Seizures in Children

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Education Gaps

The rate of misdiagnosis of seizures in children is at least 25%. Furthermore, many children presenting with a first seizure have a history of unrecognized preceding seizures that needs to be recognized to initiate appropriate treatments. Children with new-onset epilepsy often do not receive adequate counseling for seizure safety, and associated common comorbidities of epilepsy, such as learning disorders, attention-deficit/hyperactivity disorder, and behavior, remain unrecognized and untreated.

Objectives After completing this article, the reader should be able to:

1. Broadly classify various seizure types based on the current seizure classification schema.
2. Recognize seizure mimics and be able to triage patients to the correct specialty.
3. Obtain a seizure history and determine appropriate next diagnostic steps.
4. Counsel families regarding common antiseizure medications and potential adverse effects.
5. Identify commonly encountered comorbidities of epilepsy.

Abstract

Epilepsy is one of the most common neurologic disorders seen in children, with the highest incidence in the first year of life. Diagnostic accuracy can be challenging because many seizure mimics must be considered. Electroencephalography and neuroimaging can be critical in determining etiology and syndrome. Genetic testing is a high-yield endeavor, particularly in early-life epilepsies. Up to one-fourth of children with epilepsy will develop drug-resistant seizures. Comorbidities are very common in children with epilepsy, including intellectual disability in 25% and learning disability and attention-deficit/hyperactivity disorder in a significant minority. These comorbidities must be recognized and addressed as part of the child's overall care.

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ABBREVIATIONS

ADHD	attention-deficit/hyperactivity disorder
EEG	electroencephalography
FDA	Food and Drug Administration
IEP	individualized education plan
NMDA	*N*-methyl-D-aspartate
SUDEP	sudden unexpected death in epilepsy

Epilepsy is among the most common of neurologic disorders seen in children, with incidence rates ranging from 33.3 to 82 cases per 100,000 per year. (1)(2)(3)(4) The incidence is highest in the first year after birth and decreases in the teen years. The etiology remains unknown in nearly half of the patients. (4)

Population-based studies have demonstrated that nearly two-thirds of children with epilepsy achieve seizure freedom for longer than 3 to 5 years, and nearly half of all patients are able to successfully wean off antiseizure medication. (5)(6)(7)(8)(9) Unfortunately, approximately one-quarter of patients develop drug-resistant epilepsy, defined as failure of 2 or more adequate trials of antiseizure medication to control seizures. Such children are at risk for cognitive, behavioral, and psychiatric comorbidities, as well as medical concerns such as osteoporosis, seizure-induced injury, and sudden unexpected death in epilepsy.

CLINICAL APPROACH TO DIAGNOSIS

When seeing a child with possible epilepsy, the questions posed in the following subsections must be answered (Fig 1).

Is It a Seizure?

Determining whether a particular spell is truly an epileptic seizure versus a nonepileptic paroxysmal event can be challenging. Studies of children referred with a "first seizure" have shown that approximately one-quarter did not truly have an epileptic event. (10)(11) Table 1 contains descriptions of spells and lists the typical ages affected for common nonepileptic events that may be mistaken for seizures.

Seizures that arise from a focal brain region are typically preceded by a characteristic aura, which provides helpful localizing information because it usually reflects the area where the seizure arises. However, an aura is not present for seizures that are generalized in onset. Convulsive seizures and seizures that impair awareness are typically followed by a postictal state, in which the patient is sleepy and confused. Postictally, patients may also have transient focal weakness (Todd paresis) or language difficulties, depending on which area of the brain was involved in the seizure.

If This Is a Seizure, Is It Provoked?

Certain factors, most importantly high fever, may provoke seizures in children with otherwise healthy brains. Febrile seizures are common, affecting 3% to 5% of all children, and in most cases do not evolve into epilepsy. (12) A seizure would be considered to be febrile if it occurred in a child 6 months through 5 years of age without a history of epilepsy, in association with a fever (temperature >100.9° F [>38.3°C]), without evidence of an intracranial infection. Febrile seizures are considered complex if they are focal, prolonged (>10–15 minutes), or occur more than once in a 24-hour period. Febrile seizures lacking any complex features are considered simple febrile seizures.

Other provoking factors may include intracranial infection, electrolyte disturbances, hypoglycemia, and traumatic brain injury. Most cases of provoked seizures are not considered to be epilepsy, which is defined as either 2 or more unprovoked seizures occurring more than 24 hours apart or 1 unprovoked or reflex seizure with a high probability of recurrence. However, in some types of epilepsy, specific triggers may induce certain seizure types (such as photosensitive seizures in juvenile myoclonic epilepsy).

If This Is an Unprovoked Seizure, What Type of Seizure Is It?

Epilepsy classification provides a framework for diagnosis. Epilepsy in children comprises a diverse group of etiologies and syndromes. The primary goal of classification is to improve clinical epilepsy care by increasing the likelihood of finding a precise diagnosis in a more cost-effective manner with fewer investigations for the child and to identify the optimal therapy. Accurate classification is also important for epidemiologic reasons.

The International League Against Epilepsy published a revised classification of seizure types (Fig 2) and epilepsies (Fig 3) in 2017. (13)(14) The first level of classification is the seizure type, which is divided into focal, generalized, and unknown onset. A seizure is considered generalized in onset if it engages bilateral brain networks from onset and focal if it begins in 1 region or hemisphere. Generalized onset seizures can be further classified into motor or nonmotor (absence) onset. Focal seizures are further subdivided into 1) whether they are associated with impaired awareness and 2) whether they are associated with motor (tonic, clonic, atonic, or myoclonic activity) or nonmotor (behavior arrest, cognitive, emotional, sensory, or autonomic features) symptoms. Focal seizures may evolve to bilateral convulsive activity, and, thus, in any child with a generalized tonic-clonic seizure, it is imperative to ask about any premonitory symptoms suggestive of an aura.

Is This Epilepsy?

Epilepsy has been defined as 1) 2 or more unprovoked seizures occurring more than 24 hours apart or 2) 1

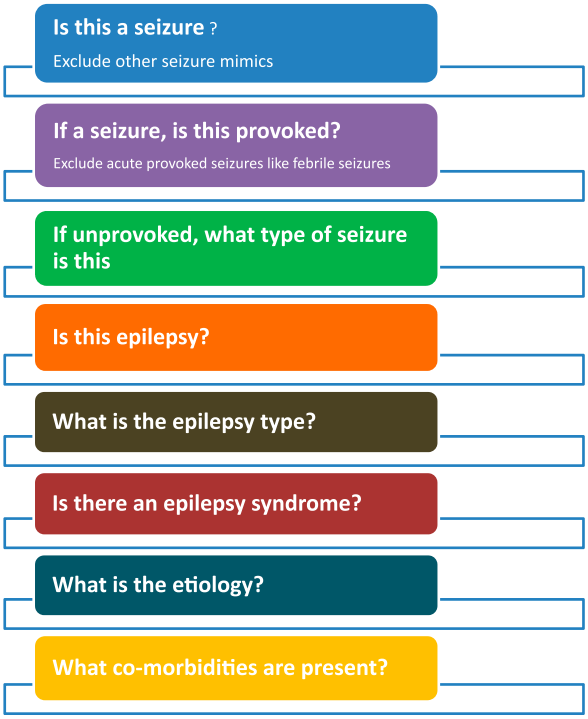

Figure 1. A clinical approach to a child presenting with possible new-onset seizures.

unprovoked or reflex seizure with a probability of recurrent seizures of at least 60% or higher over the subsequent 10 years or 3) diagnosis of an epilepsy syndrome. (15) Commonly, it is the first convulsive seizure that brings a child to medical attention. (10) In such cases, it is essential to ask about other seizure types, with more subtle signs and symptoms, such as absence, myoclonic, or focal impaired awareness seizures, because if these are present, the child can be diagnosed as having epilepsy, which commonly affects treatment decisions.

What Is the Epilepsy Type?

The second level of classification focuses on epilepsy type (Fig 3). (14) Children with generalized epilepsy have seizures in the generalized seizure onset category (ie, absence, atonic, myoclonic, tonic, clonic, and/or tonic-clonic) and commonly have generalized spike and wave discharges on interictal electroencephalography (EEG). Conversely, those with focal epilepsy may present with a variety of focal onset seizures. In focal epilepsy, the interictal EEG may be normal or can show focal or multifocal discharges. The 2017 classification added a new category, combined generalized and focal epilepsy, which is used for children with both focal and generalized onset seizures. These patients may have both focal and generalized discharges on EEG. This category includes a variety of early-onset, drug-resistant epilepsies, such as Lennox-Gastaut syndrome or Dravet syndrome. Epilepsy type is considered to be unknown if there is inadequate information for further classification.

Is There an Epilepsy Syndrome?

An epilepsy syndrome is a distinctive clinical entity that can be reliably identified by a cluster of electroclinical characteristics, including age at onset, seizure type(s), EEG characteristics (background and epileptiform abnormalities), and etiology, as well as other associated factors, such as neurocognitive delay, neurologic examination abnormalities, or imaging changes. The educational International League Against Epilepsy website (EpilepsyDiagnosis.org) provides an excellent resource for the diagnosis of epilepsy syndromes and contains parameters for diagnosis as well as videos of specific seizure types and images of characteristic EEG findings. Table 2 provides a list of epilepsy syndromes.

Epilepsy syndromes often have clear implications for etiology, treatment, and prognosis. Some syndromes are highly correlated with a single specific cause (eg, sodium voltage-gated alpha subunit 1 *[SCN1A]* mutation in Dravet syndrome), whereas others may be caused by a diverse group of genetic, structural, or metabolic etiologies, such as West syndrome or Lennox-Gastaut syndrome.

TABLE 1. **Common Seizure Mimics**

EPILEPSY MIMIC	AFFECTED AGE	CLINICAL CLUES
Benign sleep myoclonus	Neonate and early infantile	• Myoclonus of ≥1 limbs or the face, occurs in brief flurries lasting <3–5 s with pauses of variable duration • Occurs in sleep only and abolished on waking • Otherwise healthy infant
Jitteriness	Neonates	• Affects ≥1 limbs, often switching sides from event to event • Often spreads in nonanatomical pattern (ie, left leg to right arm) • Increased when the infant is unwrapped, stimulated, startled, or crying, but suppresses when the infant is wrapped or the affected limb is held gently
Benign myoclonus of infancy	Infancy	• Brief jerking of ≥1 limbs, lasting <5 s each, without altered awareness • Occurs in both wakefulness and sleep • Otherwise healthy infant
Shuddering attacks	Late infancy	• Brief stiffening with shoulder shaking like shivering, without altered awareness • Often provoked by excitement or frustration • Otherwise normal infant
Breath-holding spells—cyanotic or pallid	Infancy, early childhood	• Triggered by pain, crying, fright • Child usually cries (crying may be absent with pallid breath-holding), holds breath at the end of expiration, then becomes briefly tonic • Associated color change—cyanotic or pallid
Sandifer syndrome	Infancy, early childhood	• Back arching, dystonic posturing of the limbs, and turning/tilting of the head • May be provoked by feeding and lying flat • May be alleviated with sitting up • Often seen in neurologically abnormal children • Due to gastroesophageal reflux
Stereotypies	Infancy–childhood	• Mannerisms that may be simple (such as body rocking, head banging) or complex (such as finger movements or wrist flexion/extension) • These are interruptable by tactile and, at times, verbal stimulation • May occur in healthy individuals but are seen more commonly in those with autism or intellectual disability
Hyperekplexia	Infancy to adolescence but becomes less severe with age	• Infancy: babies are hypertonic but not spastic; excessive startle is seen with noise or touch, with flexion of limbs, and with neck retraction; this at times can be associated with apnea and cyanosis • A gentle tap using the tip of the examiner's finger on the glabella should trigger an excessive startle that does not habituate with repeated taps
Self-stimulatory behavior	Early childhood	• Rhythmic hip flexion and adduction with leg crossing, often accompanied by a distant expression • Interruptable, although the child may be irritable if interrupted
Benign paroxysmal vertigo	Early childhood	• Abrupt onset of anxiety, feeling off balance; child often grasps onto parent • May have associated nystagmus

Continued

TABLE 1. (Continued)

EPILEPSY MIMIC	AFFECTED AGE	CLINICAL CLUES
Cyclic vomiting	Childhood	• Paroxysmal events of recurrent emesis that may last hours and be interspersed and symptom-free periods of weeks to months
Daydreaming	Childhood	• Staring off, more likely to occur when engaged in quiet activity such as schoolwork • Can be interrupted with tactile stimulation
Parasomnias	Childhood and, rarely, adolescence	• Night terrors, sleepwalking, and confusional arousals are behaviors that arise out of deep non-REM sleep most commonly in the first few hours after falling asleep; they typically last longer than 3–5 min and occur intermittently • These must be distinguished from nocturnal frontal lobe seizures, which are brief (typically <2 min), very frequent (multiple per night), and occur throughout the night
Tantrums/rage attacks	Childhood to adolescence	• Tantrums are primarily seen in young children and involve relatively brief periods of behavioral dyscontrol in response to a stimulus; consciousness in not impaired • Rage reactions occur predominantly in older children and teens and, while triggered by minor stimuli, are characteristically out of proportion; patients are often aggressive during these periods, which can last for half an hour or longer
Tics	Childhood and adolescence	• Involuntary, sudden, rapid, repetitive, nonrhythmic, simple, or complex movements or vocalizations, which often occur multiple times per day • These are interruptable and can be suppressed, albeit often for only a matter of seconds • Tics abate during sleep
Periodic leg movements in sleep	Childhood and adolescence	• Repetitive stereotyped flexion of toes, ankles, knees, and hips • Resolve with waking
Vasovagal syncope	Childhood and adolescence	• Typically triggered by prolonged standing, dehydration, change in posture, warm environment, or emotional upset (eg, blood draw) • Preceded by lightheadedness, blurred vision, ringing in the ears, pallor, diaphoresis, abdominal discomfort • Loss of tone that may be followed by brief myoclonic jerks or tonic posturing • Rapid return to awareness but may remain lightheaded for a brief period thereafter
Postural orthostatic tachycardia syndrome	Adolescence	• Episodic periods of lightheadedness, chest pain, blurred vision, abdominal pain • Comes on with standing and resolves with sitting/lying down
Panic attacks	Adolescence	• Brief episodes, lasting minutes only, with sudden feeling of impending doom, accompanied by shortness of breath, choking sensation, palpitations, chest pain, paresthesia, dizziness, sweating, trembling, and feeling faint • Patient is very frightened but aware • No postictal sleepiness/confusion

Continued

TABLE 1. (Continued)

EPILEPSY MIMIC	AFFECTED AGE	CLINICAL CLUES
Narcolepsy/cataplexy	Adolescence, occasionally childhood	• Excessive daytime sleepiness, cataplexy (loss of tone in response to strong emotion), hypnagogic hallucinations, and sleep paralysis
Hemiplegic migraine	Adolescence, occasionally older childhood	• Aura of focal weakness +/- speech disturbance, visual symptoms, and paresthesia onsets before typical migraine-like headache • Often family history is positive
Psychogenic nonepileptic spells	Adolescence, occasionally childhood	• 2 main semiologies: 1) unresponsive periods without motor phenomena or 2) motor phenomena with bizarre, irregular jerking and thrashing • Often prolonged >15–30 min • Often minimal postictal phase • Frequent and refractory from onset
Cardiac syncope—long QT	Any age	• Sudden loss of consciousness, with pallor, atonia, or tonic posturing • Often triggered by fright, exercise, surprise, and immersion in water • Family history of syncope may be present

Increasingly, drug trials in pediatric epilepsy are focusing on efficacy in defined syndromes. Randomized controlled trials have documented the efficacy of hormonal treatment and vigabatrin in West syndrome (16); of add-on clobazam, rufinamide, topiramate, lamotrigine, felbamate, and cannabidiol in Lennox-Gastaut syndrome (17)(18); and of add-on stiripentol, cannabidiol, and fenfluramine in Dravet syndrome. (19)(20)(21)

Syndrome identification frequently informs prognosis regarding seizure control and remission as well as long-term neurocognitive function. For example, many early-onset syndromes, such as early myoclonic encephalopathy, West syndrome, Dravet syndrome, and Lennox-Gastaut syndrome, are associated with lifelong drug-resistant epilepsy, significant cognitive impairment, and increased mortality. (22)(23)(24) In others, such as myoclonic atonic epilepsy and epilepsy with continuous spike and wave during sleep, early seizure control can be challenging and cognitive concerns can initially be seen, but long-term outcome can still be favorable in some patients. (25)(26) In the genetic generalized epilepsies, including childhood absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy, seizures are typically controlled. Cognitive outcomes are usually favorable; however, higher rates of learning disability, executive dysfunction, and attention disorders, as well as poorer long-term psychosocial outcomes, may be seen. (27)(28) Finally, in the self-limited focal epilepsies of childhood, such as Panayiotopoulos syndrome or childhood epilepsy with centrotemporal spikes, patients may have subtle neurocognitive deficits during the active stage of epilepsy, but remission always occurs, and the long-term social prognosis is excellent. (29)(30)

For many epilepsy syndromes that are due to diverse etiologies, prognosis can be further clarified by defining underlying etiology. Many genetic, metabolic, or structural etiologies result in diffuse brain dysfunction with profound, premorbid intellectual disability that remains severe even if seizures are ultimately controlled.

Syndrome identification is more common in children than adults with epilepsy, with a defined syndrome identified in approximately one-quarter of children. (4) Some syndromes may evolve over time into other syndromes. (31)(32)

What Is the Etiology?

The advances in neuroimaging and genetics, as well as improved understanding of the role of specific autoantibodies as causal for certain epilepsies, have allowed greater accuracy in diagnosis for many children with epilepsy, potentially opening the door to a precision medicine approach. One example is the potential use of high-dose phenytoin for infants with gain-of-function mutations in the *SCN2A* channel gene who present with the syndrome of epilepsy of infancy with migrating focal seizures. Another example is resective surgery for focal cortical dysplasia.

Etiologies for epilepsy are divided into 6 subgroups: genetic, structural, metabolic, immune, infectious, and unknown. Sometimes 2 or more subgroups are involved, as in tuberous

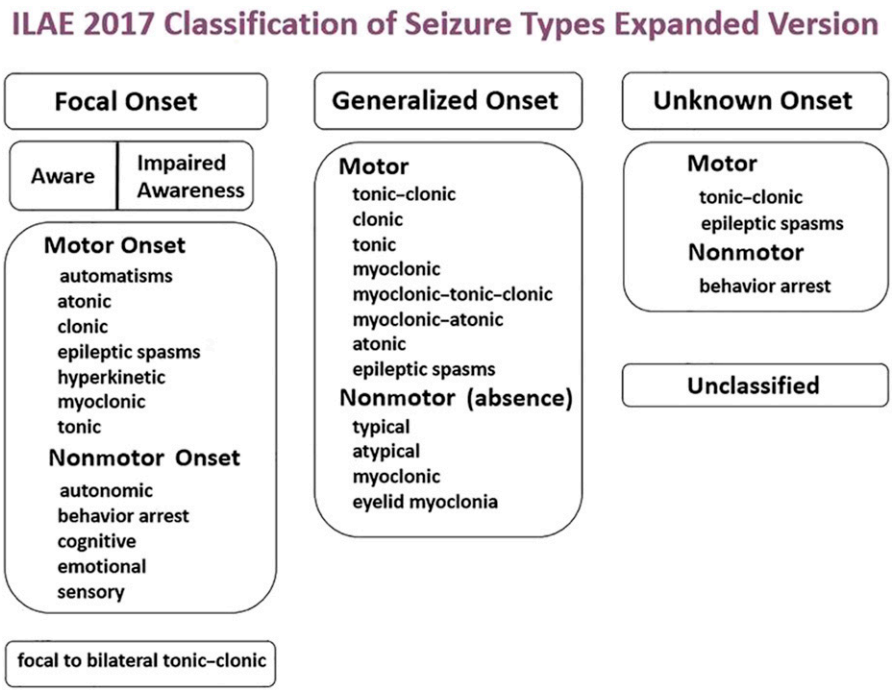

Figure 2. Classification of seizures types based on the International League Against Epilepsy. Reprinted with permission from Fisher RS, Cross JH, D'Souza C, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia*. 2017;58(4):531–542.

sclerosis, which is a genetic-structural etiology, or Leigh syndrome, which is a genetic-metabolic etiology.

A genetic etiology is defined by the epilepsy being the direct result of a known or presumed genetic defect, and seizures are the core symptom of the disorder. This category includes the generalized genetic epilepsy syndromes (also known as idiopathic generalized epilepsies), such as childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with tonic-clonic seizures alone, in which there is strong evidence from both family and twin studies of this heritable nature. Other genetic causes are associated with intellectual disability and poorer prognosis for seizure control, including cyclin-dependent kinase-like 5 (*CDKL5*), aristaless-related homeobox (*ARX*) mutations, Dravet syndrome, protocadherin 19 female-limited epilepsies, and Down syndrome. The yield of genetic testing in early-onset epilepsies is very high in both children with or without underlying malformations of cortical development. (34)(35)

Structural etiologies may be congenital (eg, cortical dysplasia) or acquired (eg, stroke, trauma). Specific structural etiologies have strong therapeutic implications, such as unilateral mesial temporal sclerosis, where seizures are typically resistant to medication but have a high likelihood of seizure freedom after resective surgery.

A metabolic etiology is defined by a child having a documented metabolic condition associated with a substantially increased risk of developing epilepsy. Examples include glucose transporter deficiency, creatine deficiency syndromes, and mitochondrial cytopathies. Many of these conditions are genetically inherited; in such cases, the term *metabolic-genetic etiology* should be used, and some have clear therapeutic implications, such as ketogenic diet therapy for glucose transporter deficiency.

An immune etiology implies clinical evidence of an immune disorder in which seizures are a core symptom. Inflammatory changes in cerebrospinal fluid (CSF) or on neuroimaging are typically present. Specific autoantibodies can usually be found on examinations of serum or CSF. Immune etiologies are commonly associated with drug-resistant seizures associated with other neurologic symptoms, which may include cognitive, behavioral, or movement disorders and that usually respond well to immunomodulatory therapies. Examples of immune etiologies include anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis, mGluR5-associated limbic encephalitis, and Rasmussen syndrome. Nonspecific voltage-gated potassium channel antibodies are commonly seen with various inflammatory disorders in children and should not generally be considered as causal for epilepsy. (36)

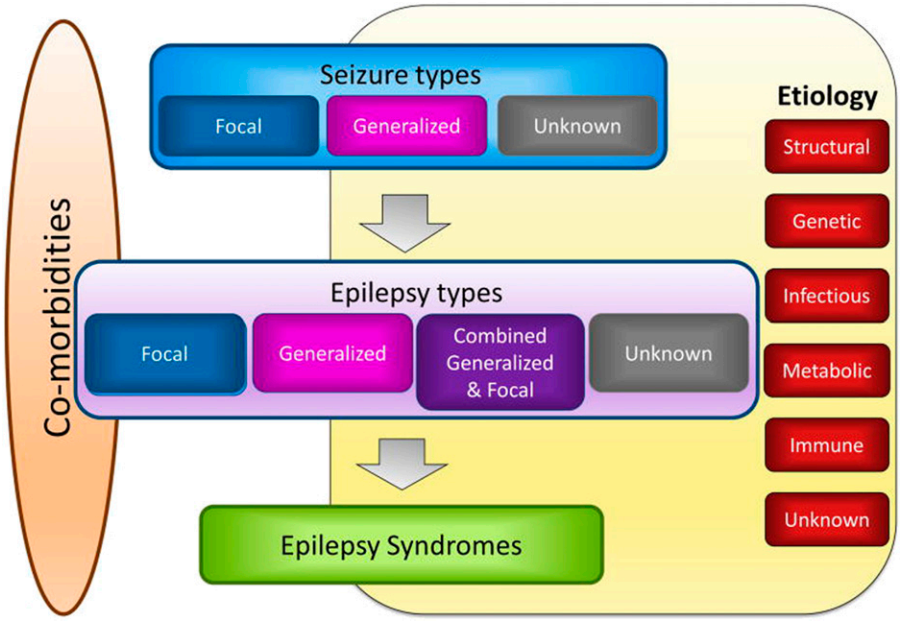

Figure 3. Schema for classification of epilepsy based on the International League Against Epilepsy. Reprinted with permission from Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):512–521.

An infectious etiology implies that epilepsy directly results from a known infection in which seizures are a core symptom of the disorder. Certain infections are more commonly seen in specific regions of the world, and examples include neurocysticercosis, tuberculosis, human immunodeficiency virus, cerebral malaria, cerebral toxoplasmosis, and congenital infections such as Zika virus and cytomegalovirus. Identification of specific infectious etiologies may carry implications for certain therapies.

The term *unknown* simply means that the nature of the underlying cause is not currently known. Epilepsies with normal imaging and no documented genetic, metabolic, immune, or infectious etiology are included in this category.

What Comorbidities Are Associated?

Cognitive, psychological, behavioral, and other medical comorbidities commonly coexist and may affect quality of life even more profoundly than seizures. Identification and treatment of these common symptoms are essential in the holistic care of a child with epilepsy (Table 3).

Unfortunately, in many patients, neurocognitive delays are a direct result of the underlying cause of epilepsy and are not improved with better seizure control. Conversely, in other patients, very frequent seizures and/or epileptiform discharges may further exacerbate cognitive and behavioral impairment, leading to an epileptic encephalopathy. In these situations, improved seizure control often results in developmental gains, and, thus, diagnosis and initiation of effective therapy is urgent. Specific syndromes such as West and continuous spike and wave during sleep are commonly associated with epileptic encephalopathy. Other factors that may affect the prevalence and severity of comorbidities include adverse effects of antiseizure medication and other treatments, social stigma and overprotection, and sleep disruption.

CLINICAL ASSESSMENT

History

A detailed clinical history is crucial to accurate diagnosis and should be obtained from the child (when possible) as well as directly from the person who witnessed the event. Children as young as 3 years of age can provide very useful information regarding both aura and postictal phase. The provider should obtain a complete description of the event from beginning to end, including details of the seizure itself, any potential preceding aura, and the postictal period, including witnessed postictal focal deficits. In addition to obtaining a careful verbal description of seizures, it is often helpful for the witness to "mime" the event. With a detailed history, the provider can often identify whether the spell(s) in question represents a seizure versus another paroxysmal event (Table 1).

The medical history should include maternal pregnancy history, delivery history (including birthweight, Apgar

TABLE 2. Epilepsy Syndromes Based on Age at Presentation

SYNDROME	CHARACTERISTIC SEIZURE TYPES	DEVELOPMENT	INVESTIGATIONS	NATURAL HISTORY
Neonatal/infantile onset				
Benign familial neonatal seizures	Focal clonic or tonic, often with apnea and cyanosis	Normal	Interictal EEG usually normal, MRI normal Genetics (AD inheritance with incomplete penetrance)—*KCNQ2* mutations in most, occasional *KCNQ3* or *SCN2A*	Remission occurs by 6 mo of age 10%–30% may have seizures later in life
Early myoclonic encephalopathy	Focal or multifocal myoclonus Focal seizures	Profoundly impaired	EEG: suppression burst pattern MRI usually normal Some cases found to have metabolic or genetic etiologies No identifiable cause in many cases	Drug-resistant seizures Early mortality due to profound neurologic impairment
Ohtahara syndrome	Tonic spasms and focal seizures	Delay, often severe	EEG: suppression burst pattern MRI often reveals structural lesion Genetic and metabolic testing should be performed if MRI normal	Drug-resistant seizures Early mortality common due to profound impairment Improved outcomes may be seen in cases amenable to surgical resection

Continued

TABLE 2. (Continued)

SYNDROME	CHARACTERISTIC SEIZURE TYPES	DEVELOPMENT	INVESTIGATIONS	NATURAL HISTORY
Epilepsy in infancy with migrating focal seizures	Multifocal clonic or tonic seizures that are often subtle and associated with autonomic features	Severe delay	EEG background typically slow with multifocal interictal and ictal discharges MRI usually shows mild global atrophy Genetic etiologies (*KCNT1*, *SCN2A*, others) and metabolic causes (congenital disorders of glycosylation) should be excluded	Drug-resistant seizures Early mortality common due to profound impairment
West syndrome	Clusters of epileptic spasms	Normal to severe delay at onset Over time, 70%–90% develop intellectual disability, often severe	EEG usually shows hypsarrhythmia MRI often shows structural abnormality Genetic and metabolic testing should be performed if MRI is normal	Often evolves to other drug-resistant epilepsies over time—focal/multifocal or Lennox-Gastaut syndrome
Dravet syndrome	Hemiconvulsive seizures, often prolonged and triggered by fever	Normal at seizure onset	EEG nonspecific	Seizures remain drug resistant

Continued

TABLE 2. (Continued)

SYNDROME	CHARACTERISTIC SEIZURE TYPES	DEVELOPMENT	INVESTIGATIONS	NATURAL HISTORY
	Later develop other seizure types, including myoclonic, absence, atonic, GTCS	All children develop variable degrees of intellectual disability over time, with delay evident by the late preschool years	MRI normal or mild atrophy Severe, pathogenic *SCN1A* mutations are seen in >85% of patients	All children develop variable degrees of intellectual disability over time, with delay evident by the late preschool years
Benign familial and nonfamilial infantile epilepsy	Brief focal seizures, often occurring in clusters	Normal	Interictal EEG and MRI are normal Genetic studies reveal causal mutations in many cases (*PRRT2, SCN2A, KCNQ2* or *3*)	Remission typically occurs within 1 y of onset
Myoclonic epilepsy in infancy	Myoclonic seizures, often activated by startle, noise, or touch	Development is normal at onset A minority develop cognitive delays over time	Interictal EEG often shows generalized spike-wave MRI is normal No causal genes or metabolic disorders	Myoclonic seizures remit typically by 5 mo to 6 y after onset 10% may develop other seizure types later in life
Genetic epilepsy with febrile seizures plus	Variable—some family members have only febrile seizures that may persist beyond age 6 y, others have variable types of generalized or focal seizures	Development is normal at onset and usually remains normal over time	Interictal EEG is usually normal but may show generalized or focal discharges MRI is normal Genetic studies are normal, although other first-degree relatives have a history of seizures	Typically self-limited, with remission by puberty

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TABLE 2. (Continued)

SYNDROME	CHARACTERISTIC SEIZURE TYPES	DEVELOPMENT	INVESTIGATIONS	NATURAL HISTORY
Childhood onset				
Childhood absence epilepsy	Typical absence seizures as only type in childhood and occur multiple times each day Minority develop GTCSs in adolescence	Development is normal, but higher rates of learning disorders and ADHD	Interictal EEG shows normal background or may show occipital intermittent rhythmic delta; usually see bursts of 3-Hz generalized spike-wave discharge; absence seizures are often triggered by hyperventilation	Most will remit and be able to stop antiseizure medications by late childhood
Epilepsy with myoclonic absences	Absence seizures with rhythmic myoclonic jerks of upper limbs, superimposed on tonic arm abduction May also develop other generalized seizures, especially GTCSs	Approximately half have a degree of intellectual disability, usually mild	Interictal EEG shows normal background with generalized discharges Ictal EEG shows 3-Hz generalized spike-wave discharge, with the myoclonic jerks time-locked	Variable evolution, with approximately 40% having remission of epilepsy; better prognosis if myoclonic absence seizures are the only seizure type

Continued

TABLE 2. (Continued)

SYNDROME	CHARACTERISTIC SEIZURE TYPES	DEVELOPMENT	INVESTIGATIONS	NATURAL HISTORY
Epilepsy with eyelid myoclonia	Eyelid myoclonia, consisting of brief rhythmic 4- to 6-Hz jerks of the eyelids, with upward deviation of the head and eyes, occurring multiple times each day; often followed by brief absence seizure May develop other types of generalized seizures, such as GTCS	Most have normal cognition, but borderline intellectual function or variable degrees of intellectual disability may be seen	Interictal recording shows normal background and brief bursts of fast generalized polyspike and wave Eye closure and photic stimulation often trigger eyelid myoclonia with high-amplitude generalized polyspike or spike-wave	Seizures, especially eyelid myoclonia is usually drug resistant; GTCSs respond better than eyelid myoclonia Remission is rare
Myoclonic atonic epilepsy	Myoclonic-atonic seizures are classic; also usually have atypical absence, myoclonic, GTCS, atonic, and, possibly, tonic seizures	Development is typically normal at onset; cognition often slows during periods of frequent seizures; many children are left with variable degrees of intellectual disability	Interictal EEG may be normal at onset; over time there is evolution to high-amplitude slowing of the background and generalized 2- to 5-Hz spike-wave discharge	Approximately two-thirds remit by early-mid childhood One-third have a more persistent course; this subgroup often presents with earlier onset and more frequent tonic seizures

Continued

TABLE 2. (Continued)

SYNDROME	CHARACTERISTIC SEIZURE TYPES	DEVELOPMENT	INVESTIGATIONS	NATURAL HISTORY
Lennox-Gastaut syndrome	Atonic, tonic, atypical absence, myoclonic, focal, and GTCSs; nocturnal tonic seizures, which are often clinically subtle, are an early clue to diagnosis	Most children are delayed before onset; delay becomes more profound over time, with most in the moderately to severely delayed range	Interictal EEG shows diffuse, high-amplitude background slowing with frontally predominant, slow spike-wave (typically <2 Hz); generalized paroxysmal fast activity is characteristic in sleep	Epilepsy does not remit and seizures remain drug resistant
Epileptic encephalopathy with electrical status epilepticus in sleep	No mandatory seizure type; seizures may include focal with or without impaired awareness as well as generalized seizures, particularly absence and atonic	A regression in cognition and behavior is seen at the time the EEG shows continuous spike-wave in sleep	Interictal EEG in wakefulness often shows focal or multifocal discharges but rarely may be normal; in sleep, there is marked activation of near continuous, slow spike-wave discharges	Treatment must address both seizures and continuous spike-wave on EEG; relapses are common until adolescence, when this pattern seems to remit; many children are left with intellectual disability
Panayiotopoulos syndrome	Focal seizures with prominent autonomic features, especially retching, and eye deviation, which often are seen shortly after falling asleep or just before waking	Development is usually normal	Interictal EEG shows a normal background with high-amplitude, focal or multifocal spikes, which typically increase in sleep, and are located in the occipital, centrotemporal, or parietal regions	Remission typically occurs within 1-2 y of onset; cognitive and social outcomes are excellent

Continued

TABLE 2. (Continued)

SYNDROME	CHARACTERISTIC SEIZURE TYPES	DEVELOPMENT	INVESTIGATIONS	NATURAL HISTORY
Benign epilepsy of childhood with centrotemporal spikes	Focal seizures with tonic or clonic activity and/or paresthesia of 1 side of the lower face or tongue, drooling, and dysarthria; may evolve to twitching of the ipsilateral arm/hand Seizures may also secondarily generalize in sleep Seizures are most common shortly after falling asleep or just before waking	Development is usually normal	Interictal EEG shows a normal background with high-amplitude, focal or multifocal spikes, which typically increase in sleep, and are located in the centrotemporal region	Remission typically occurs within 1–2 y of onset; cognitive and social outcomes are excellent
Gelastic seizures with hypothalamic hamartoma	Gelastic or dacrystic seizures—very brief paroxysmal bouts of abnormal laughter or crying, not in response to emotional stimuli	Normal development at onset; over time, many develop behavioral and cognitive concerns	Often normal early on; may see temporal discharges; with time, many evolve to show generalized spike-wave discharge	Seizures are refractory but may respond well to surgery
Adolescent onset				
Juvenile absence epilepsy	Typical absence seizures that occur less than daily to a couple of times per day; most also develop GTCSs within a few years of onset	Normal development but may have higher rates of ADHD and learning disorders	3- to 4-Hz generalized spike-wave discharge, superimposed on normal background	Typically drug responsive but low rate of remission

Continued

TABLE 2. (Continued)

SYNDROME	CHARACTERISTIC SEIZURE TYPES	DEVELOPMENT	INVESTIGATIONS	NATURAL HISTORY
Juvenile myoclonic epilepsy	Early-morning myoclonus, often triggered by sleep deprivation; GTCSs; approximately 40% have absence seizures, which are infrequent and subtle	Normal cognition; may have higher rates of ADHD	Fast, generalized atypical spike-wave discharge, often triggered by photic stimulation	Typically drug responsive but low rate of remission
Epilepsy with GTCS alone	GTCSs, often provoked by sleep deprivation	Normal cognition	Normal background with generalized polyspike or spike and wave	Typically drug responsive but low rate of remission
Variable age at onset				
Sleep-related hypermotor epilepsy	Hypermotor seizures, often with prominent vocalization; seizures are brief but frequent, with explosive onset, and occur commonly from sleep	Development is typically normal although intellectual disability may be seen	Interictal EEG is often normal but may show frontal discharges Ictal recordings may also be noninformative or may show ictal rhythm typically over the frontal region	Variable outcome, depending on etiology
Mesial temporal lobe epilepsy	Focal aware or impaired awareness seizures that may evolve to bilateral convulsive events; auras are common and may include epigastric rising, déjà or jamais vu, olfactory or gustatory hallucinations	Development may be normal but many patients complain of memory problems	Interictal EEG may show slowing or focal discharges over frontotemporal or temporal regions	Often drug resistant, particularly if a structural etiology is present; in such patients, surgical resection may be curative

Continued

TABLE 2. (Continued)

SYNDROME	CHARACTERISTIC SEIZURE TYPES	DEVELOPMENT	INVESTIGATIONS	NATURAL HISTORY
Rasmussen syndrome	Focal motor seizures that progressively increase in frequency and severity over time, often culminating in epilepsia partialis continua	Normal cognition at onset; over time, develop progressive hemiparesis, hemianopsia, and if dominant hemisphere, language deficits	EEG may be normal at onset or show focal discharges; over time, see increased background slowing over affected hemisphere, with increased hemispheric discharges; EEG may show ictal pattern with focal motor seizures but often does not show a clear ictal rhythm with epilepsia partialis continua MRI shows progressive hemispheric atrophy on side contralateral to hemiparesis	Seizures are drug resistant; most patients eventually undergo hemispherotomy
Febrile infection-related epilepsy syndrome	Focal or multifocal seizures that onset after a nonspecific febrile illness but then rapidly progress over 3–7 d to superrefractory status epilepticus	Normal at onset	EEG shows diffuse slowing and multifocal discharges and seizures	High morbidity and mortality; survivors are typically left with drug-resistant seizures and moderate to severe cognitive delay

AD=autosomal dominant; ADHD=attention-deficit/hyperactivity disorder; EEG=electroencephalography; GTCS=generalized tonic-clonic seizure; MRI=magnetic resonance imaging.

TABLE 3. **Common Comorbidities in Children and Teens with Epilepsy**

COMORBIDITY	COMMENTS
Intellectual disability	Affects ~25% of children with epilepsy and skewed toward more severe intellectual disability More common with specific syndromes and etiologies and in children with early-onset, drug-resistant seizures
Learning disabilities	Affects up to half of children with epilepsy Location of seizure onset is, in part, predictive of specific disability (ie, dominant temporal lobe epilepsy is commonly associated with verbal memory and language delays)
Attention-deficit/ hyperactivity disorder	Affects ~30% of children with epilepsy Attention deficit without hyperactivity is more common Girls and boys affected equally
Autism	Risk is 7.4-fold higher in children with epilepsy Risk factors include intellectual disability, specific syndromes (West syndrome) and specific etiologies (tuberous sclerosis, certain genetic disorders)
Anxiety	Affects up to 25% of children with epilepsy Often coexists with other comorbidities Less related to epilepsy variables, but higher risk with positive family history of mood disorders
Depression	Affects up to 20% of children with epilepsy Often coexists with other comorbidities Less related to epilepsy variables, but higher risk with positive family history of mood disorders
Behavior problems	Risk of internalizing problems is higher than that of externalizing problems
Sleep problems	Sleep may be affected by nocturnal seizures, effects of medication, co-sleeping

scores, need for resuscitation), and neonatal course. Developmental history should evaluate gross motor, fine motor, speech/language, and social domains, assessing for evidence of developmental delay, plateau, or regression.

Because many types of epilepsy have a genetic basis, a detailed family history is recommended. Sometimes, these details may not be known at the initial assessment but can be obtained at later visits.

In addition, as noted previously herein, the so-called first seizure may just be the first witnessed or identified seizure. (10) Families should be questioned about more subtle symptoms of seizures, including early morning jerks, episodes of "zoning out," nocturnal arousals, and bed-wetting.

Physical and Neurologic Examinations

Detailed physical and neurologic examinations should be performed in every child presenting with a possible seizure and should include measurement of the child's head circumference, cardiac examination, abdominal examination assessing for organomegaly, and a dermatologic examination using a Woods lamp (to look for signs of neurocutaneous syndromes). In active infants and toddlers, most of the neurologic examination is often based on observation—does the child use both hands equally when playing with a toy, is there tremor or dysmetria when reaching out for a book, does the child have any gait abnormalities, etc. The examiner should pay attention to symmetry—are there differences in strength or reflexes on one side of the body compared with the other side. By modifying the neurologic examination based on the age and cognitive ability of the patient, most physical features can be assessed.

INVESTIGATIONS

Electroencephalogram

An EEG performed during both wakefulness and sleep is recommended for any child who has a first unprovoked seizure. The purpose of obtaining an EEG early in the evaluation is multifold: assessment for background abnormalities, which might suggest a focal lesion; evaluation of epileptiform abnormalities that could help confirm a seizure; exclusion of more frequent but subtle seizures; evaluation of risk of seizure recurrence; identification of abnormalities that would prompt additional testing; classification of an epilepsy syndrome; and guidance for medication management. (37)

Some, but not all, studies have shown a higher yield if EEG is performed within 24 hours of the seizure. (38)(39) The ability to obtain a routine EEG within 24 hours can be

TABLE 4. **Treatable Metabolic Etiologies Leading to Seizures**

ETIOLOGY	CLUES AND TREATMENT
Pyridoxine-dependent or pyridoxal-5-phosphate–dependent epilepsy	Clues Early-onset refractory epilepsy Encephalopathy Developmental delay Treatment Pyridoxine supplementation (pyridoxine-dependent epilepsy)
Biotinidase deficiency	Clues Early-onset epilepsy (myoclonic, tonic-clonic, spasms) Developmental delay Skin rash Vision and hearing loss Treatment Biotin supplementation
Glucose transporter deficiency (GLUT-1)	Clues Neonatal- or infantile-onset epilepsy Early-onset absence seizures (<3 y) Developmental delay Microcephaly Ataxia Treatment Ketogenic diet
Cerebral folate deficiency	Clues Intractable generalized tonic-clonic seizures in infancy or childhood Treatment Folinic acid
Creatine deficiency (3 forms: guanidinoacetate methyltransferase [GAMT] deficiency, L-arginine:glycine amidinotransferase [AGAT] deficiency, and creatine transporter (CRTR) deficiency)	Clues Infantile-onset epilepsy Intellectual disability and developmental delay Microcephaly Autism spectrum disorder Treatment GAMT: oral creatine monohydrate, ornithine supplementation, and arginine-restricted diet AGAT: oral creatine monohydrate
Serine deficiency	Clues Microcephaly Intractable epilepsy Severe delay Treatment L-serine (+/- glycine) supplementation
Late-infantile neuronal ceroid lipofuscinosis (CLN2)	Clues Developmental regression Myoclonic epilepsy Vision loss Treatment Cerliponase alfa (recombinant tripeptidyl peptidase 1)

challenging unless a child is hospitalized or the facility has the ability to perform studies in an emergency department setting. In addition, nonspecific findings such as postictal slowing can still be present 24 to 48 hours after a seizure and should, therefore, be interpreted with caution.

Hyperventilation and photic stimulation should be performed during routine EEG because the yield of these activation procedures is higher in children compared with adults. (37) Hyperventilation typically is associated with activation of generalized epileptiform discharges and

TABLE 5. Actionable Genetic Epilepsies

GENE	ASSOCIATED SYNDROME/DISORDERS	POTENTIAL THERAPIES
KCNQ2/KCNQ3	Benign familial neonatal epilepsy	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin (sodium channel blockers)
	KCNQ2 encephalopathy	Ketogenic diet in refractory
SCN1A	Dravet syndrome Generalized epilepsy with febrile seizures plus Febrile seizures Mesial temporal sclerosis	AVOID sodium channel blocking medications
KCNT1	Epilepsy in infancy with migrating focal seizures	Quinidine
mTORopathies	Tuberous sclerosis	Mammalian target of rapamycin inhibitors (sirolimus, everolimus)
	Focal cortical dysplasia type II Familial focal epilepsy with variable foci	Vigabatrin
GRIN2A	Epilepsy-aphasia spectrum disorders	Memantine
SCN2A/SCN8A (gain of function)	Migrating focal epilepsy of infancy	Sodium channel blockers
CHRNA4	Sleep-related hypermotor epilepsy	Avoidance of benzodiazepines Nicotine supplementation

triggering of absence seizures in children and teens with childhood or juvenile absence epilepsy. Intermittent photic stimulation, starting at a low frequency (1–3 Hz), should be performed. Characteristically, flash frequencies of 1 to 3 Hz provoke occipital spikes in neuronal ceroid lipofuscinosis. (40) A photoparoxysmal response is often seen in some early childhood epilepsy syndromes, such as Dravet syndrome or myoclonic atonic epilepsy, and in adolescents with juvenile myoclonic epilepsy, where myoclonus is often triggered in untreated patients. (41)

Sleep deprivation is suggested to increase the yield of EEG and can be particularly helpful for activation of focal epileptiform abnormalities that may not be present during the awake recording, (41) to evaluate for electrical status epilepticus in sleep, or for generalized paroxysmal fast activity in Lennox-Gastaut syndrome.

TABLE 6. Commonly Prescribed First-Line Seizure Medications

MEDICATION	USE	DOSE RANGES (MONOTHERAPY)	COMMON ADVERSE EFFECTS
Ethosuximide	Absence epilepsy	20–60 mg/kg per day	Gastrointestinal upset, nausea, decreased appetite
Lamotrigine	Focal seizures Generalized tonic-clonic seizures	5–13 mg/kg per day	Drug rash/Stevens-Johnson syndrome
Levetiracetam	Focal seizures, absence seizures, myoclonic seizures, generalized tonic-clonic seizures	40–60 mg/kg per day	Mood changes (irritability, anger, sadness, depression)
Oxcarbazepine	Focal seizures	600–2,100 mg per day divided twice daily	Rash, hyponatremia
Topiramate	Focal seizures Generalized seizures	200–400 mg per day divided twice daily	Word-finding difficulty Weight loss Decreased sweating
Valproic acid	Focal seizures Absence seizures Myoclonic seizures Generalized tonic-clonic seizures	25–60 mg/kg per day divided 2 or 3 times daily	Increased appetite Hair loss Polycystic ovarian syndrome

TABLE 7. **Commonly Used Rescue Medications**

MEDICATION	DOSAGE RANGE
Clonazepam	Oral dissolving tablets (non–FDA-approved indication): 0.25- to 2-mg tablets
Diazepam	Oral/buccal/IV (FDA approved for age ≥30 d [IV only]; non–FDA-approved indication [oral/buccal]): 0.2 mg/kg (maximum, 5–10 mg) Rectal (FDA approved for ages ≥2 y): 0.5 mg/kg (age 2–5 y), 0.3 mg/kg (age 6–11 y), 0.2 mg/kg (age ≥12 y)
Midazolam	Oral/buccal (non–FDA-approved indication): 0.3 mg/kg (maximum, 10 mg) Intranasal (FDA approved for ages ≥12 y): 0.2 mg/kg in each nostril (maximum, 10 mg total) Intramuscular (non–FDA-approved indication): 0.2 mg/kg (maximum, 10 mg) Intravenous (non–FDA-approved indication): 0.2 mg/kg (maximum, 10 mg)
Lorazapam	Oral/buccal (non–FDA-approved indication): 0.1 mg/kg (maximum, 4 mg) Intravenous (non–FDA-approved indication): 0.1 mg/kg (maximum, 4 mg)

FDA=Food and Drug Administration; IV=intravenous.

However, there are several important caveats to EEG interpretation in children. First, because there are EEG findings, which when limited to childhood are considered normal variants, the EEG recording should be interpreted by a reader skilled in pediatric EEG. Second, epileptiform abnormalities can be seen in approximately 3% of healthy children without epilepsy, and even a higher number with developmental disorders such as autism or attention-deficit/hyperactivity disorder (ADHD) (42)(43)(44)(45)(46)(47)(48) Thus, a diagnosis of epilepsy cannot be made solely based on epileptiform discharges on EEG. Third, normal EEGs can be seen in up to 10% of patients with epilepsy. (49) Finally, children with a skull defect from a previous neurosurgical intervention (ie, shunt, craniotomy, etc) can demonstrate a focal EEG finding known as a breach rhythm, which can be easily misinterpreted as focal epileptiform abnormalities, particularly if the EEG reader is unaware of the clinical history. (50)

Neuroimaging

In the evaluation of seizure, the question of whether neuroimaging should be performed and how urgently is common. In many instances, the first seizure prompts an evaluation in the emergency department, and head CT is frequently performed, although this is not necessarily optimal practice due to radiation risk and lower yield. Urgent imaging should be limited to cases suggestive of an acute intracranial process, such as stroke, central nervous system infection, hemorrhage, or tumor.

Most children who present with generalized onset seizures, normal neurodevelopment, and normal examination findings do not require neuroimaging. Conversely, most children who present with focal onset seizures should undergo elective magnetic resonance imaging (MRI), looking for a potential structural etiology. The exceptions to this rule are children with a clearly defined self-limited focal epilepsy syndrome, such as childhood epilepsy with centrotemporal spikes or Panayiotopoulos syndrome. (38) The MRI should be performed using a seizure or epilepsy protocol, which includes thin cuts through the hippocampi and sequences aimed at identification of malformations of cortical development (ie, double inversion recovery that suppresses CSF and white matter). MRI should be performed in cases of neonatal seizures because the most common etiologies are structural changes, such as hypoxic-ischemic encephalopathy, infarction, hemorrhage, and, less commonly, cortical malformations. An MRI is also strongly recommended for new-onset, afebrile seizures before age 3 years.

Imaging is not indicated for simple febrile seizures. In children with complex febrile seizures with focal signs and symptoms, postictal motor deficits, or febrile status epilepticus, brain MRI should be performed.

Metabolic Investigations

With the first afebrile seizure, a metabolic screen including glucose, electrolytes with calcium and magnesium, and renal function studies is typically obtained, although there is little evidence to support or refute this practice. More extensive metabolic testing looking for inborn errors of metabolism is indicated if there are other suggestive symptoms, including unexplained global delay or regression,

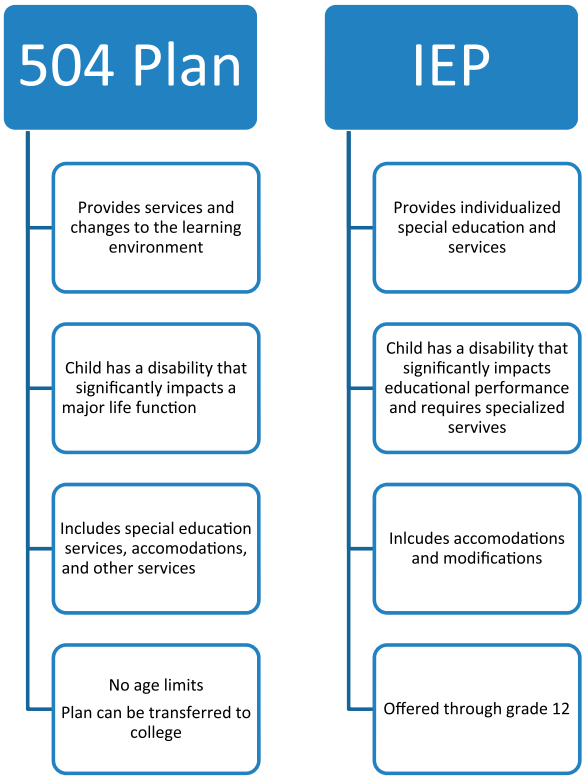


Figure 4. Differences between an individualized education plan (IEP) and a 504 plan.

organomegaly, unusual odor, or acute presentation with altered level of consciousness, multiorgan dysfunction, and vomiting, or if there are similarly affected siblings. Several metabolic disorders have specific treatments that can prevent progressive neurologic deterioration, and these metabolic disorders must be excluded in the appropriate clinical setting (Table 4).

Genetic Investigations

Genetic disorders are increasingly recognized as an important etiology, particularly in early-onset epilepsies. In a study of neonatal-onset epilepsies, pathogenic mutations were found in 83% with an epileptic encephalopathy and 30% with a structural brain malformation. (35) Similarly, of children with epilepsy onset before 3 years of age who underwent genetic testing, causal mutations were found in 40% and yields of greater than 15% were found regardless of delay, seizure type, or age at onset. (34) Thus, genetic evaluations are critical in early-life epilepsies and should include both a chromosomal microarray and an epilepsy gene panel. Whole exome sequencing is also commonly considered.

Other indications for genetic testing include unexplained delay, associated dysmorphic features, structural brain abnormalities, and other symptoms suggestive of a specific genetic etiology or unexplained drug-resistant epilepsy.

Increasingly, genetic disorders may lead to precision medicine, informing the choice of optimal medication and identifying therapies that will worsen seizures (Table 5).

Immune Studies

Autoimmune epilepsy is rare in children but must be considered in the setting of acute-onset seizures, drug-resistant seizures, encephalopathy, and other neurologic signs, particularly movement disorders, in a previously healthy child. Concern for this etiology is heightened if there is a family or personal history of autoimmune disorders (DM1, thyroid disease, rheumatoid arthritis, etc). Although imaging studies may be normal, many patients show MRI T2 hyperintensities, particularly in mesial temporal regions. If the clinical presentation is suspicious for an autoimmune cause, investigations should include inflammatory markers (erythrocyte sedimentation rate, C-reactive protein); CSF for cell count, protein, immunoglobulin G, and immunoglobulin G index; CSF and blood for neuronal autoantibodies; and blood for antithyroid antibodies.

The most common autoimmune epilepsy in children is NMDA receptor antibody encephalitis, which presents with new-onset seizures, encephalopathy, personality change, and orofacial dyskinesias. The diagnosis is confirmed by anti-NMDA receptor antibodies in the blood and/or CSF, and this disorder typically responds favorably to immunomodulatory therapy.

Rasmussen encephalitis is a rare, drug-resistant epilepsy that presents with progressive worsening of focal motor seizures, often with evolution to epilepsia partialis continua, progressive hemiparesis and hemianopsia, and possibly language dysfunction if the dominant hemisphere is affected. The MRI is normal at seizure onset but shows progressive hemispheric atrophy over time. Although this disorder is felt to be immune-mediated, neuronal antibodies are typically absent, and it is poorly responsive to immunotherapy. Hemispherectomy is ultimately required in most patients.

Febrile illness–related epilepsy syndrome is characterized by the acute onset of seizures that rapidly progress to refractory status epilepticus in the setting of previously normal development with a nonspecific febrile illness in the preceding 2 weeks. There is no evidence of intracranial infection. Although an immunologic etiology has been suspected in the past, results of neuronal antibody testing are negative. The current consensus is that this disorder is not immune but rather due to overwhelming neuroinflammation. Prognosis is poor, with significant morbidity and mortality.

Evaluation for Infectious Causes

An infectious etiology should be pursued in all children who present with new-onset seizures in the setting of fever. A lumbar puncture is strongly recommended for patients with febrile seizures in the first 12 months after birth (certainly in the first 6 months after birth) and in those presenting with febrile status epilepticus, to exclude intracranial infection. In children who present with seizures, fever, and new focal neurologic deficits, an infectious evaluation should be performed; however, neuroimaging to exclude a space-occupying lesion should be performed before lumbar puncture.

MANAGEMENT

Counseling

Counseling regarding seizure safety and first aid should be provided to all families whose child has been diagnosed as having a seizure disorder, and, ideally, this education should be extended to all caregivers, including grandparents, teachers, babysitters, coaches, and older siblings. In the event of further seizures, caregivers should be counseled to roll the child onto his or her side, place nothing in the mouth, and time the seizure. In select cases when the child has a history of prolonged seizures, or the family lives a distance from emergency medical services help, provision of home seizure rescue medication and the parameters for its use should be addressed, although many of these agents have not been Food and Drug Administration (FDA)–approved for this purpose. Generally, it is advised to call emergency medical services for seizures that persist longer than 5 minutes if no home rescue medication is available or for seizures that persist for longer than 5 minutes after rescue medication is administered.

In children with epilepsy, a seizure action plan should be drafted and updated yearly for the school and any extracurricular activity the child attends. The caregiver should be able to identify a seizure and know when and how to administer rescue medication.

Although some activity restrictions are required for safety reasons, excessive limitations should be avoided because they negatively affect peer interactions and self-esteem. Drowning accidents are the biggest risk in children with epilepsy, with most drownings occurring in the bath or pool. Thus, showers are recommended in place of baths. Children can swim but should be under direct adult supervision. Active sports participation is generally encouraged (see https://www.epilepsy.com/living-epilepsy/parents-and-caregivers/about-kids/playing-sports-and-other-activities), and there is no evidence of increased risk of seizures related to contact sports. (51)(52)

It is generally recommended that children with epilepsy continue to receive their scheduled vaccines, including influenza immunization, because the illnesses themselves can exacerbate seizures and lead to other complications (49). Although many immunizations may rarely trigger febrile seizures, there is no evidence that they increase the risk or worsen the course of epilepsy. In children with Dravet syndrome, vaccines often unmask the underlying disorder, and in many instances, children who experience febrile seizures after vaccination have an underlying *SCN1A* mutation.

Medication Management

The goal of antiseizure medication is to reduce the frequency of seizures without untoward adverse effects. The ideal therapy will result in no seizures and no adverse effects. Medications should be chosen based on the seizure type, epilepsy syndrome, etiology, medication adverse effect profile, and the child's other medical comorbidities. Certain antiseizure medications may worsen specific seizure types, such as exacerbation of absence seizures by sodium channel blockers such as oxcarbazepine, carbamazepine, or phenytoin. Prophylactic medication is often not initiated after a first unprovoked seizure, unless there are factors suggesting a high likelihood of recurrence, such as specific syndromes or etiologies. Children who present in status epilepticus are more likely to be administered antiseizure medication due to increased risk of subsequent prolonged seizures; however, in such cases, provision of a home rescue medication is also needed. Commonly prescribed first-line medications are listed in Table 6, and commonly used rescue medications are listed in Table 7.

There is generally overreliance on medication levels. Medications are generally considered to be therapeutic if the child is having no seizures and no adverse effects. Levels should be considered if there are ongoing seizures despite high doses, if one is adding a new medication that can have pharmacokinetic interactions with another drug, or to check compliance. If medication levels are assessed, they should be obtained during trough level times, just before the next dose being given. Random drug levels often result in inappropriate reduction of medication doses with breakthrough seizures. Certain medications do require periodic monitoring of blood counts and liver enzyme levels.

Drug-Resistant Epilepsy

Despite choosing the correct medications at adequate doses, some children continue to experience ongoing seizures. When sustained seizure freedom is not attained despite trials of 2 or more properly dosed medications, due to lack of efficacy the epilepsy is defined as drug resistant. (53) Children with drug-resistant epilepsy should be referred to a comprehensive epilepsy center to evaluate for possible epilepsy surgery (respective surgery, callosotomy, or neuromodulation

[vagus nerve or brain stimulation]) or consideration of additional therapies, including dietary therapies (ketogenic diet, modified Atkins diet, low glycemic index diet).

Referral to a Pediatric Epilepsy Center

Most children with epilepsy can be managed conjointly by a general pediatric neurologist and a general pediatrician. However, more complex cases should be referred to a pediatric epilepsy center for further evaluation. One of the biggest questions to be answered by such a referral is, "Is this child a candidate for epilepsy surgery or another precision therapy?" Early epilepsy surgery may be associated with improved developmental outcomes and earlier reduction or elimination of seizures. Indications for referral include the following (54):

- Age younger than 2 years
- Epilepsy is not controlled within 2 years of onset or after trials of 2 medications
- Intolerable adverse effects are experienced
- Disabling seizures
- Imaging demonstrating a focal unilateral lesion consistent with seizure signs and symptoms
- Epileptic encephalopathy, with lack of expected developmental progression, plateauing, or regression coincident with seizure onset or increase in frequency
- An etiology that requires special dietary or medical management, eg, glucose transporter deficiency, Dravet syndrome

COMMON COMORBIDITIES

As with any medical condition, there are numerous comorbidities associated with epilepsy.

Intellectual Disability and Learning Disorders

Approximately 25% of children with epilepsy have comorbid intellectual disability and nearly half have other learning disorders. Even in the so-called benign childhood epilepsy syndromes, it is common for there to be learning or behavioral impairment. Cognitive problems may be the direct result of the underlying etiology for the epilepsy, and thus do not significantly improve even if seizure control is achieved (developmental encephalopathy). Conversely, in other cases the degree of intellectual disability correlates strongly with severity of epilepsy and improves with better seizure control (epileptic encephalopathy).

Children with epilepsy should be screened for cognitive delays before school entry, or if epilepsy onset is later, at the time of diagnosis, and then periodically thereafter. If delays are present the pediatrician should inform parents of their right to request their child be evaluated for an individualized education plan (IEP) or a 504 plan (Fig 4). Both plans can cover modifications or accommodations to the classroom or educational materials, but an IEP would cover individualized special education services, whereas a 504 plan is more broadly aimed at providing the child with access to the proper learning environment.

Attention-Deficit/Hyperactivity Disorder

Attentional issues and ADHD are common in children with epilepsy, but there are 2 differences from the general pediatric population. First, the inattentive subtype of ADHD is more common in children with epilepsy. This subtype causes less disruption in the classroom and diagnosis can be delayed compared with those who are also hyperactive. Second, the sex ratio is equal in children with epilepsy, with girls affected as commonly as boys. ADHD is most common with comorbid intellectual and developmental disabilities and in patients with drug-resistant epilepsy. It is recommended that all children with epilepsy be screened for ADHD starting at school entry, with screening repeated annually. In the past it had been thought that stimulant class medication could provoke or cause seizures. However, this perception is erroneous, and stimulant medications such as methylphenidate are safe and effective for comorbid ADHD in children with epilepsy. (55)

Mood/Anxiety

There is a bidirectional relationship between mood disorders and epilepsy, suggesting common pathogenic mechanisms between these 2 conditions. Persons with epilepsy are more likely to have comorbid mood disorders, and those with mood disorders are at increased risk for seizures compared with the general population. (56) Mood concerns may be exacerbated by stressors associated with having epilepsy, the need to take daily medications, medication adverse effects, and activity restrictions. Although all antiseizure medications carry a black box warning for suicidality, certain medications may have greater potential for psychiatric adverse effects, including levetiracetam (depression and rage) and perampanel (homicidality). Given the frequency with which comorbid mood disturbances exist in children and teens with epilepsy and the potential adverse effects of antiseizure medications on mood, screening for anxiety and depression should be performed on a regular basis, with appropriate referrals to psychiatry and psychology specialists as indicated. (57)(58)

Sleep

Sleep affects many areas of a child's, life including school performance and seizure control. Sleep deprivation and

disrupted sleep can lead to breakthrough seizures. Children with neurologic disability are at risk for sleep apnea, both obstructive and central, which, in turn, is associated with worse seizure control. Melatonin is important for regulation of the circadian rhythm. Melatonin levels are frequently low in children with drug-resistant epilepsy and those with comorbid visual impairment, and melatonin supplementation may improve sleep in selected patients. (59) A regular sleep schedule is important and should not be an area of debate with caregivers.

Bone Health

Bone health can be impaired in children with epilepsy for several reasons, including reduced physical activity (particularly in wheelchair-bound children), reduced vitamin D levels and sunlight exposure, and the effects of antiseizure medications on bone health. (60)(61) Given the high prevalence of vitamin D deficiency in children with epilepsy, the authors recommend routine vitamin D, at a dose of 400 to 1,000 IU per day. Higher doses may be needed for documented deficiency. The physician should be aware of the likelihood of reduced bone mineral density and increased risk of bone fractures in children with epilepsy.

Sudden Unexpected Death in Epilepsy and Epilepsy-Related Injury

Sudden unexpected death in epilepsy (SUDEP) is a rare but devastating complication of epilepsy, affecting approximately 1 child per 4,000 person-years. (62) SUDEP is defined as an unexpected death in a person with epilepsy that is unrelated to an accident or seizure emergency. SUDEP is most commonly seen in adolescents and young adults with poorly controlled epilepsy who have frequent nocturnal convulsive seizures. (63) It is typically unwitnessed and occurs predominantly during sleep. The etiology of SUDEP is not clear but it is likely the result of postictal suppression of cardiac and respiratory drive. Although discussion of this complication can make many providers uncomfortable, many parents, who have witnessed their child have seizures, are worried about the risk of death. Furthermore, information on this topic is readily accessible online. Although it is easy to avoid discussion in an attempt to spare the family undue distress, this is a concern that keeps many parents awake at night, and often they are grateful that a provider discusses this topic.

ADOLESCENT ISSUES

In teenagers with epilepsy, driving is frequently a topic of interest. The driving laws vary considerably from state to state (https://www.epilepsy.com/driving-laws), but most require a seizure-free period before obtaining a license. In some states, physician attestation is required, whereas others rely on self-report of seizure freedom or recurrence. For many teenagers, obtaining a driver's license is a source of stress and anxiety. What should be included in the discussion on driving is the importance of medication adherence and proper reporting should breakthrough seizures occur. It should be highlighted to the teen that these requirements are to keep not only them safe but are for the safety of other drivers and pedestrians.

Pregnancy and hormonal concerns must also be addressed with adolescent females with epilepsy. The incidence of unplanned pregnancies is higher in women with epilepsy compared with those without. (64) Many antiseizure medications reduce the efficacy with oral contraceptives (particularly estrogen-containing preparations). Potential options to reduce failure rates include using a high-estrogen pill (≥50 μg of ethinyl estradiol); using an additional barrier method, such as a condom or diaphragm; or using long-acting forms of contraception, such as intrauterine devices or implants. Estrogen-containing oral contraceptives also interact with lamotrigine, significantly reducing its levels and increasing the risk of breakthrough seizures. If an oral contraceptive is started in a woman taking lamotrigine, levels should be monitored closely because a dose increase will likely be needed. Some women also experience a worsening of seizures around menses (catamenial epilepsy), and an oral contraceptive or other hormonal therapy can be helpful in preventing this pattern. Pregnancy presents a variety of considerations, including the risk to the fetus from antiseizure medication, alterations in antiseizure medication levels in pregnancy, and, ultimately, seizure control. When a woman is taking a medication with teratogenic potential, the specific risks must be discussed and, if possible, an alternative medication offered.

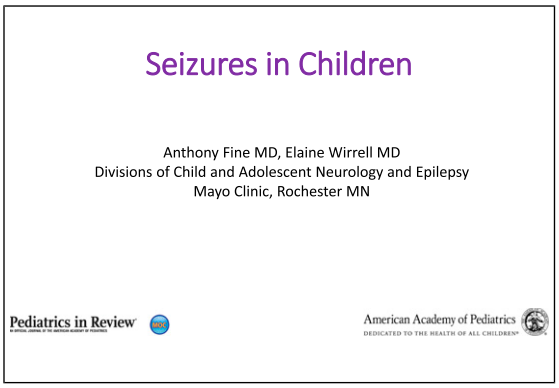
Finally, the transition to an adult provider should be introduced early in adolescence and should incorporate a planned educational process that will prepare the teen and family for ultimate care in the adult setting. When brought up just before actual transfer of care, the move often does not go as smoothly for either the patient or the providers. The age at transition varies between centers, but in cognitively healthy teenagers, transfer to adult care typically occurs by age 18 years, or the time these teens graduate high school. In developmentally delayed teens, the transition is often harder to complete by this age, and they often see multiple pediatric subspecialists. Families feel more comfortable if they are provided a transition document and

know that the future provider they will see is familiar with their case. (65)(66)

Summary

- According to expert consensus, seizure classification is important for the diagnosis and management of patients with epilepsy, as well as for providing counseling and prognostication.
- Based on collective research evidence and consensus, electroencephalography (EEG) should be performed in all children presenting with an afebrile seizure. The timing of the first EEG is debatable based on some research evidence that the yield of EEG may be higher in the first 24 hours; however, the availability of urgent EEG is often limited. Further maneuvers, such as a sleep-deprived recording, hyperventilation, and photic stimulation, can further increase the yield of routine EEG. (38)(39)
- Based on consensus and practice guidelines, referral to a pediatric epilepsy center should be performed in children younger than 2 years and in children with medically refractory epilepsy and disabling seizures, with an epileptic encephalopathy, or with an etiology that requires special dietary or medical management. (54)
- Children with epilepsy are more likely to have comorbid intellectual disability, depression, anxiety, attention-deficit/hyperactivity disorder, and poor bone health compared with peers.
- Sudden unexpected death in epilepsy is a rare complication of epilepsy seen in approximately 1 child per 4,000 person-years. (62) All families of children with epilepsy should be counseled regarding this potential complication, especially those with frequent nocturnal convulsions. (63)

To view teaching slides that accompany this article, visit **http://pedsinreview.aappublications.org/content/41/7/321.supplemental.**



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PIR Quiz

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1. A 3-year-old typically developing boy with no previous medical or seizure history presents after experiencing an 18-minute seizure. Mom reports that he has had fever up to 102.5°F (39.1°C) at home and suddenly became unresponsive, with jerking of all arms and legs. On arrival at the emergency department he was febrile and slightly disoriented, without any tonic-clonic movements. Within a few minutes he is awake, alert, and frightened by his surroundings. You explain to the first-year resident that your impression is that this patient had a complex febrile seizure because of which of the following seizure characteristics?
    A. Associated with disorientation.
    B. Atypical.
    C. Generalized.
    D. Prolonged.
    E. Unprovoked.
2. A 7-year-old boy presents with a first unprovoked seizure. A routine electroencephalogram is requested to include sleep and wakeful states as well as hyperventilation and photic stimulation. Which of the following is the most optimal timing for this investigation to be completed?
    A. After a lumbar puncture.
    B. At the 1-week follow-up visit.
    C. During the presenting seizure.
    D. In the emergency department setting.
    E. Within 24 hours of the seizure.
3. A quality improvement project of emergency department procedures indicates that the house staff is appropriately requesting magnetic resonance imaging (MRI) on children who present with focal seizures and those with suspected stroke, tumor, or central nervous system infection. Children who are also at high risk and should routinely undergo MRI include those with which of the following conditions?
    A. History of absence seizures.
    B. Family history of seizure.
    C. Previous diagnosis of autism.
    D. Tonic-clonic seizure lasting more than 10 minutes.
    E. Unprovoked afebrile new-onset seizure at age younger than 3 years.
4. You are following a 2-year-old boy with epileptic encephalopathy. After initial assessment with electroencephalography, a comprehensive metabolic panel, and brain MRI, the etiology of his seizures remains unclear. In this situation, which of the following evaluations carries the highest likelihood of determining the etiology of the epileptic encephalopathy in this patient?
    A. Diffusion tensor imaging studies.
    B. Genetic studies.
    C. Metabolic studies for inborn errors of metabolism.
    D. Mitochondrial metabolism studies.
    E. Toxicology screening.
5. A well-behaved 8-year-old girl with a history of well-controlled seizures is struggling to keep pace with her classwork. The individualized education plan team reports that she has high average intelligence and average academic abilities. The teacher reports that her performance is inconsistent. Her parents note that although homework takes longer for this daughter than their other children, she does it independently. Which of the following is the most appropriate next step in evaluation of this young girl?
    A. Functional behavioral analysis.
    B. Rating scales for attention-deficit/hyperactivity disorder.
    C. Brain MRI.
    D. Screening for mood disorders.
    E. Sleep study.

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