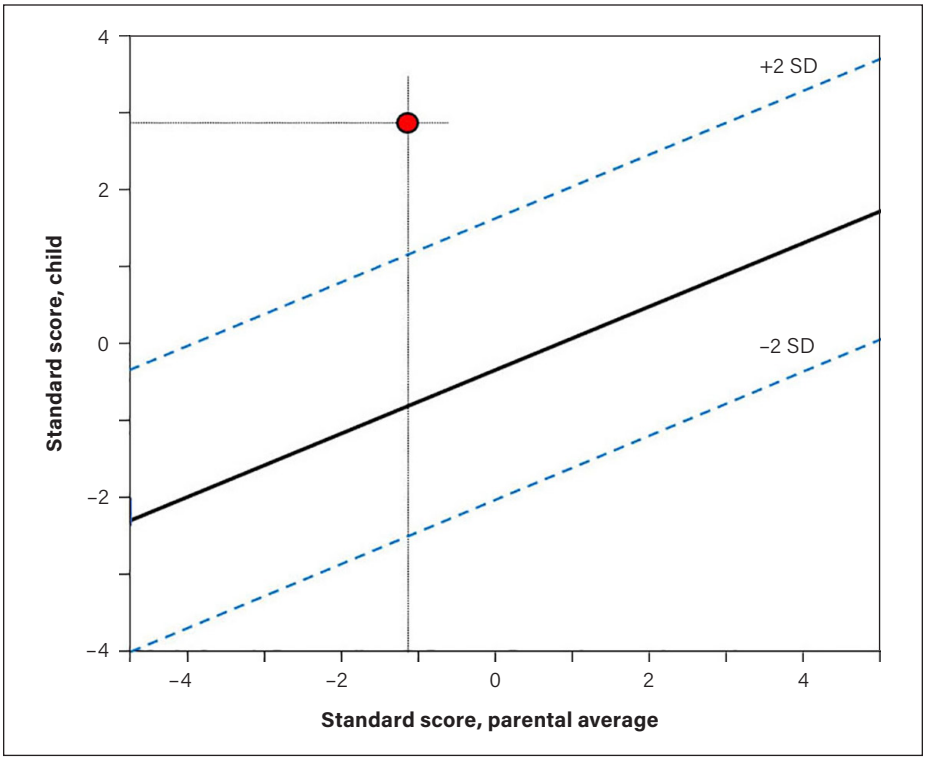

Figure 3. Weaver Curve for a Child With Macrocephaly

The solid black line represents the mean, and the dashed blue lines represent 2 SDs from the mean. The patient, a 9-month-old boy, had a head circumference (ie, occipital frontal circumference [OFC]) of 49.5 cm (19.5 in), which was greater than the 97th percentile for age and sex on the World Health Organization (WHO) child growth standards. The child's head circumference was compared with the head circumferences of his parents using a Weaver curve. The standard score (SS) was calculated using the child's OFC compared with the mean for age and sex divided by the SD based on Nellhaus data from the Weaver article cited below. The SS of the child was +2.93. His father had a head circumference of 52 cm (20.5 in), which corresponded to an SS of -2.95. His mother had a head circumference of 57.5 cm (22.6 in), corresponding to an SS of +1.83. The parental average was -1.12. When plotted together, the child's head size is macrocephalic in relationship to his parents' head sizes. (This Weaver curve was generated based on the technique described in the reference cited below.)

Information from Weaver DD, Christian JC. Familial variation of head size and adjustment for parental head circumference. J Pediatr. *1980;96(6):990-994.*

Congenital hydrocephalus typically is due to aberrant brain development, such as in the case of congenital aqueductal stenosis.[202] Congenital hydrocephalus often is multifactorial. Some patients have an underlying genetic disorder.[204] Associated maternal risk factors include a lack of prenatal care, drug or alcohol use, diabetes, and use of certain drugs in pregnancy (eg, antidepressants, vaginal metronidazole); fetal risk factors include male sex and intrauterine growth restriction.[204,207]

SIGNS

Clinicians should consider hydrocephalus in patients with progressive macrocephaly or a head circumference measurement that crosses more than two major growth curve percentile lines. Signs and symptoms include bulging of the fontanelle (if patent), splaying of cranial sutures, vertical gaze palsy, poor feeding, and increased muscle tone.[202,204]

EVALUATION

In neonates and infants with a patent anterior fontanelle, US is the first-line approach for rapid assessment of intraventricular hemorrhage and ventriculomegaly.[204,208] MRI study can clarify whether hydrocephalus is communicating or noncommunicating. Additional MRI study sequences can be obtained to evaluate the flow of cerebrospinal fluid to assess for suspected aqueductal stenosis.[209] Rapid-sequence MRI study can assess ventricle size without the need for sedation.[210]

COMPLICATIONS AND ASSOCIATED RISKS

Without intervention, hydrocephalus can cause progressive neurologic deficits with a risk of deterioration to coma and death. Early signs of increased intracranial pressure include headaches, vision changes, vertical gaze palsy, vomiting, ataxia, and somnolence.[190,202] As pressure increases, injury to the periventricular white matter increases.

Cerebrospinal fluid diversion often is needed in patients with hydrocephalus. Shunt-related complications are common. Symptoms of shunt malfunction are the same as those with increased intracranial pressure. Fever, pain, or swelling at the shunt site is concerning for shunt infection.[204]

MANAGEMENT AND REFERRAL

If hydrocephalus is suspected or identified, immediate referral to a pediatric neurosurgeon is indicated. Patients who are symptomatic and show signs of increased intracranial pressure should be evaluated urgently.[202,204]

Endoscopic third ventriculostomy may be performed early as an alternative to shunt placement and may be combined with choroid plexus cauterization to reduce cerebrospinal fluid production.[204,211] This minimally invasive procedure consists of the creation of an opening in the floor of the third ventricle to allow greater flow of cerebrospinal fluid beyond a potential point of obstruction. This procedure may precede shunt placement in some cases.[211]

Shunting is the most common surgical treatment for hydrocephalus. Cerebrospinal fluid is shunted through a tube from the ventricle down the neck and into the peritoneum (most commonly), or into the cardiac atria, pleural cavity, or gallbladder.[204] Most children do not require activity restrictions related to the shunt, but avoidance of contact sports or situations in which the shunt tubing could become fractured or dislodged is recommended.[204,212]

Programmable shunt valve pressure settings can be adjusted using a magnetic device. The settings should be reviewed by the neurosurgeon if the patient recently has been exposed to magnetic devices (eg, MRI study), as this could result in changes in the shunt pressure settings.[204]

Case 4, cont'd. Other than head shape, physical examination results for TT are normal, including the neurologic examination. She has no features that suggest an underlying genetic disorder. The family history does not indicate any possible congenital syndromes. Cranial ultrasound shows normal brain anatomy with sagittal craniosynostosis. There are no signs of increased intracranial pressure. You refer TT and her parents to a *multidisciplinary craniofacial practice to discuss surgical management options.*

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Posttest Questions

FP Essentials subscribers may complete the posttest at https://www.aafp.org/pubs/fpe/quiz.html to earn 5 AAFP Prescribed CME credits. Credit may be claimed for 2 years from the date of this edition. Each question has only one correct answer. An explanation for each correct answer is provided at the end.

1. Which one of the following statements about childhood seizures is correct?

- ☐ A. A seizure is considered status epilepticus if it is a generalized tonic-clonic (ie, convulsive) seizure lasting 5 minutes or longer.
- ☐ B. A seizure that occurs in an afebrile patient with hypoglycemia is considered an unprovoked seizure.
- ☐ C. Multiple provoked seizures are considered epilepsy.
- ☐ D. Febrile seizures occur in 8% to 10% of children between ages 6 months and 5 to 6 years.

2. Which one of the following seizure types in children is considered a neurologic emergency?

- ☐ A. Childhood absence epilepsy.
- ☐ B. Epileptic (infantile) spasms.
- ☐ C. Focal to bilateral tonic-clonic seizures.
- ☐ D. Juvenile myoclonic epilepsy.
- ☐ E. Temporal lobe epilepsy.

3. Which one of the following statements about the use of advanced diagnostics to evaluate children with seizures is true?

- ☐ A. The American Academy of Neurology (AAN) practice parameter recommends that an electroencephalogram be performed during wakefulness and sleep for a child with a first unprovoked seizure.
- ☐ B. For children with new-onset seizures, the AAN and American College of Radiology (ACR) recommend that neuroimaging with computed tomography scan be obtained.
- ☐ C. Hyperventilation and photic stimulation have not been shown to be useful in identifying underlying epilepsy syndromes.

4. Which one of the following physical examination findings in a child with seizures is correctly paired with its associated genetic disorder?

- ☐ A. Facial angiofibromas are associated with tuberous sclerosis complex.
- ☐ B. Hypopigmented macules (ash leaf spots) are associated with Sturge-Weber syndrome.
- ☐ C. Macrocephaly is associated with Angelman syndrome.
- ☐ D. Port-wine stain is associated with neurofibromatosis.

5. Which one of the following statements about seizure recurrence in children is correct?

- ☐ A. Approximately two-thirds of children who experience a febrile seizure will have a second febrile seizure, with most recurrences within 1 year.
- ☐ B. The risk of developing epilepsy among children with febrile seizures is estimated at 1%, which is the same as the risk in the general population.
- ☐ C. The likelihood of unprovoked seizure recurrence is highest within the first 1 to 2 years after the first such seizure.
- ☐ D. Longer duration of a first febrile seizure increases the risk of recurrence.

6. Which one of the following statements is true of epilepsy and epilepsy syndromes?

- ☐ A. Developmental and epileptic encephalopathies usually are pharmacoresponsive.
- ☐ B. Epilepsy affects approximately 1% of children in the United States.
- ☐ C. To make a diagnosis of epilepsy, more than one unprovoked seizure must have occurred.
- ☐ D. Two-thirds of epilepsies can be classified further as specific electroclinical syndromes.

7. Which one of the following statements is true of antiseizure drugs?

- ☐ A. Carbamazepine primarily is used to manage absence seizures.
- ☐ B. Lamotrigine primarily is used to manage myoclonic seizures.
- ☐ C. Levetiracetam can cause mood or behavioral changes.
- ☐ D. Valproic acid is preferred for its safety during pregnancy.

8. Rescue drugs (eg, benzodiazepines) typically are not prescribed for out-of-hospital management of status epilepticus.

- ☐ A. True.
- ☐ B. False.

9. Which one of the following statements is true of integrative medicine therapies and nonpharmacotherapy options for epilepsy management?

- ☐ A. Taking ginseng (*Panax ginseng*) with lamotrigine can help reduce the risk of drug reaction with eosinophilia and systemic symptoms (DRESS).
- ☐ B. The ketogenic diet has been shown to result in a modest (ie, 25%) decrease in seizure frequency.
- ☐ C. St. John's wort (*Hypericum perforatum*) can reduce the plasma concentration of several antiseizure drugs.
- ☐ D. Several integrative medicine therapies are approved by the Food and Drug Administration for epilepsy management.

10. Hypokinetic movement disorders are relatively uncommon in childhood. Which one of the following is a type of hypokinetic movement disorder?

- ☐ A. Akinesia.
- ☐ B. Ataxia.
- ☐ C. Chorea.
- ☐ D. Dystonia.

11. Which one of the following statements is true of tics in children?

- ☐ A. Persistent (chronic) tic disorder is defined as motor or phonic tics that persist for at least 6 months.
- ☐ B. Palilalia is an example of a simple phonic tic.
- ☐ C. Tics characteristically are suppressible, and are reduced when the child is intensely focused or engaged.
- ☐ D. Tics do not occur during sleep.

12. Which one of the following statements is true of chorea in children?

- ☐ A. One year of prophylaxis with daily oral penicillin or monthly intramuscular penicillin injections is required for patients with Sydenham chorea.
- ☐ B. Along with chorea, sensorineural hearing loss is possible in patients who have had kernicterus.
- ☐ C. The legs and torso most commonly are affected by chorea.
- ☐ D. Sydenham chorea typically begins 1 to 2 weeks after the inciting infection.

13. Which one of the following statements about dyskinetic cerebral palsy and dystonia is correct?

- ☐ A. Dyskinetic cerebral palsy is the most common type of cerebral palsy.
- ☐ B. Early-onset primary torsion dystonia is estimated to account for 80% to 90% of early-onset dystonia cases in Ashkenazi Jewish patients.
- ☐ C. Symptoms of dopa-responsive dystonia (Segawa disease) typically begin after age 10 years with progressive dystonia.
- ☐ D. Symptoms of dyskinetic cerebral palsy typically begin after age 4 years.

14. Which one of the following statements about childhood tremor and ataxia is correct?

- ☐ A. Essential tremor, or benign familial tremor, is characteristically a slow tremor that is present at rest.
- ☐ B. First-line drugs for essential tremor are gabapentin and topiramate.
- ☐ C. Finger dysmetria is seen in two-thirds of children with acute cerebellar ataxia (ACA).
- ☐ D. Management of ACA with intravenous immunoglobulin is necessary because most cases do not resolve spontaneously.

15. Repetitive, nonpurposeful, rhythmic movements that demonstrate some degree of volitional control, such as flapping of the hands and arms, are categorized as which one of the following?

- ☐ A. Benign neonatal sleep myoclonus.
- ☐ B. Jitteriness.
- ☐ C. Shuddering.
- ☐ D. Stereotypies.

16. Which one of the following statements about craniosynostosis and positional plagiocephaly is correct?

- ☐ A. Approximately 50% of craniosynostosis cases are associated with an underlying genetic disorder (syndromic).
- ☐ B. The incidence of craniosynostosis is estimated to be approximately 1 case in 1,000 live births.
- ☐ C. Positional plagiocephaly is estimated to occur in 5% to 10% of infants age 6 months.
- ☐ D. Positional plagiocephaly can be confused with unilateral lambdoid craniosynostosis.

17. Which one of the following statements about microcephaly or associated conditions is correct?

- ☐ A. Cytomegalovirus infection is characterized by microcephaly and purpura (*blueberry muffin rash*).
- ☐ B. Canavan disease and adrenoleukodystrophy are examples of leukodystrophies that cause microcephaly.
- ☐ C. Microcephaly due to maternal phenylketonuria is preventable.
- ☐ D. Sotos syndrome is characterized by microcephaly and seizures.

18. Which one of the following is true of microcephaly?

- ☐ A. It typically is identified when the head circumference measures 3 or more SDs below the mean.
- ☐ B. Symptomatic cytomegalovirus infection is associated with a 50% risk of microcephaly.
- ☐ C. It typically does not increase the risk of vision and hearing deficits.
- ☐ D. The most likely causes include rubella, varicella, and cytomegalovirus infection.

19. Which one of the following statements about macrocephaly is correct?

- ☐ A. Benign enlargement of the subarachnoid space (BESS) in infancy is an autosomal dominant inherited macrocephaly.
- ☐ B. It should be suspected if a child's head circumference increases by more than 2 cm/month in the first 6 months of life.
- ☐ C. It is defined as an occipitofrontal circumference that is 1.5 SDs above the mean for age and sex.

20. Which one of the following statements is true of hydrocephalus?

- ☐ A. Placement of a shunt for hydrocephalus management requires activity restrictions.
- ☐ B. Endoscopic third ventriculostomy is a minimally invasive procedure that can precede shunt placement in some cases.
- ☐ C. Skull radiography is the first-line imaging approach for rapid assessment of neonates with suspected hydrocephalus.

Posttest Answers

Question 1: The correct answer is A.
A seizure is considered status epilepticus if it is a generalized tonic-clonic (ie, convulsive) seizure lasting 5 minutes or longer, a focal seizure lasting 10 minutes or longer, or recurrent seizures without a return to baseline function in between. *See page 8*.

Question 2: The correct answer is B.
Epileptic (infantile) spasms constitute a neurologic emergency. *See Table 1*.

Question 3: The correct answer is A.
The American Academy of Neurology (AAN) practice parameter recommends that an electroencephalogram be performed during wakefulness and sleep for a child with a first unprovoked seizure. *See page 12.*

Question 4: The correct answer is A.
Facial angiofibromas are associated with tuberous sclerosis complex. *See Table 4*.

Question 5: The correct answer is C.
Most unprovoked seizures are isolated events. The likelihood of seizure recurrence is highest within the first 1 to 2 years after the initial seizure. *See page 13.*

Question 6: The correct answer is B.
Epilepsy is the most common neurologic condition in children, and affects approximately 1% of children in the United States. *See page 15.*

Question 7: The correct answer is C.
Adverse effects of levetiracetam include sedation, dizziness, and mood changes. Severe changes in behavior can occur, such as aggression, irritability, worsening of suicidal thoughts, and psychotic symptoms. *See page 16.*

Question 8: The correct answer is B.
Rescue drugs often are prescribed for out-of-hospital management. These are benzodiazepines, including lorazepam, diazepam, clonazepam, and midazolam, which are available in a variety of formulations. *See page 18.*

Question 9: The correct answer is C.
St. John's wort (Hypericum perforatum) can reduce the plasma concentration of several antiseizure drugs. *See page 19.*

Question 10: The correct answer is A.
Hypokinetic movement disorders include akinesia, bradykinesia, and rigidity. *See page 20.*

Question 11: The correct answer is C.
Tics characteristically are suppressible, and are reduced when the child is intensely focused or engaged. *See page 20.*

Question 12: The correct answer is B.
Chorea due to kernicterus (ie, bilirubin encephalopathy) typically is caused by exposure to toxic levels of unconjugated bilirubin from hemolytic diseases of the newborn. The three classic neurologic sequelae of kernicterus include: choreoathetosis or dystonia involving all limbs (mainly upper); sensorineural hearing loss; and oculomotor impairments. *See page 22.*

Question 13: The correct answer is B.
Early-onset primary torsion dystonia is estimated to account for early-onset dystonia in 50% to 60% of non-Jewish populations, and 80% to 90% of cases in Ashkenazi Jewish patients. *See page 23.*

Question 14: The correct answer is C.
Finger dysmetria is seen in two-thirds of children with acute cerebellar ataxia. *See page 25.*

Question 15: The correct answer is D.
Stereotypies are movements that are repetitive, nonpurposeful, rhythmic, and demonstrate some degree of volitional control. Common examples include head banging, rocking, jumping, or flapping of the hands and arms, often occurring when the child is excited or bored. *See page 26.*

Question 16: The correct answer is D.
Positional plagiocephaly is asymmetric deformation of the skull often caused by infant positioning or torticollis. This can be confused with unilateral lambdoid craniosynostosis. *See page 27.*

Question 17: The correct answer is C.
Microencephaly can be caused by phenylketonuria. It is preventable with dietary restriction of maternal phenylalanine. *See Table 11.*

Question 18: The correct answer is D.
The infections most likely to cause microcephaly include rubella, toxoplasmosis, varicella, and cytomegalovirus and Zika virus infections. *See page 32.*

Question 19: The correct answer is B.
Macrocephaly should be suspected if the head circumference is greater than 2 SDs above the mean, serial measurements cross two or more major growth curve percentile lines over time, or head circumference increases rapidly (ie, more than 2 cm/month in the first 6 months of life). *See page 34.*

Question 20: The correct answer is B.
Endoscopic third ventriculostomy may be performed early as an alternative to shunt placement and may be combined with choroid plexus cauterization to reduce cerebrospinal fluid production. This minimally invasive procedure may precede shunt placement in some cases. *See page 36.*

Notes

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