EPILEPSY

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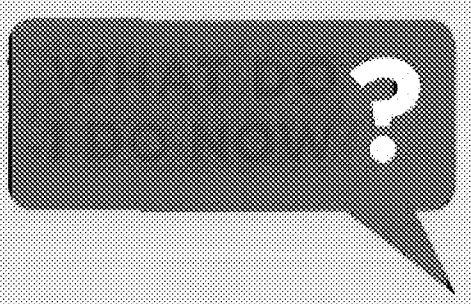
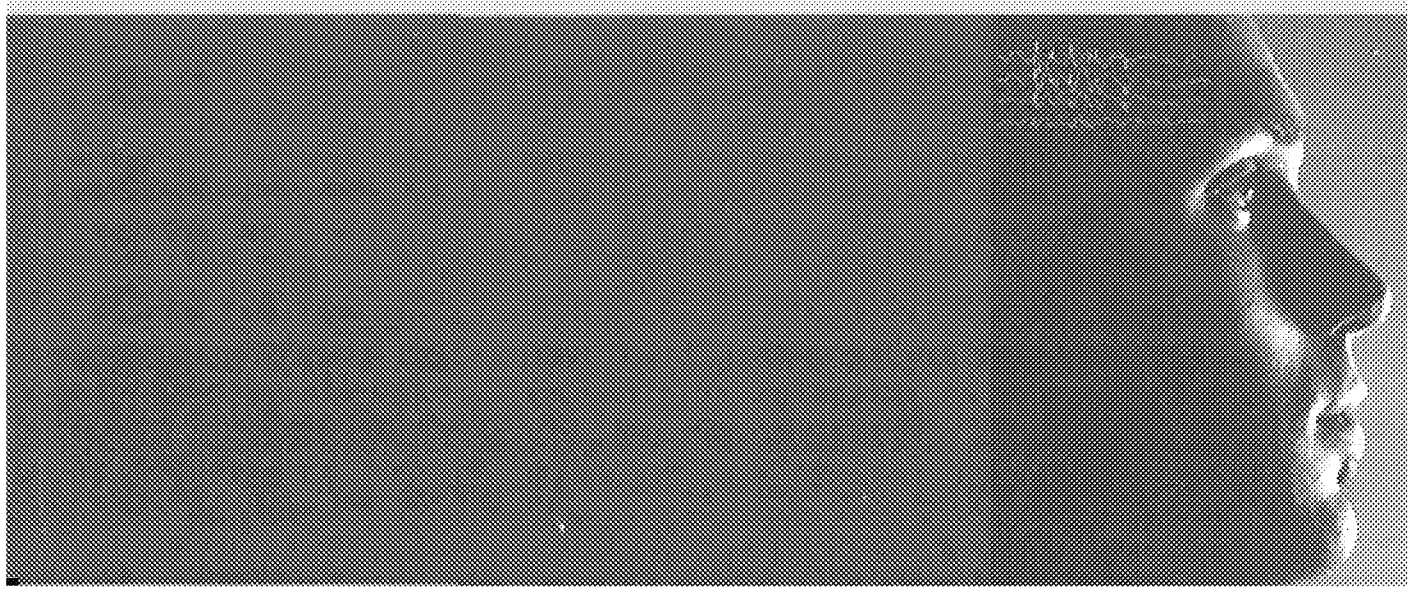


EPILEPSY

CARL W. BAZIL, DEREK J. CHONG,
DANIEL FRIEDMAN



Epilepsy

What Do I Do Now?

Epilepsy

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To our patients, who have taught us the most about epilepsy, and that a life with epilepsy can be every bit as full as life without it.

Preface

Epilepsy is a diverse and sometimes complicated condition. It is also very common, such that all neurologists, and nearly all physicians, will encounter patients with epilepsy. Perhaps more than most other conditions in neurology, epilepsy is further complicated by potential interactions with other medical conditions and with a patient's lifestyle.

This volume contains numerous case examples, meant to illustrate scenarios that commonly arise in the clinical care of patients with epilepsy and ways of approaching them. The first section has chapters that address diagnostic questions: How to approach a first seizure? What about diagnostic challenges, such as confusion with syncope or parasomnias? Drug therapy is indicated for nearly all patients with epilepsy, so the second section contains various scenarios dealing with anticonvulsant drugs, including choosing from the large number of drugs available in each epilepsy syndrome, choosing drugs in specific patient populations, drug interactions, and when (if ever) it may be appropriate to withdraw anticonvulsant treatment in a patient with epilepsy. If drug therapy is not completely effective or is otherwise unsatisfactory, alternatives are discussed in the third section. Finally, the fourth section looks at lifestyle and other issues: the mood and cognitive disorders so prevalent in epilepsy, the topic of sudden death in epilepsy, issues of bone health and sleep disorders, and implications for driving and work.

Each epilepsy patient is different—these are only a few examples. But we hope you will find this volume useful in thinking about the problems you encounter in treating people with epilepsy.

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Safety is of primary importance in patients with epilepsy. This is particularly concerning with driving and in work or other activities that may place the patient and others at risk should a seizure occur. The risk of seizure recurrence must be considered on an individual basis before recommendations can be made, but general guidelines are also helpful in discussing this topic with patients.

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SECTION I

Diagnostic Questions

1 Febrile Seizures and Other Seizures in Infants

A 9-month-old previously healthy boy is brought to the emergency room with two convulsive seizures and a fever of 103°F. He was born full term and has had normal development. Two days prior, he was at his well baby visit and received several immunizations. On the day of admission, his mother noted that he "was burning up" and several hours later he had a 1-minute-long convulsive seizure. He had another seizure in the ambulance. He was given antipyretics and rectal diazepam. He has a cousin who also had seizures with fevers. His parents want to know if seizures will recur, how he should be treated, and what his risk is for developing epilepsy.

What do you do now?

Febrile seizures (seizures that occur with fever in the absence of known epilepsy, CNS infection, or metabolic disorder) can occur in children between 6 months and 5 years of age. They are typically divided into simple and complex febrile seizures. Simple febrile seizures last less than 15 minutes and occur once within a 24-hour period. Complex febrile seizures are prolonged, recur within 24 hours, or have obvious focal features (e.g., clonic activity of one limb). A careful history and physical examination is necessary to evaluate for potentially life-threatening infections and to determine if the child was neurologically intact prior to the seizures and if the fever preceded the seizure, as mild hyperpyrexia may follow seizure activity. In infants less than 12 to 18 months of age, signs of meningitis may be difficult to appreciate and lumbar puncture should be considered to exclude CNS infection. In the case of simple febrile seizures, EEG and brain imaging is typically not warranted unless there is a history of preceding neurologic abnormality.

Febrile seizures are common, with an incidence of 2% to 5% before age 5. Febrile seizures tend to recur: approximately 40% of patients will have another febrile seizure, but only 9% experience 3 or more days with febrile seizures. Age of onset is an important factor, as infants less than 1 year of age have a 50% chance of recurrence, whereas the rate is only 20% in those with onsets at 3 years of age or older. Other predictors of recurrence include a family history of febrile seizures, a low fever or a short duration of fever prior to the seizure, or complex febrile seizures. The number of risk factors

TABLE 1-1 **Febrile Seizures and Risk Factors for Subsequent Epilepsy**

	Increased Risks:
Age of febrile seizure	Ages < 3 months and > 5 years
Duration	> 15 min
Frequency	Seizure recurrence within 24 hours
Focal Features	Obvious (unilateral clonic activity, Todd's paresis)
Family history	Afebrile seizures in parent or sibling
Baseline Neurological status	Abnormal

present increased the risk of febrile seizure recurrence: two or more factors predict a 30% chance, and 3 or greater risk factors purports a 60% risk.

There is no evidence that the number of febrile seizures influences the risk of subsequent epilepsy. Furthermore, there is no evidence that simple febrile seizures lead to any measurable brain injury. The neurologic impact of prolonged febrile seizures and febrile status epilepticus is unknown, but preliminary imaging studies show effects on hippocampal structures. This suggests that febrile status epilepticus, like other forms of status epilepticus, should be identified early and treated aggressively.

The rate of subsequent afebrile seizures (i.e., epilepsy) following a simple febrile seizure is low and is likely no greater than in the general population. Some clinical features, such as febrile seizures before 12 months of age and a family history of epilepsy or febrile seizures, may suggest a genetic predisposition to seizures such as the generalized epilepsy with febrile seizures plus (GEFS+) syndrome, and these patients are at a slightly higher risk of developing epilepsy. Patients with complex febrile seizures have a higher rate of subsequent epilepsy, with approximately 6% to 8% having unprovoked seizures by age 25. If there are focal features and the seizures are repetitive or prolonged, the risk is much higher. Other factors that increase the risk for subsequent epilepsy include neurologic abnormalities prior to the seizure, younger age at onset, or a family history of epilepsy. Rarely, febrile seizures are the first manifestation of severe myoclonic epilepsy of infancy (SMEI or Dravet syndrome), a catastrophic epileptic encephalopathy of infancy, most often due to a mutation in the SCN1A gene. This disorder typically presents with complex febrile seizures before age 1 in otherwise normally developing infants A genetic test is available and should be used to screen these patients, as many with this typically sporadic genetic abnormality will experience developmental abnormalities in the following years.

While the peak incidence of febrile seizures occurs between 18-24 months of age, a large proportion of all seizures occur before age 1. Afebrile seizures in infancy are often due to structural, genetic (single gene), chromosomal, or metabolic abnormalities. Sometimes, afebrile or unprovoked seizures have a benign course, such as in benign neonatal convulsions or benign infantile seizures. These epilepsy syndromes typically occur in otherwise neurologically normal infants, spontaneously remit, and have only a modestly elevated risk of epilepsy later in life. Other conditions, such as

early infantile epileptic encephalopathy (Ohtahara syndrome), West syndrome, Dravet syndrome (discussed above), early myoclonic epilepsy, and myoclonic epilepsy in infancy, are associated with difficult-to-treat epilepsy and significant developmental delay. Because of the poor prognosis of many seizures presenting in infancy, it is important to emphasize the benign nature of febrile seizures to parents, who are justifiably anxious.

TREATMENT

Because of the benign nature of most febrile seizures, prophylactic treatment with antiepileptic drugs (AEDs) is usually not recommended. While AEDs such as phenobarbital, primidone and valproic acid have been shown to suppress future febrile seizures, they do not prevent the development of subsequent epilepsy and are often associated with neurocognitive side effects that typically outweigh any benefits. The use of antipyretics such as acetaminophen does not appear to prevent seizure recurrence. This suggests that a high temperature alone does not provoke febrile seizures and other factors, such as inflammatory cytokines, are the proconvulsant stimulus. Acetaminophen and ibuprofen are considered safe and effective antipyretics to use in these children, but parents should be advised they are being used primarily for comfort. Current practice parameters have instead recommended acute abortive therapies such as rectal diazepam (0.5 mg/kg) (max 20 mg) or midazolam administered intranasally (0.2 mg/kg; divided per nostril) (max 10 mg total) or bucally (0.5 mg/kg)*, to limit the duration of seizures and prevent hospitalization. In rare patients where recurrence is frequent or caregivers are unable to administer abortive treatment, prophylactic treatment with an oral benzodiazepine (e.g. lorazepam, clonazepam) during a febrile illness or chronic antiepileptic treatment, typically phenobarbital, can be considered.

This child had a complex febrile seizure because he had two seizures several hours apart. In addition, he has a family history of epilepsy. These two factors suggest he may have a reduced seizure threshold and is at increased risk for developing subsequent epilepsy. At this time, no available treatment can reduce that risk. He also has a high risk of febrile seizure recurrence because of the age of onset being <1 year of age. He should continue to be immunized as scheduled, including influenza vaccines, to reduce the number of childhood febrile illnesses. In addition, because his

seizures were repetitive, his parents could be instructed in the use of an abortive therapy to prevent seizure clusters. As with most patients, the use of chronic AEDs is not recommended in this case.

*Nasal and buccal routes of midazolam administration are not US FDA approved.

KEY POINTS TO REMEMBER

- Febrile seizures occur between 6 months and 5 years of age.
- Simple febrile seizures occur in neurologically normal children without acute CNS infections, last less than 15 minutes, are nonfocal, and do not recur in a 24-hour period.
- Most simple febrile seizures are not associated with a significantly increased risk of subsequent epilepsy.
- Rarely, febrile seizures are the first manifestation of Dravet syndrome.
- Febrile seizures tend to recur, but prophylactic AED use is not usually recommended because of the adverse effects of chronic AED exposure.
- Abortive therapies may be useful in patients with clusters or prolonged therapies.

Further Reading

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2 Benign/Idiopathic Partial Epilepsies (IPE) of Childhood

A 10-year-old boy presents to your office with his mother. About 2 years ago, he awoke with a stomach ache and slept on the floor of his mother's room. About 1 hour later, his mother awoke to see him in the midst of the tonic phase of a tonic-clonic seizure. It lasted 1 minute, with postictal confusion for 5 minutes. An overnight EEG showed high amplitude but simply configured epileptiform discharges over the central region with a negativity at C4 and a positivity at F4. They were rare during wakefulness but very frequent during sleep. He was started on phenobarbital but then was switched to oxcarbazepine due to another generalized tonic-clonic seizure. A year ago, he awoke with difficulties with speech that lasted the entire day and his oxcarbazepine dose was increased to 300 mg twice daily. About 1 month ago he began having choking episodes just prior to falling asleep. This occurred for several days in a row, although he is amnestic to many of the events.

His total seizure count includes three known generalized nocturnal convulsions and numerous episodes with a sense of choking, mostly during

the night. He has associated issues with depression, anxiety, headaches, and difficulty concentrating. The rest of his history and review of systems is negative except for non-migrainous headaches over the frontal convexity. A first cousin on his mother's side had a diagnosis of benign rolandic epilepsy.

His mother is worried about the continued seizures and is wondering whether the diagnosis and treatment plans are correct.

What do you do now?

Benign childhood epilepsy with centrotemporal spikes (BECTS) is often referred to as BECTS or simply benign rolandic epilepsy. It is the most common idiopathic partial epilepsy (IPE). Similar to his case, seizures classically occur shortly after falling asleep or just prior to awakening, though any pattern of sleep-awake or awake-only seizures can occur. The seizures during wakefulness are exclusively simple partial events, often with unilateral paresthesias of the oral mucosal surfaces; unilateral clonic or tonic activity involving the face, lips, and tongue; dysarthria; and drooling. Stiffness of the jaw or tongue and a choking sensation are common. Unlike this case, patients typically recall the wakeful part of the seizures and are rarely confused during them. Seizure duration is typically seconds to minutes.

Typical nocturnal seizure activity includes:

1. Brief hemifacial seizures with speech arrest and drooling while still conscious.
2. Hemifacial seizures with loss of awareness, gurgling, or grunting that may progress to vomiting.
3. Secondary generalized tonic-clonic seizures.

Postictal Todd's paresis may occur; this would be a clue to a partial origin. The typical age of onset is 7 to 8 years but varies widely from age 3 to 13. Younger patients tend to present with hemiconvulsions.

Rarely, status epilepticus can occur. Other variants may occur, such as partial motor seizures changing lateralization, paresthesias, jerking of a single limb, abdominal pain, blindness, and vertigo.

The "benign" term is evidenced by over 99% of cases remitting by age 18 in case series of about 400 patients. Many practitioners begin weaning off medication around age 16 if there have been no seizures in the past 6 months. It is notable that a small subset of BECTS patients who develop atonic, atypical absence or myoclonic seizures, termed "pseudo-Lennox" syndrome, may have cognitive losses despite eventual seizure remission.

BECTS can occur with a known structural abnormality, but seizures in these cases also typically remit. In the patient presented above there was one unusual seizure, with symptoms lasting over a day. If his seizures were not responding to medication, it would be reasonable to obtain an MRI of the head. Otherwise, MRI scanning of the head is considered unnecessary in

patients with a normal neurological examination and typical seizures and EEG findings. The classic EEG finding is the presence of large-amplitude but often simply configured spike or sharp waves with large after-going slow waves, with a dipole: the negativity is central and positivity is seen frontally (Fig. 2.1, 2.2). The epileptiform discharges may be unilateral or bilateral, either synchronous or independent. They may occur during wakefulness but become activated by non-REM sleep and drowsy states. If the diagnosis is in doubt, repeating the EEG with a sleep state can be helpful, although it needs to be interpreted in the clinical context. It appears that only 10% of children with these rolandic spikes actually have the clinical seizures. The EEG may evolve in terms of location and may even show atypical spike locations. However, finding generalized discharges, spike-wave runs, or other types of partial seizures would significantly change the diagnosis and thus prognosis.

There is a familial component, sometimes with an autosomal dominant inheritance. Linkage analysis has implicated chromosome 15q14, though BECTS appears to be heterogeneous. Many siblings show the same centro-temporal spikes on EEG, though they may not necessarily have the

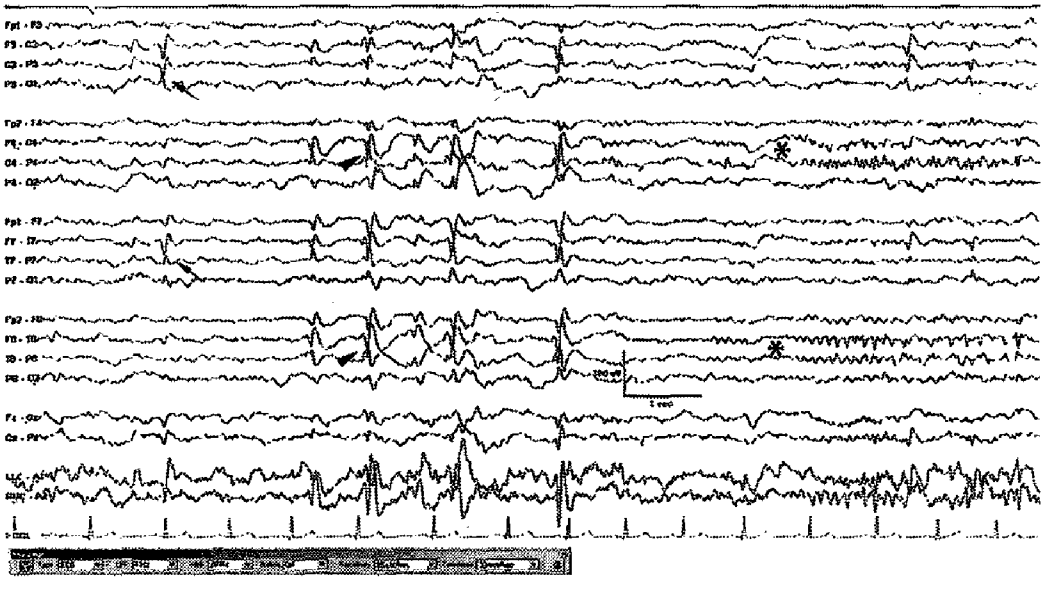

FIGURE 2-1 Epileptiform discharges typical of benign rolandic epilepsy or BECTS. The discharges are lateralized with a broad field over left (*arrows*) temporal (T7) and central postero-central (P3) and the right (arrowheads) temporal (T8) or central (C4-P4) regions. Note the relatively simple configuration to the majority of the discharges. In this example, the spike discharges preceded the onset of one of the patient's typical nocturnal hemiconvulsive seizures from sleep arising from C4-T8 (*).

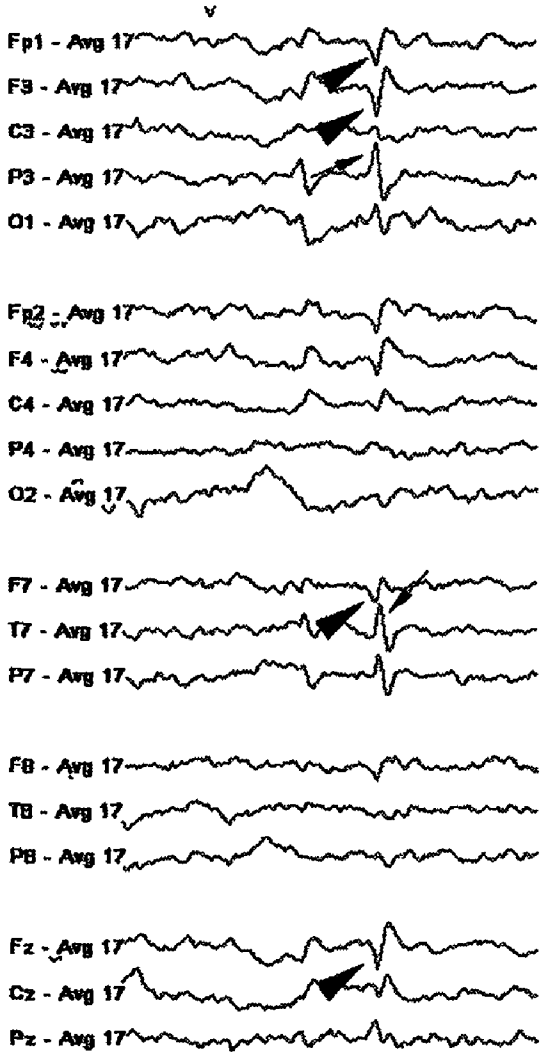

FIGURE 2-2 The first spike in Figure 2.1 displayed in Common Average Referential montage, highlighting a typical dipole: upwards negativity over P3, T7, and P7 (*arrows*) and downwards positivity over Fp1, F3, and Fz. The dipole is classically described as being obvious on long bipoar montage, though it often requires closer review, as in this case.

clinical seizures. In patients with unusual presentations, the presence of similar centro-temporal spikes in their siblings would be more supportive of BECTS. Many believe the pathophysiology to be due to abnormal brain maturation, with changes in synapses (pruning or development of more inhibitory connections) or with changes in the electrical characteristics of ion channels with time. There is an increased rate of migraine and other headaches with BECTS.

AED treatment does not improve the chance of remission, and there have been no reports of sudden unexplained death in epilepsy with BECTS.

However, many patients and families may elect to use AEDs to limit seizures prior to spontaneous remission. Generalized convulsions tend to respond to AEDs, but partial seizures have only a 50% to 65% chance of responding fully. There have been case reports of carbamazepine, phenobarbital, and lamotrigine exacerbating the spike activity and worsening neuropsychological function, though these are also the most likely AEDs to be used which limits interpretation.

A centrally acting carbonic anhydrase inhibitor, sulthiame, has shown efficacy in Europe for the treatment of the BECTS seizures and normalizing the EEG, but it is not available in the United States. A small study in Canada showed that sulthiame was associated with neuropsychological worsening.

As a group, the IPEs account for about 20% of epilepsies of childhood and adolescence. Along with lacking structural abnormalities detectible by MRI, patients are typically neurologically and intellectually otherwise normal, though visuospatial, auditory processing, and general learning disabilities appear to be more common in the IPEs. Many patients will benefit from neuropsychological assessment to address any potential deficiencies.

Early-onset benign occipital epilepsy, the second most common IPE, is also known as Panayiotopoulos syndrome. It is more commonly seen in girls, with a typical age of onset of 5 years (range between 2 and 8 years). Tonic eye deviation, nausea, and vomiting are characteristic components, though autonomic involvement (including syncope) and secondary generalization may occur. In addition, there may be positive or negative visual phenomena of any type, but these are not the primary features. Seizures occur nocturnally, though some patients have daytime events as well. The duration of seizures varies, but they can last up to 30 minutes. A history of febrile seizures is common (17%). The seizure disorder remits within 1 to 2 years, though some patients may go on to develop BECTS. Because of the quick remission and typically rare events, treatment is often not required. Abortive therapy for prolonged seizures includes orally dissolvable clonazepam, rectal diazepam and midazolam (buccal or intranasal) being among the options with fast onset, although lorazepam PO may also be effective.

Late-onset benign occipital epilepsy is known as the Gastaut type. The age range of onset is broader (3 to 16 years), with a peak of 8 years of age. The classic semiology is of elementary visual hallucinations (colors, shapes),

though tonic eye deviation and eyelid closures may also occur. Ictal blindness, when it occurs, is brief. Seizures are simple partial at onset, though they may progress to cloud consciousness or may secondarily generalize. They often occur daily and in many cases are followed by a migraine headache. Because occipital lesions may present with simple visual hallucinations, MRI of the brain is recommended. Treatment is necessary for most patients due to the frequency of seizures and the postictal migraine. The greatest data are with use of carbamazepine, but complete seizure freedom was not always attained, and other agents can be considered. Some cases (about 5%) continue into adulthood.

KEY POINTS TO REMEMBER

- Idiopathic partial epilepsies of childhood are benign syndromes. They are often familial and typically without structural abnormalities on MRI.
- BECTS is well defined, with onset at ages 3 to 13 (peak 7 to 8) years. More than 99% of cases remit by age 18.
- BECTS seizures are simple partial during the day or night, though nocturnal convulsions may occur.
- Early-onset benign occipital epilepsy presents with tonic eye deviation, nausea, vomiting, or autonomic (Panlotopolous syndrome) involvement (including syncope); remission usually occurs within 1 to 2 years, an treatment is required only when seizures are frequent or prolonged.
- Late-onset benign occipital epilepsy presents with daily elementary visual hallucinations and postictal migraine (Gastaut-type). Most cases require treatment. Not all patients will attain seizure freedom on AEDs, but most cases will remit by adulthood.
- The EEG in idiopathic partial epilepsies shows high-voltage spikes with a horizontal dipole, and they are activated by sleep. In BECTS there is a broad field over the central and temporal regions (Fig. 2.1, 2.2). In occipital epilepsies localization is less specific, occasionally with extra-occipital spikes, but will attenuate with eye opening.

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3 Nonconvulsive Seizures in Acutely Ill Patients

The patient is a 30-year-old woman with type I diabetes mellitus and hypothyroidism who developed altered consciousness and headache 3 days after a cesarean section for failed progression of labor. She had an uncomplicated pregnancy and operative course. She complained of a severe headache and then became lethargic and less responsive. Her laboratory studies were significant for serum glucose of 261 mg/dL and proteinuria. An emergent CT of the head revealed no abnormalities and a lumbar puncture revealed a normal CSF profile with negative cultures and herpes simplex virus PCR. She was treated with empiric antibiotics and acyclovir for presumed encephalitis and magnesium for possible eclampsia. An MRI demonstrated restricted diffusion in the right temporo-parieto-occipital region without significant FLAIR abnormalities (Fig. 3.1). The patient's mental status improved but then continued to fluctuate. EEG was performed urgently and demonstrated right occipital epileptiform discharges and frequent 30- to 90-second-long focal seizures from the right posterior quadrant (Fig. 3.2). She was treated with

additional magnesium and intravenous levetiracetam. She continued to have frequent electrographic seizures and fluctuating mental status. During the seizures, she had slowed responses, did not blink to visual threat on the left, and had left-sided neglect.

What do you do now?

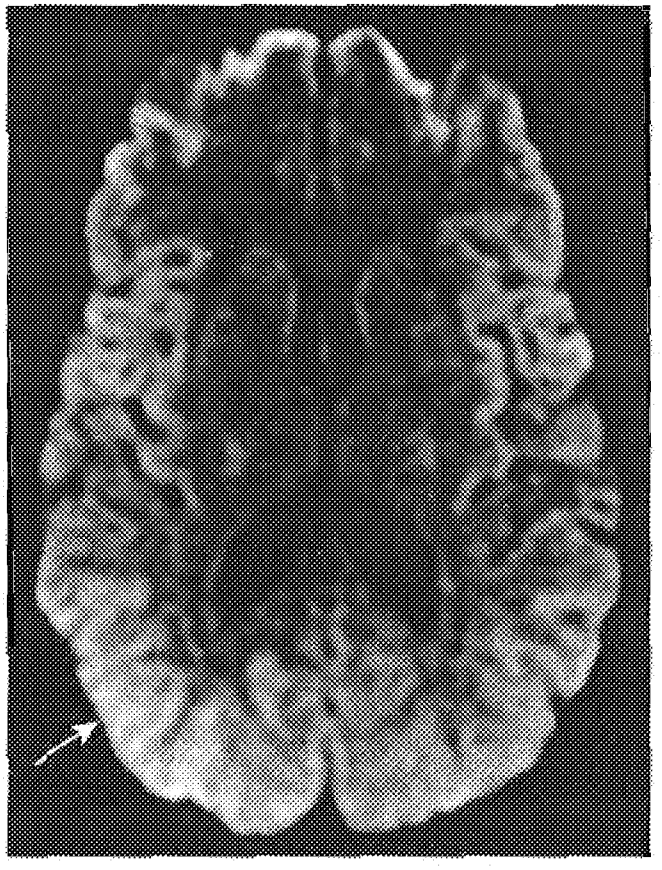

FIGURE 3-1 Diffusion-weighted MRI showing an area of restricted diffusion in the right temporo-parieto-occipital region (*arrow*).

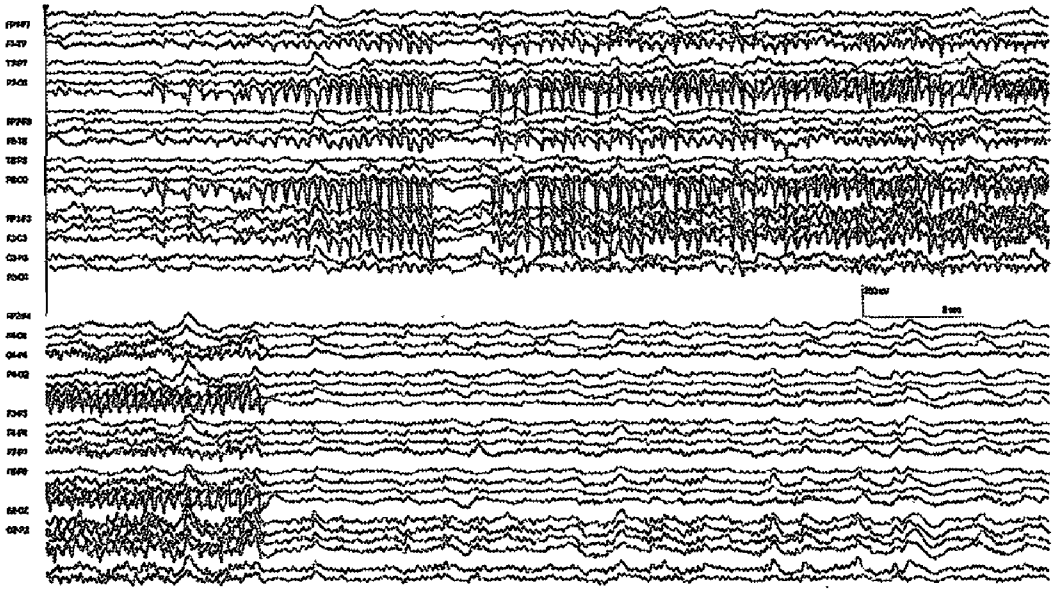

FIGURE 3-2 *EEG recording demonstrating an electrographic seizures arising from the right posterior quadrant.*

This patient likely has acute focal neurologic symptoms from a disorder of cerebrovascular permeability such as eclampsia or posterior reversible encephalopathy syndrome. One of the manifestations of her injury is a focus of increased cortical excitability and frequent nonconvulsive seizures (NCS). Because she does not return to her baseline mental status between seizures, she is considered to be in nonconvulsive status epilepticus (NCSE). By definition, NCS have no obvious tonic or clonic motor activity. They are increasingly recognized as a common occurrence in hospitalized patients with acute brain injury. The most common manifestation of NCS and NCSE is altered or fluctuating mental status, but NCS can be associated with other subtle signs such as face and limb twitching, nystagmus, eye deviation, pupillary abnormalities, and autonomic instability. None of these signs are highly specific for NCS and they are often seen under other circumstances in brain-injured or critically ill patients; thus, EEG monitoring is necessary to make the diagnosis. A routine 30-minute EEG may miss about 50% of NCS found on prolonged recording. Therefore, continuous EEG monitoring (cEEG), when available, is preferable for NCS diagnosis in brain-injured patients. In some series, NCS occurred in 19% to 36% of patients with acute brain injury who had altered mental status or coma

undergoing cEEG. NCS can also occur in patients with systemic conditions, such as sepsis, in the absence of acute brain injury as well. Table 3.1 lists conditions associated with NCS in hospitalized patients.

Though NCS are common in acutely brain-injured and critically ill patients, evidence that they worsen outcomes and require prompt identification and treatment is mixed. In some populations, such as elderly patients with NCSE, aggressive treatment is actually associated with worse outcomes. To date, there has not been a prospective controlled trial to determine if treating NCS or NCSE improves neurologic outcomes. In the absence of definitive evidence of their harm, much of the justification for identifying and treating NCS in the critically ill comes from human and animal data demonstrating that seizures can lead to neuronal injury and worsen the extent of the inciting injury.

In the absence of evidence of their harm and the potential morbidity associated with continuous intravenous infusions of anesthetics, many experts suggest a less aggressive approach to the treatment of NCSE. The 3 principles of this strategy are:

1. Trials of several nonsedating, rapidly titratable antiepileptic drugs (AEDs).
2. Treatment of the precipitating injury.
3. Avoidance of medications and electrolyte imbalances that may provoke seizures.

AEDs available in intravenous preparations are the best first-line agents in these patients, as there are no issues about amount or time for absorption. There are sufficient data for the use of phenytoin (and fosphenytoin) and valproate for the treatment of status epilepticus, including complex partial status epilepticus, to suggest these agents as first-line agents for NCSE. Unlike intravenous phenytoin, valproate has no hemodynamic effects and does not require electrocardiographic and blood pressure monitoring during rapid administration. Therefore, it may be a preferable agent in some hemodynamically unstable patients. Typical loading doses are 18 to 20 mg/kg for phenytoin and 20 to 25 mg/kg for valproate (30 to 40 mg/kg if the patient is on P450 enzyme-inducing drugs already). After administering a loading dose, the patient and EEG should be reevaluated. If there is

TABLE 3-1 **Causes of NCS in Hospitalized Patients**

Exacerbation of preexisting epilepsy
AED withdrawal
Acute neurologic insult
Cerebrovascular disease: ischemic stoke, intracerebral hemorrhage, subarachnoid hemorrhage
Infection: meningitis, encephalitis, brain abscess
Head trauma
Anoxia
Brain tumors
Demyelinating disorders
Supratentorial neurosurgical procedure
CNS autoimmune disorders
Acute systemic insult
Electrolyte imbalances: hyponatremia, hypocalcemia, hypomagnesemia, hypophosphatemia
Hypoglycemia; hyperglycemia with hyperosmolar state
Vitamin deficiency: pyridoxine
Illicit drug use (e.g., cocaine)
Toxins
Hypertensive encephalopathy, eclampsia, posterior reversible encephalopathy
Hypotension
Renal or hepatic failure
Multisystemic autoimmune disorders such as systemic lupus erythematosus
Medications: side effects/toxicity, withdrawal
Alcohol withdrawal
Systemic infection/sepsis

Adapted from Abou Khaled KJ, Hirsch LJ. Advances in the management of seizures and status epilepticus in critically ill patients. *Critical Care Clin.* 2006;22:637.

return to baseline mental status or absence of electrographic seizures on EEG, the loaded AED should be continued at maintenance doses (approximately 5 mg/kg/day for phenytoin, approximately 15 mg/kg/day for valproate). If the patient is not returning to baseline mental status, the EEG should be reevaluated. If there is evidence for ongoing seizure activity, a supplemental bolus of about 25% of the initial drug dose can be given. A serum drug level should be checked following the administration of the second bolus. The initial target serum levels should be approximately 20 mg/dL for phenytoin and 100 mg/dL for valproate. Additional boluses can be given to reach these target levels if the patient is still having frequent seizures. If, however, the patient is still having NCSE with an acceptable serum level of the initial anticonvulsant, adding a second drug should be considered. If the initial treatment was phenytoin, one could give a loading dose of valproate, or vice versa. Attention should be paid to the complex pharmacokinetic interaction between these two drugs when used in combination, and obtaining frequent serum and free drug levels is often helpful. Valproate can rarely contribute to thrombocytopenia and interfere with platelet function in addition to factor XIII so there are specific situations where its use should be deferred.

An alternate intravenous drug is levetiracetam, typically given in an initial dose of 1,000 to 2,000 mg. Limited evidence suggests that it is effective as an add-on drug for status epilepticus. It has no drug–drug interactions and no hemodynamic effects, making it an ideal choice for critically ill patients with multiple medical problems. Recently, an intravenous formulation of lacosamide has become available. There has been only anecdotal evidence supporting its use in refractory status epilepticus with initial loading doses of 200 to 300 mg. Phenobarbital, either via intravenous or oral administration, can be used in cases of refractory NCSE though caution should be used due to the risk of excess sedation and respiratory depression. Finally, several oral agents can be rapidly loaded or started at full therapeutic doses. These include pregabalin, gabapentin, topiramate, and zonisamide. These may be reasonable agents to add when the patient is not responding to first- or second-line therapy.

EEG patterns and seizures in brain-injured patients often look different than those in ambulatory patients with epilepsy. Many patients have

EEG patterns that, while periodic, may not be classified as definitely ictal. These patients may have rhythmic or periodic discharges, such as lateralized or generalized periodic epileptiform discharges (PLEDs, GPEDs) or rhythmic delta activity, slower than 3 Hz, that do not display typical ictal spatial or temporal evolution. However, these patterns can also be interictal or not epileptiform at all (e.g., triphasic waves in metabolic encephalopathies), making it difficult to diagnose NCSE even by EEG. One strategy for determining if a periodic pattern is a probable seizure and contributing to decreased mental status is to attempt to abolish the pattern with low doses of a rapid-acting benzodiazepine and see if there is an improvement in the level of consciousness. A trial is positive (consistent with NCSE) if there is an improvement in the EEG and the patient's examination. If the periodic pattern is abolished but the patient remains encephalopathic or comatose, the trial is equivocal. A protocol for performing a diagnostic benzodiazepine trial is shown in Table 3.2. If a trial is positive, AEDs, as discussed above, should be started.

TABLE 3-2 Benzodiazepine Trial Protocol for the Diagnosis of NCSE

Inclusion Criteria: Patients with neurologic impairment and rhythmic or periodic epileptiform discharges on EEG

Monitoring: EEG, pulse oximetry, BP, ECG, respiratory rate, with dedicated nurse

Antiepileptic Drug Trial

Give sequential low doses of rapidly acting short-duration benzodiazepine such as midazolam at 1 mg/dose.

Repeat clinical and EEG assessment between doses.

Trial is stopped after any of the following:
- Persistent resolution of the EEG pattern (and exam repeated)
- Definite clinical improvement
- Respiratory depression, hypotension, or other adverse effect
- A maximum dose is reached (such as 0.2 mg/kg midazolam, though higher may be needed if on chronic benzodiazepines)

Adapted from Jirsch J, Hirsch LJ. Nonconvulsive seizures: developing a rational approach to the diagnosis and management in the critically ill population. *Clin Neurophysiol.* 2007;118(8):1660-1670.

There is no good evidence to guide clinicians on how long to treat patients who have acute seizures, both convulsive and nonconvulsive, in the setting of brain injury or toxic-metabolic abnormalities. If the abnormality is entirely reversible, such as sepsis or metabolic derangements, anticonvulsant treatment is unlikely to be necessary after the acute hospitalization. However, if seizures are due to acute brain injury, a longer course of treatment is sometimes favored. The duration of treatment should be tailored to the type of injury and persistence of radiologic and EEG abnormalities. While many patients with acute brain injury carry a risk of later developing epilepsy, this is not prevented by prolonged AED treatment.

One month after her hospitalization, the patient in this case had a repeat MRI that was normal and a normal EEG. She was at a low risk of seizure recurrence, and levetiracetam was tapered off.

KEY POINTS TO REMEMBER

- **Nonconvulsive seizures are common in patients with acute brain injury or critical illness.**
- **Manifestations of nonconvulsive seizures are subtle and not specific; therefore, EEG recording is often required to make the diagnosis.**
- **Routine EEG recording can miss 50% of patients with nonconvulsive seizures; prolonged continuous EEG monitoring increases the diagnostic yield.**
- **Nonconvulsive status epilepticus should be treated quickly with rapidly administered nonsedating AEDs; more aggressive treatment with continuous intravenous anesthetic infusions may be reserved for patients who do not respond to standard AEDs.**
- **In some critically ill patients, it is difficult to determine if a periodic or rhythmic EEG pattern is ictal or interictal. A diagnostic trial of short-acting benzodiazepines may be helpful.**

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4 Psychogenic Nonepileptic Seizures

Martha is a 56-year-old, right-handed woman who has had seizures since about age 20. At that time, she was diagnosed with temporal lobe epilepsy. She reports being treated with sodium valproate (Depakene) for several years with resolution of symptoms. Episodes recurred at age 51 and now occur on a daily basis, despite trials of eight anticonvulsant medications at therapeutic doses, as well as a vagus nerve stimulator. They almost invariably occur shortly after taking her morning dose of lamotrigine.

In her 20s, seizures consisted of episodic confusion lasting at most a few minutes. She had a single possible generalized convulsion in the past. Since seizures recurred 5 years previously, they are different: she feels things "slow down" and speech is difficult. She is sometimes unable to speak but is able to understand everything that occurs. She has no automatisms although she has occasional twitching. Episodes last up to 90 minutes and are followed by headache and sleepiness.

There are no known risk factors for epilepsy. Her son used drugs extensively in childhood and adolescence; however, this is now resolved. She also reports that her ex-husband was emotionally abusive; this occurred in the time before seizure onset. Medications on evaluation included escitalopram (for depression) and lamotrigine. Prior EEG reports over the past 25 years have shown right temporal, right central, and/or generalized epileptiform activity.

What do you do now?

Refractory epilepsy is usually defined as the failure of two or more appropriate anticonvulsant drugs at maximally tolerated concentrations. This woman clearly falls into that category. In general, once a patient is considered refractory, video-EEG monitoring is indicated to confirm the diagnosis and to guide further therapy. As with an unfortunately large percentage of other patients, this woman met the criteria many years before the referral was made.

Video-EEG monitoring is the only way to absolutely confirm the diagnosis of epilepsy. In most patients, a careful history is sufficient for epilepsy diagnosis and confirmatory tests (particularly imaging, usually with MRI, and EEG) can support the diagnosis. However, we do know that the EEG can be abnormal in a small subset of patients without epilepsy, and that it can be normal in patients with epilepsy. With video-EEG monitoring, patients who are documented to have epilepsy can have treatment redirected—either to another appropriate anticonvulsant drug or in some cases to epilepsy surgery. An important subset of these patients, however, will be found to have nonepileptic events, usually psychogenic nonepileptic seizures (PNES). In this case treatment must be redirected toward the treatment of this disorder.

Historical information can help in raising the suspicion for nonepileptic seizures; however, no finding is absolute (Table 1). Eye closure during seizures has been associated with PNES, but the sensitivity of 52-96% and specificity of 97% of patients is among the best. Asynchronous movements during the seizure is also a good predictor of PNES, but only when frontal lobe seizures are excluded, as bizarre movements typify this type of epilepsy (see chapter 5). Patients with documented tongue biting or incontinence have been considered more likely to have epileptic seizures, but both are seen in PNES. When seizures are described to arise from sleep, it is often thought that they must be epileptic; however, a patient may appear to be asleep but actually be quietly awake. Recording of actual spells can help to make this distinction. Patients with PNES are more likely to have a history of psychiatric problems and/or abuse, but these are common in epilepsy patients overall.

Not only family members but also physicians can be misled by witnessing an actual event or seeing a videotape. Again, characteristics may be suggestive of psychogenic or epileptic seizures, but studies show that even

TABLE 4-1 Clinical Characteristics of Epileptic versus Psychogenic Nonepileptic Seizures

Suggestive of epileptic seizure	Suggestive of psychogenic nonepileptic seizure
Tongue biting	No tongue biting or mild laceration of tongue tip
Incontinence	No incontinence
Eyes open during unresponsiveness	Eyes closed during unresponsiveness (esp. forced eye closure)
Clinical stereotypy	Clinical variability
Crescendo progression	On-off progression
Seizures beginning during sleep or wakefulness	Episodes beginning only during wakefulness
Duration 1-3 minutes	Duration over 5 minutes
Postictal confusion	Rapid return to baseline
Random occurrence	Induced and/or alleviated by suggestion
History of head injury, other structural brain lesion	No head injury, normal brain imaging
No history of physical/sexual abuse, psychiatric disease	History of physical/sexual abuse, psychiatric disease
Response to AEDs	No response to AEDs (patients may respond somewhat to positive psychotropic effects)
Epileptic EEG abnormalities	Normal EEG

trained epileptologists will mistakenly identify these seizure types about 30% of the time.

Another characteristic of PNES is that they are suggestible. This is true of seizure onset and can be used to advantage when trying to record the events. Patients may identify particular "triggers" such as stressors. Placebo injections have been used with the suggestion that these can produce seizures; however, many consider this misleading presentation unethical as it is not possible for patients to give truly informed consent. Many centers

therefore use more conventional "suggestion" such as hyperventilation or intermittent photic stimulation. While it is true that these can in fact provoke certain epileptic seizures, the intent is actually similar to a placebo: suggestion to the patient that a seizure will occur. Suggestion is also, however, important in resolving events. Some patients can be taught to stop their events, for example with deep breathing.

About a third of patients with PNES have concurrent epileptic seizures. This can further confuse the diagnosis, particularly when epileptic activity is seen on the EEG. Usually, the clinical description is quite distinct and (if both epileptic and nonepileptic seizures are documented with video-EEG) the patient and/or caregiver can be taught to distinguish between them. If there is a strong suspicion of concurrent epileptic seizures, patients need to continue taking an anticonvulsant while treatment for psychogenic events occurs. However, in some cases it may be safe to reduce the number of drugs in patients who have been treated with escalating anticonvulsants for events that prove to be nonepileptic. Finally, and perhaps most challenging from a diagnostic standpoint, patients can have an exaggerated response to an epileptic seizure. This is most confusing when a simple partial seizure (difficulty to confirm with EEG) is in itself not disabling but results in a panic reaction or another form of psychogenic response. As with concurrent epileptic seizures, both conditions then need to be addressed in treatment.

What exactly are PNES? There are many psychiatric diagnoses associated, including panic disorder, but most patients likely have a dissociative disorder. Malingering can occur, however is probably rather rare even if there is perceived secondary gain. It is always better to assume that the patient is not malingering and to treat accordingly. A patient with a conversion disorder who is accused of malingering will be angry and will not receive proper treatment; a malingerer who is treated for conversion disorder will be no worse off. Trained psychologists or psychiatrists can address this problem to bring events under control; psychotherapy and hypnosis are proven to be helpful, and any underlying diagnosis such as generalized anxiety disorder should also be treated. It is important for the neurologist to remain involved particularly in the short term, as a sense of abandonment or not being taken seriously is common in these patients and can exacerbate the condition.

In the case described, the patient actually brought a video of an event. This appeared nonepileptic visually: it was not stereotyped, did not have a progression typical of epileptic seizures, was prolonged, and did not fit the clinical characteristics of any particular seizure. She appeared conscious and talking, with eyes closed. However, video-EEG monitoring was performed for confirmation. She did in fact have frequent epileptiform discharges from the right temporal lobe; however, the episodes in question were not clinically or electrographically consistent with epileptic seizures. So although she was at risk for concurrent epileptic seizures (present in about a third of patients with PNES), her current seizures were not epileptic and needed to be treated as such. She had come to associate nonepileptic events with lamotrigine dosing; when changed to an extended-release form at night (accompanied by a strong suggestion that they would improve!), episodes improved tremendously.

KEY POINTS TO REMEMBER

- Psychogenic nonepileptic seizures (PNES) occur in up to 25% of refractory epilepsy patients, and a definitive diagnosis can be made only through video-EEG monitoring.
- Characteristics of PNES include clinical variability, ictal eye-closure, on-off progression, long duration, and suggestibility. They occur more often in women than in men and are associated with psychiatric disease and a history of physical or sexual abuse. Episodes are more likely to be epileptic if they are associated with tongue biting, injury, or incontinence and if they occur directly from sleep. However, none of these guidelines are absolute.
- PNES often occur in patients who also have epileptic seizures, adding to the diagnostic confusion.
- Psychotherapy is essential for successful treatment of these patients; hypnosis has also been shown effective.
- The neurologist needs to remain involved after diagnosis to assure the patient that care will continue, to treat coincident epileptic seizures if suspected or present, and to communicate with treating mental health professionals.

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5 Frontal Lobe Seizures

The patient is a 28-year-old right-handed woman with a history of depression and anxiety who was referred to the epilepsy monitoring unit for evaluation of recurrent episodes of agitation, abnormal movements, and bizarre speech for the past 2 years. The episodes typically occur at night as she is falling asleep or waking up. Family members describe jaw clenching, turning over in bed, thrashing of all four limbs, pelvic thrusting, agitation, and nonsense speech. The episodes are usually 30 seconds long. Within 1 minute, she is lucid and is aware that she had a seizure. She had a MRI and routine interictal EEG; results were normal. A prior video-EEG recording at another hospital showed no electrographic correlate to her event and she was diagnosed with psychogenic nonepileptic seizures.

During the current admission, prolonged video-EEG monitoring revealed no interictal abnormalities. She had two of her typical episodes. The EEG was obscured by

muscle artifact during the episode. In addition, she had numerous brief stereotyped arousals at night characterized by slight rightward head deviation and mouth movements and scissoring of both legs.

What do you do now?

Paroxysmal events with complex motor and behavioral features present a particular diagnostic challenge to neurologists. Patients with psychogenic nonepileptic seizures (PNES) often have motor manifestations that are traditionally thought of as "atypical" for convulsive epileptic seizures. This may include asynchronous tonic or clonic movements of the extremities, side-to-side head movements, opisthotonic posturing, and pelvic thrusting. In addition, there may be complex vocalizations, often with an emotional component. However, these features may also be present in simple or complex partial seizures of frontal lobe origin. Patients with frontal lobe seizure may have retained awareness. As awareness of PNES has increased over the years, there are patients who are incorrectly suspected of having PNES based on the description of their events by the patient or family. In one series, 19% of patients referred for diagnostic video-EEG monitoring with suspected PNES were ultimately found to have epileptic seizures. Even with ictal video-EEG recording, the diagnosis can be difficult to make. Scalp EEG can be obscured by muscle artifact in seizures with significant hypermotor features at onset. In other cases, seizure onset may be restricted to areas that are too small or distant to the scalp to be associated with an EEG correlate. Simple partial seizures restricted to the supplemental motor area or medial frontal lobe may produce complex behaviors without alteration of consciousness or scalp EEG correlate. For similar reasons, these patients may have normal interictal EEGs as well. While this occurs in a minority of patients, it is important to remember that the sensitivity of ictal video-EEG recording is not 100%.

Additional testing may be necessary if the clinical suspicion for epilepsy remains high. This may include the use of modified electrode montages to detect ictal or interictal abnormalities or ictal single photon emission computed tomography (SPECT) to examine for areas of seizure-related hyperperfusion. Careful inspection of high-resolution 3T MRI to examine for subtle lesions, such as cortical dysplasias, in the frontal lobe in the setting of suspicious events may be helpful, although often unrevealing. Medication withdrawal may provoke a longer or more widespread seizure with associated electrographic correlate or unequivocal clinical features. However, despite additional testing, the final determination of whether paroxysmal events are epileptic in nature may ultimately be made by clinical criteria. Therefore, it is often necessary to record several of the spells in

question in an epilepsy monitoring unit to allow careful review of the features of the spells and ancillary testing of behavior.

Some features of the paroxysmal events, especially when present in combination, are more suggestive of epileptic seizures. Frontal lobe seizures often emerge from sleep, while PNES are always from wakefulness. However, some patients with PNES may appear asleep at seizure onset but the EEG pattern preceding the event is that of wakefulness. In one series less than 1% of patients had PNES occur within seconds of an arousal. Stereotyped events arising from electrographic sleep have an organic cause, of which seizure, parasomnia or movement disorder would be most likely. Epileptic seizures tend to be stereotyped in nature, with similar motor activity and vocalizations with each event. Seizures originating in the frontal lobe tend to be brief, usually less than 30 seconds in duration, with explosive onsets and little postictal confusion, although patients may be amnestic to having had the seizure when asked the following morning. Depending on the pattern of seizure spread, the seizure can also be prolonged and have a prominent postictal state. Seizures of frontal lobe origin tend to be frequent and can occur dozens of times per day. In some cases, not all of the seizures are as prolonged or severe and they may have very subtle manifestations. In patients with suspected frontal lobe seizures, special attention

TABLE 5-1 Common Features of Frontal Lobe Seizures in Adults

Sudden onset and termination
Brief duration
Frequent occurrence
Often nocturnal, arising from electrographic sleep
Complex motor automatisms, including thrashing, jumping, pedaling, pelvic thrusting, grasping, shaking, sexually suggestive movements
Vocalizations
Stereotyped pattern
Frequently misdiagnosed
Interictal and ictal scalp EEG often unrevealing

Adapted from Williamson et al. Seizures of frontal lobe origin. *Ann Neurol* 1985;18:497

should be paid to arousals from sleep. If these have features that are stereotyped or similar to the start of their typical clinical spell, as in the patient described here, it is likely these are brief seizures that support the epileptic nature of the clinical spell. The treatment of frontal lobe seizures is no different than other partial onset seizure disorders.

KEY POINTS TO REMEMBER

- **Paroxysmal events with bizarre and complex behaviors are a diagnostic challenge.**
- **Frontal lobe seizures may have motor features and vocalizations that can be confused with psychogenic nonepileptic seizures.**
- **Frontal lobe seizures tend to be brief and frequent and of abrupt onset, and often occur from sleep.**
- **Scalp ictal and interictal EEG may be nondiagnostic; additional investigations and careful clinical investigations may be necessary.**

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6 Seizure Versus Parasomnias

A 56-year-old right-handed man was referred for repeated episodes of nocturnal confusion. He believes that "sleepwalking" episodes began about 4 to 5 years ago. He says these were never witnessed. On one episode, he arose at about 2:30 in the morning and went to his office as if it were the middle of the workday. He believes he recalls going to the office but that it seemed like a "dream" at the time. In another episode, 3 or 4 years previous to evaluation, he was at his office and was found to be hitting his head against a wall. He does not remember this beginning or occurring but believes that this episode may have begun while awake. He was confused for up to 20 minutes afterward. The most recent episode occurred about 3 weeks previously, when he suddenly found himself in the kitchen with a laceration on his forehead. He again reports confusion, but the entire episode was unwitnessed. He feels that these episodes improved with the addition of clonazepam and risperidone (Risperdal).

Also, in the previous few months he reports three episodes of fecal incontinence during sleep. This was not

associated with any other manifestations such as evidence of wandering, urinary incontinence, tongue biting, or soreness. He reports isolated episodes of urinary incontinence in the past as well, also during sleep.

He has had a sleep-onset insomnia for many years, requiring up to 6 hours to fall asleep. During that time he mainly reports staying in bed and resting, although he sometimes arises to read. He gets up at about 8 a.m. and sometimes feels refreshed. He naps for about 1 hour per day. He reports snoring and awakening "gasping for air," although this has not occurred recently.

More recently, he also reports declining memory and concentration. He worked as a vice president of a publishing company but was laid off several months previously.

There is no history of risk factors for neurologic disease except that his sister has epilepsy of an unknown type that began in childhood; he believes it is now under control on medication.

What do you do now?

The differential of nocturnal seizures and parasomnias is not an unusual one. Both are typically unwitnessed, and the patient may have limited or no memory of the actual event. This patient could have unrecognized nocturnal seizures, and events clearly occurring from wakefulness would make this more likely. If present, seizures could be occurring more frequently than known, which could be contributing to memory loss and difficulty concentrating. On the other hand, he could have sleepwalking episodes with associated confusion, or an independent sleep disorder (such as obstructive sleep apnea) exacerbating either seizures or sleepwalking.

With epilepsy or conditions potentially confused with epilepsy, a careful history is by far the most important part of making a diagnosis. Both seizures and parasomnias can be paroxysmal, and in many cases they have similar clinical semiology. Some characteristics can help to distinguish between seizures and parasomnias (Tables 6.1 and 6.2), but none are absolute. For example, it is highly unusual to have incontinence during sleepwalking, but it can occur. Parasomnias most commonly confused with epilepsy are cataplexy, sleep attacks (sudden, irresistible onset of sleep), night terrors, and REM behavior disorder. Any paroxysmal episode occurring only during sleep should raise the suspicion of a sleep disorder, although cataplexy and sleep attacks occur with the patient awake. Clinicians should be mindful that many patients with sleep disorders have excessive daytime somnolence, and daytime attacks can occur during naps. Conversely, there are many epilepsy syndromes where attacks occur predominantly or exclusively during sleep, particularly benign rolandic epilepsy and nocturnal frontal lobe epilepsies. Seizures associated with juvenile myoclonic epilepsy or awakening grand mal epilepsy tend to occur shortly after awakening but can also occur from sleep. Partial epilepsy of frontal lobe onset tends to occur predominantly during sleep and in some patients may be entirely restricted to sleep. Temporal lobe seizures begin more during wakefulness, but partial seizures can be subtle (even unrecognized) and evolve into more obvious, grand mal seizures when beginning during sleep. Excessive daytime somnolence is suggestive of an underlying sleep disorder, particularly narcolepsy but also restless legs syndrome, sleep apnea, and periodic limb movements. A report of sleepiness can be helpful in diagnosis, but frequent nocturnal seizures will also disrupt sleep and result in similar symptoms.

TABLE 6-1 **Seizure Versus Non-REM Parasomnias**

	Seizure	Sleep Drunkenness	Sleep Terrors	Somnambulism	Somniloquy	Sleep Enuresis	PLMS RLS
Incontinence	+	-	-	-	-	+	-
Tongue biting	+	-	-	-	-	-	-
Confusion	+	+	+	+	+	-	-
Tonic-clonic movements	+	-	-	-	-	-	-
Drooling	+	-	-	-	-	-	-
Amnesia	+	+	-	+	+	-	-
Occur awake	+	-	-	-	-	-	-

PLMS/RLS: periodic limb movements of sleep/restless legs syndrome

TABLE 6-2 Seizure Versus REM Parasomnias

	Seizure	Nightmare	Cataplexy	Sleep Paralysis	Hypnic Hallucinations	REM Behavior Disorder
Incontinence	+	-	-	-	-	-
Tongue biting	+	-	-	-	-	-
Confusion	+	-	-	-	-	-
Tonic-clonic movements	+	-	-	-	-	-
Drooling	+	-	-	-	-	-
Amnesia	+	-	-	-	-	-
Occur awake	+	-	+	+	+	-

PARASOMNIAS FREQUENTLY CONFUSED WITH EPILEPSY

There are many normal and abnormal sleep phenomena that can be confused with seizures. Sleep terrors can usually be distinguished from seizures by their exclusive occurrence in sleep combined with the characteristic dream imagery, predominant fear, and rapid recovery. Abnormal movements, prolonged confusion, drooling, and tongue biting are suspicious for seizure. Sleepwalking (somnambulism), somniloquy (sleep talking), and sleep enuresis (bedwetting) are very common in childhood but rare in adults. Nightmares consist of frightening dreams that often awaken the patient from sleep and can be accompanied by agitation. A history usually identifies these as benign events; however, if specific dream imagery is not recalled, a history of sudden fear followed by confusion might be mistaken for nocturnal seizures.

REM behavior disorder is characterized by agitated, sometimes violent movements occurring during REM sleep. Patients typically report that a dream sequence occurs during the episode. The history of bizarre, semipurposeful behavior with confusion may be impossible to distinguish from seizures or postictal behavior. Unlike most partial seizures, REM behavior disorder is restricted to sleep and usually occurs in the early morning, when REM is most prevalent. The memory of a dream sequence, if present, is helpful in distinguishing the two.

The primary tool for investigation of seizures is the EEG. This test records the change in electrical activity on the scalp over time. In routine polysomnography, only the central and occipital regions are recorded, and the parameters are set primarily for recognition of sleep structure. In a full EEG, all areas of the scalp are recorded.

For most patients with suspected epilepsy, a routine EEG is performed, lasting about 30 minutes. While it is unlikely that an actual seizure will be recorded in that time, some patients will show interictal abnormalities called "spikes" or "sharp waves." These markers of epilepsy are present in up to 90% of patients with epilepsy, although repeated or prolonged studies may be needed to identify these. Interictal epileptiform discharges are rarely seen in individuals without epilepsy; these occur in about 2% of children and 0.5% of adults.

When the diagnosis remains in doubt, a definitive study is video-EEG monitoring. This is typically performed as an inpatient. EEG is recorded continuously, and the patient remains on a video camera until a typical episode takes place. In the case of rare episodes, patients may be weaned off medications, deprived of sleep, or stressed in other ways to encourage more frequent episodes. If episodes occur nearly every night, and particularly if other parasomnias are in the differential, video-EEG polysomnography may be performed as an outpatient. Most systems in current use for polysomnography have the potential to record a full EEG simultaneously with routine polysomnographic channels. The event(s) in question, once recorded, can then be examined using both techniques. Seizure activity may be difficult to confirm on a more limited polysomnography montage and setting but much clearer with a full EEG (Fig. 6.1).

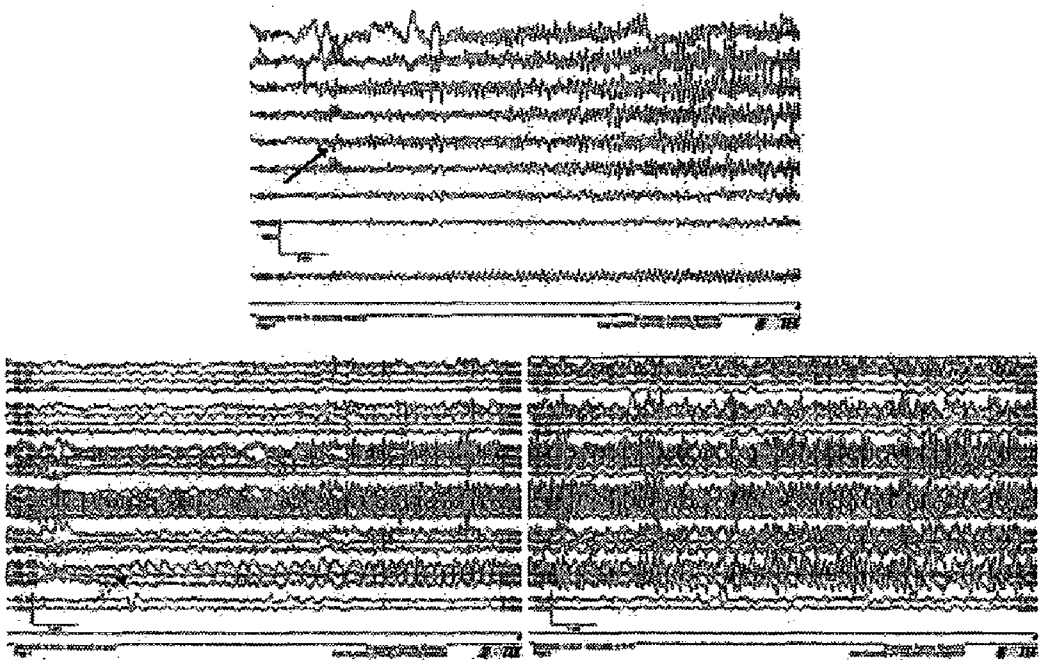

FIGURE 6-1 Temporal lobe seizure. Top: polysomnography. The seizure discharge can be seen (*arrow*), but it appears diffuse and evolution is difficult to appreciate; thus it would be difficult to confirm as an electrographic seizure. Bottom: Electroencephalography. The electrographic seizure is clearly seen, initially in the right subtemporal chain (*arrow*) with spread to adjacent electrodes.

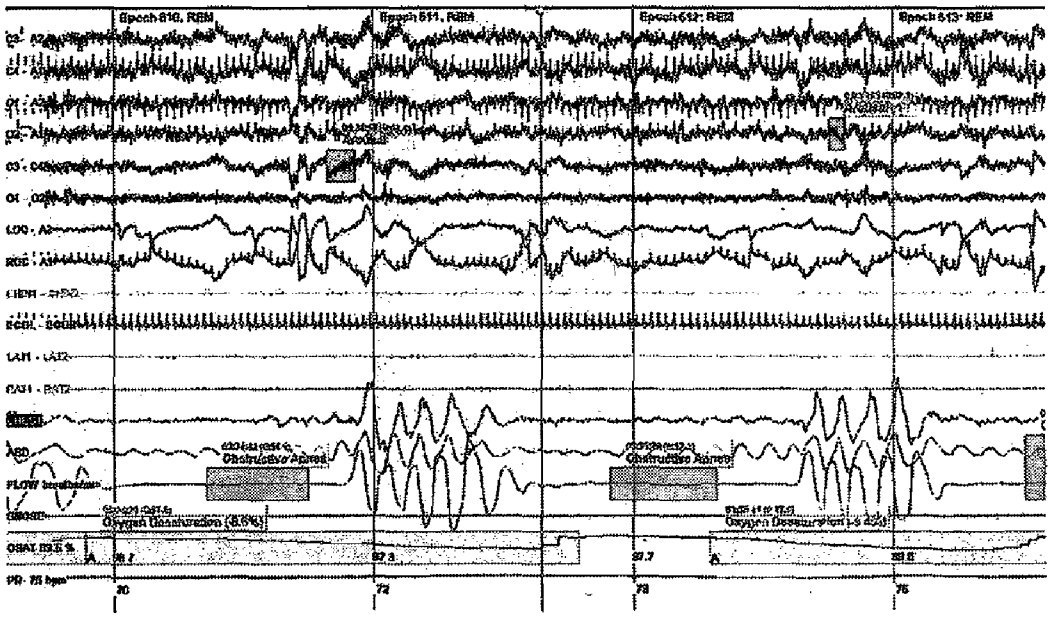

FIGURE 6-2 *Obstructive sleep apnea in patient with concurrent frontal lobe epilepsy. In this 2-minute segment, several obstructive hypopneas are seen with associated oxygen desaturations (overall apnea-hypopnea index 64.5/hour).*

The patient described was admitted for video-EEG monitoring and had overnight polysomnography during the admission. He was found to have frequent nocturnal episodes consistent with frontal lobe partial seizures; these resolved with gabapentin 1200mg given solely qhs. He also had significant obstructive sleep apnea (Fig. 6.2), which was successfully treated with positive airway pressure. With treatment of both conditions his cognitive function and daytime drowsiness improved remarkably.

Seizures and sleep disorders are of course both treatable. Anticonvulsant treatments are covered extensively in other chapters, but the choice may be influenced if there are concurrent sleep disorders. Gabapentin and pregabalin are known to treat restless legs syndrome; benzodiazepines (particularly clonazepam) are useful for many arousal disorders and REM behavior disorder. In subjects with obstructive sleep apnea clinicians should avoid agents more likely to cause weight gain (such as valproate and pregabalin) and may prefer agents that tend to cause weight loss (topiramate or zonisamide).

KEY POINTS TO REMEMBER

- **The differential of paroxysmal events occurring during sleep includes seizures and parasomnias. These can sometimes be distinguished through a careful history; a secondhand report by an observer or, if possible, a video of the event can be particularly helpful.**
- **EEG may identify patients at higher risk for epilepsy, but definitive diagnosis is best made through overnight polysomnography (usually with a full EEG) for nightly events. Less frequent episodes may require inpatient video-EEG monitoring, ideally with at least one polysomnography.**
- **Both parasomnias and seizures can be exacerbated by a concurrent sleep disorder. These are frequently undiagnosed, including obstructive sleep apnea. There should be a low threshold for recommending polysomnography in these patients.**
- **Sleep disorders and seizures are treatable, but correct diagnosis is essential.**

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7 Seizure Versus Syncope

A 68-year-old, right-handed physician presents with sudden loss of awareness and possible seizure. He reports sleep deprivation and fatigue due to a recent return from overseas and a flu-like illness. He reports that he felt faint at work and went to sit down, and a witness said that he became pale, began vomiting, and then had loss of awareness for about 5 seconds with trembling. Afterward, he quickly returned to full awareness. He had a second similar episode after continued vomiting; he reports that this occurred while he was sitting. There were no violent movements during either of these, no tongue biting, and no incontinence.

He reports that he has had two possible similar episodes in the past but has never had episodes of nocturnal incontinence, tongue biting, or apparent convulsion.

His medical and surgical history are unremarkable except for hypertension, which is well controlled on atenolol and enalapril (Vasotec).

What do you do now?

The differentiation between seizure and syncope is common in neurology and in epilepsy. There are features that are classic for each condition; when a thorough history is available, the distinction can often be made with relative certainty. A history of prolonged lightheadedness after standing for a long time on a hot day, followed by sudden loss of awareness and falling, with abrupt return to consciousness is typical for syncope. However, a complete history is not always available. The patient may not recall the onset of the event and will typically be unaware of his or her condition during loss of awareness. Onlookers may or may not be present, and even if a firsthand account is available, it can be incomplete at best and misleading at worst.

General characteristics of syncope and seizure are shown in Table 7.1. Although these are useful as a guideline, there are always exceptions. Incontinence, for example, is common with a generalized tonic-clonic seizure but can also occur with syncope. Long periods of lightheadedness or dizziness are suggestive of syncope, but some patients with epilepsy have a long prodrome that can appear similar. Perhaps most confusing is the presence of clonic movements. Most physicians and many neurologists immediately assume the presence of these is highly suggestive of seizure. In reality, however, clonic movements are common with syncope, although they are typically more irregular and of shorter duration than those usually seen

TABLE 7-1 Characteristics of Syncope Versus Seizure

Seizure	Syncope
Random occurrence	Setting of dehydration, prolonged standing
Any position	Usually standing, sometimes seated
Brief aura (<1 minute)	Long prodrome (up to 30 minutes)
Loss of awareness 1-2 minutes	Loss of awareness for seconds (can be longer if remains upright)
Rhythmic tonic-clonic movements	No movements or brief, irregular clonus
Tongue or lip biting common	Slight tongue or lip biting, rare
Postictal confusion	Rapid recovery

with a generalized seizure. An onlooker (even a trained healthcare professional) cannot always be expected to reliably note or later describe the difference. The clonic movements appear to occur with decreased cerebral perfusion, as can be seen by diffuse attenuation of the EEG (Fig. 7.1).

Further workup depends on the nature of the presentation. Blood chemistries may be useful in determining whether the patient has hypoglycemia or dehydration. In cases suspicious for seizure, an imaging study of the brain (usually MRI) is often performed. EEG can be a useful screen for epilepsy, although a normal study does not completely rule out the possibility of seizures. Most research suggests that a single routine EEG has only about a 50% chance of showing abnormalities in patients with known epilepsy. Depending on the degree of suspicion a longer study may be warranted; many laboratories can now perform high-quality ambulatory studies that allow recordings of up to 3 days. This increases the yield of epileptiform activity if present, probably because this may best be seen in deep sleep, a condition almost never recorded in routine office EEGs.

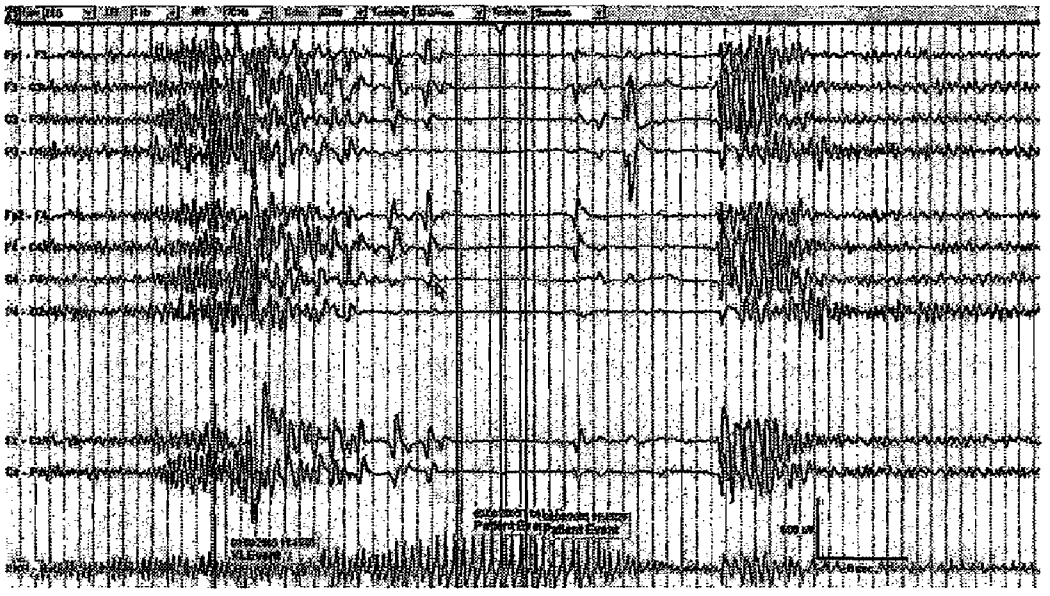

FIGURE 7-1 Hypoxia with clonic movements in a 2-year-old child. Normal EEG activity is seen on the left, which evolves into diffuse slowing during an episode of breath holding, then severe diffuse attenuation in the center. As the child begins breathing, the pattern is reversed. Diffuse tonic and clonic activity was seen during the period of severe attenuation, similar to that seen in cardiogenic or vasovagal syncope..

In the case described, the episodes are most consistent with syncope or convulsive syncope. This is supported by the setting of probable dehydration, vomiting, and possible Valsalva maneuver. An EEG and MRI were performed mainly due to the description of convulsive movements; both were unremarkable. A Holter monitor study was also normal. An echocardiogram and carotid Dopplers were also performed due to his age and potential cerebro-vascular etiology, and both were unremarkable. The patient was cautioned regarding dehydration and sleep deprivation, and no additional treatment was recommended.

KEY POINTS TO REMEMBER

- Seizures are frequently confused with syncope; particularly when details of lost awareness are not complete, both may need to be considered in the differential.
- Convulsive movements can occur in syncope, although they are typically briefer and more irregular than in a tonic-clonic seizure.
- Various characteristics of the setting and the event itself can often be helpful in distinguishing seizure from syncope, but no absolute rules exist.
- An epileptiform EEG can be helpful in confirming that a patient is at risk for seizures, although a normal EEG does not rule out epilepsy.
- When suspicion for syncope is high, a cardiac workup may be indicated.

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SECTION II

Treatment Considerations: AEDs

8 First Unprovoked Seizure

An 18-year-old university student was witnessed to have a 2- to 3-minute generalized tonic-clonic seizure. He recalls having flu-like symptoms the day of the seizure when he suddenly felt "off" just prior to the seizure. He was unable to describe the event in more detail, except awakening feeling very confused with pain. During the convulsion he sustained a fracture-dislocation of the right shoulder.

What do you do now?

A single seizure is not yet technically epilepsy; in fact, 10% of the population are expected to have a seizure, though only 1% meet the definition of epilepsy—that is, having recurrent, unprovoked seizures. Thus, for some brains, there existed a "perfect storm" of factors that led to the seizure, and many will not be exposed to the same conditions and thus seizures will not recur. There has been much debate about whether to treat after a single seizure, and there are now rough guidelines but still much gray area for personal preferences.

If there were major provocations prior to the seizure, the goal is to avoid the provocations if possible instead of starting medications to stop seizures. Major provocations include initiation of prescription medications (meperidine [Demerol], imipenem, and bupropion [Wellbutrin] in particular), sudden withdrawal of medications (benzodiazepines, any other medication that can be used to treat epilepsy), exposure to certain illicit medications (stimulants such as cocaine, amphetamines), extreme intoxication or withdrawal from alcohol, exposure to toxins, and metabolic derangements. Cerebral injuries such as strokes, brain tumors, and head trauma are considered provocations if acute, but if seizures are occurring in the chronic stage, the chance of recurrence is considered high. Two weeks was recently chosen as the cutoff, as seizures that occur after this period should be treated prophylactically.

Minor provocations are less clearly defined. We know that sleep deprivation, stress, and hormonal fluctuations appear to be associated with seizures in some individuals, but it could be argued that many brains are exposed to the same provocations yet not all will seize—thus the seizure threshold must be at least lower than average.

The findings of large observational and prospective studies have been consistent, and overall about 46% of people experiencing a single seizure will have a recurrence. Factors that increase risks are listed in table 8.1, pushing that risk of recurrence up to 70% to 90%, versus 20% to 30% in those without any risks. Thus, EEG and MRI of the brain are the standard of care to help with prognostication and treatment decisions. The EEG may show epileptiform activity, but is often normal or indeterminate. For instance, focal slowing implies some electrical abnormality of the brain that may convince some clinicians to treat, particularly if it is quite prominent, but it remains unclear how to address this finding. There were also early papers describing a benign

TABLE 8-1 New Onset Seizures: Known Risk Factors for Seizure Recurrence*

partial-onset seizures
epileptiform activity on EEG
Neurologic abnormalities on examination or by history (i.e., learning disorders)
Structural abnormalities in the cerebrum

*With none of these factors, the risk of recurrence in children and adults may be as low as 20%, with all factors, this rate of recurrence is roughly 80%.

variant of phantom spike-wave (WHAM: wake, high amplitude, anterior, male) with a higher rate of subsequent epilepsy. This study was never repeated, which makes the data difficult to interpret when this situation is seen.

Studies assessing risk have used routine 30-minute EEGs, but technology for longer-term ambulatory studies are now easily accessible. While the 30-minute study may suffice, a 24-hour or longer study may allow for state changes and overall a greater yield to find an abnormality. A normal long-term continuous study tends to provide greater confidence, though this has not yet been proven to be true. In fact, patients often are seen to have completely normal long-term EEG off AEDs for weeks prior to a definite seizure during inpatient monitoring. There are differing MRI sequences and field strengths as well. Generally speaking, coronal sections need to be tilted to the axis of the hippocampus to better identify its abnormalities, with coronal FLAIR and STIR being particularly helpful sequences; thus, writing "epilepsy protocol" or "attention hippocampus" on the requisition can be helpful. There is little doubt that a 3T magnet, when calibrated well, provides greater detail than a 1.5T MRI and small regions of cortical dysplasia may be more easily identified.

It has been shown rather convincingly that early treatment with an AED reduces the risk of a second seizure when compared to withholding treatment, but the difference in recurrence rates between these two groups vanished after 2 years. This is particularly true in those without risks. In other words, early treatment does not appear to protect the patient from developing epilepsy.

Thus, for most, the risk of medications is greater than the risk of a second seizure, particularly for those without risk factors for recurrence, as about 70% would not have a second seizure anyway. Others have argued that because the risk of recurrence in higher in the first 2 years, and specifically

the first 6 months, it is reasonable to treat even low-risk patients in the short term, knowing that it does not appear to have any protective effects on seizure recurrence once discontinued. One way to compromise is that if there were major or minor provocations that clearly led to the seizure occurring, and no reason to believe those provocations will improve in the short term, treatment can be offered for 6 months or more. Similarly, if the consequences of a second seizure in the short term are high, reducing the risk with an AED may be preferred.

In the case presented above, the healing of the shoulder fracture was important and medications were initiated, with a plan to reassess the patient's risk for recurrence in 6 months.

KEY POINTS TO REMEMBER

- **10% of the population is expected to have at least one seizure.**
- **The nonstratified risk of recurrence is just below 50%. The risk may be as low as 20% to 30% in those without learning disabilities, and a normal physical examination, EEG, and MRI, but as high as 70% to 90% in higher-risk individuals.**
- **To treat or not after a single unprovoked seizure? There is no correct answer, as treatment may limit recurrence, but does not alter the tendency to develop epilepsy. The reduction in seizure recurrence with treatment appears to vanish after 2 years**
- **Most experts prefer to defer treatment for low-risk patients, both adults and children, but take into account the ratio of risk:benefit in each specific case. No treatment, short-term (3-6 months) treatment, or chronic treatment are all reasonable options.**

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9 Initial Treatment of Idiopathic Generalized Epilepsy

A 36-year-old woman presents to your office for consultation. Her first seizure was a witnessed convulsion 13 years ago that occurred the morning following overconsumption of alcohol. A workup at that time was unremarkable; she was diagnosed with a provoked seizure and no medication was initiated. Within the next two years, she had two more seizures, both in a similar circumstance of overindulgence of alcohol. She abstained from alcohol and was seizure-free for 11 years ending 3 weeks ago. She had just moved across the country with her two young children following a divorce and had been fatigued after driving through the night. The seizure occurred the next morning. She was told by coworkers that she turned her head to the right, then started trembling. She awoke groggy but otherwise well in the hospital. She noted it was about the start of her menses when the seizure occurred. A CT scan of the head and a routine EEG were normal. With the history of four seizures, three with definite provocation and another with multiple relative stressors and precipitants, you requested further testing. A 3T MRI head was normal, but

an overnight ambulatory EEG surprisingly showed frequent spike-wave and polyspike-wave discharges, reaching 5 Hz, primarily during sleep and drowsiness and continuing in the first 2 hours of awakening in the mornings. There were also 1- to 3-second bursts of paroxysmal fast (11 Hz) activity. Based on the seizures and the EEG, you diagnose her with an idiopathic generalized epilepsy.

What do you do now?

Idiopathic generalized epilepsy (IGE), previously referred to as primary generalized epilepsy (PGE), refers to a presumed genetically low threshold for seizures, which has been borne out by discovering an association with many ion channel and some non-ion channel genes in these disorders. The number of gene loci identified for the IGEs are too numerous to detail here. From an electrophysiology standpoint, IGE is commonly thought of as being due to abnormal regulation of thalamo-cortical circuitry, and thus seizures typically affect both hemispheres simultaneously.

IGE is currently subclassified into syndromes by their clinico-electrical characteristics (table 1), but overall is thought to comprise 20% of all epilepsy cases, and juvenile myoclonic epilepsy (JME) about 10%, so essentially half of IGE. Similar to all IGE, there is a spectrum to the severity to JME. Some patients have so few myoclonic jerks and no generalized convulsions that they may be unaware of their condition, believing themselves

TABLE 9-1 Idiopathic Generalized Epilepsy Syndromes: Characteristics

	Age of Onset-Peak (Range)	Remission?	EEG	Seizure Types
Juvenile Myoclonic Epilepsy	14.6 (12-18)	Rare, considered lifelong	4-6Hz Polyspike-wave and/or spike-wave activity	Myoclonic, absence, GTC
Childhood Absence Epilepsy	5 (2-10)	50-65% remit by mid-adolescence	3-Hz spike-wave, 5-30second duration	Absence GTC (imparts poorer prognosis)
Juvenile Absence Epilepsy	Puberty (10-17)	Majority do not remit	3- or >3-Hz spike-wave, polyspike	Absence GTC Myoclonic (rare)
IGE with GTCs only	20 (5-50)	Likely lifelong	4-6Hz Polyspike-wave and/or spike-wave activity	GTC only

to be simply clumsy in the mornings. These patients will report dropping their comb easily or spilling their coffee when sleep-deprived. Other patients are highly refractory to multiple medications. The peak age of onset is 14.6, with a range classically between 12 and 18 years of age. Between 10% and 33% of the JME population will experience absence seizures, often presenting earlier, and later having generalized tonic-clonic seizures (GTCs) and myoclonic seizures. The myoclonus can be unilateral or bilateral and often affects the arms more than the legs. Falls are unusual. Clusters of myoclonic seizures often precede the GTCs. It is well known that sleep deprivation, alcohol, and menses can provoke seizures. Cocaine and marijuana can also exacerbate the condition.

The gold-standard treatment for JME and other IGEs are the valproic acid (VPA) formulations, but because of side effects, teratogenicity, and drug–drug interactions many practitioners resort to VPA only if other broad spectrum agents fail to control seizures. Sodium valproate (Depakene) can be difficult on the gastrointestinal tract and must be given three times daily, but it is available in sprinkles and a liquid preparation. Divalproex sodium (Depakote DR) is bioequivalent but better tolerated and can be given twice daily. The extended-release formulation may have 10% to 20% less absorption than the others but can be taken once daily. Lamotrigine and levetoracetam are commonly used, in addition to zonisamide and topiramate. Phenobarbital and primidone are no longer commonly used due to poor tolerability. Felbamate would be reserved for very refractory cases. Clonazepam is helpful for controlling the jerks but tends not to improve the GTCs. Ethosuximide may treat the absence seizures but again will not treat the other seizure types. Acetazolamide may help with GTCs but is not as effective at controlling the jerks. Phenytoin, carbamazepine, and other partial agents have been shown to worsen the condition in a percentage of patients. Lamotrigine, too, may exacerbate the myoclonus in a small percent, possibly related to certain gene defects of the heterogeneous genetic abnormalities that make up JME.

Similar to most IGEs, medications are generally effective, with 90% of JME cases responding to VPA. JME is a lifelong condition, essentially requiring lifelong treatment, as seizures tend to recur quickly after AED withdrawal. The EEG classically shows 4- to 6-Hz generalized spike-wave and polyspike-wave activity with an otherwise normal background (Fig. 9.1),

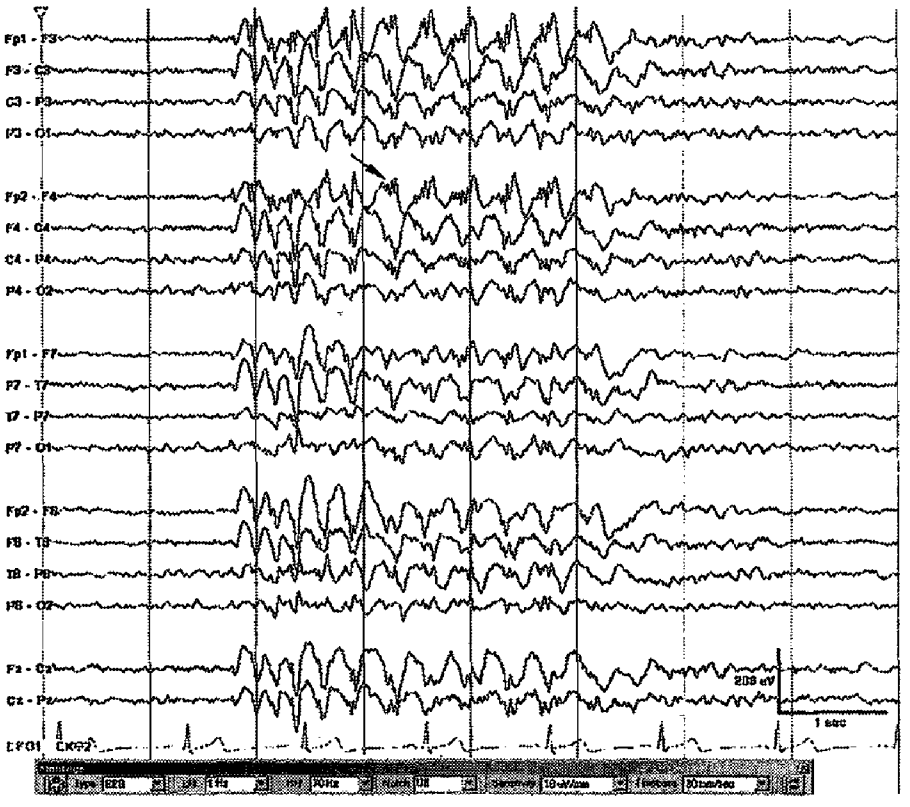

FIGURE 9-1 Classic 4 to 6-Hz spike/polyspike wave activity in a 26 year old patient with JME. Although this finding is classic for JME, this patient also exhibited 3Hz poly-spike wave activity and bursts of irregular, poorly-defined epileptiform activity. Arrow points to a polyspike.

though when treated these discharges may appear more fragmented. Unlike partial epilepsies, many believe that the amount of epileptiform activity on EEG may correlate with the risk for clinical seizure activity.

The only IGEs that spontaneously remit are typical childhood absence epilepsy (CAE), and only about 50% of cases actually remit. CAE was also known as 'pyknolepsy', and the seizures can also be referred to as 'dieleptic' events. The peak age of onset is 5, with a broad range between 2 and 10 years of age. Febrile convulsions are obtained in the history in 10% of cases. Absence seizures last on average 9 seconds, with a range of 5 to 30 seconds. The EEG shows classic 3-Hz spike-wave activity (Fig. 9.2), which may be very short and asymptomatic, but when longer than 2 seconds it is typically associated with some type of cognitive disturbance or clear pause in activity. About 40% of patients also have GTCs, which seems to impart a worse prognosis. Ethosuximide treats the absence seizures, but not GTCs. It can be poorly tolerated in terms of gastrointestinal side effects, headaches,

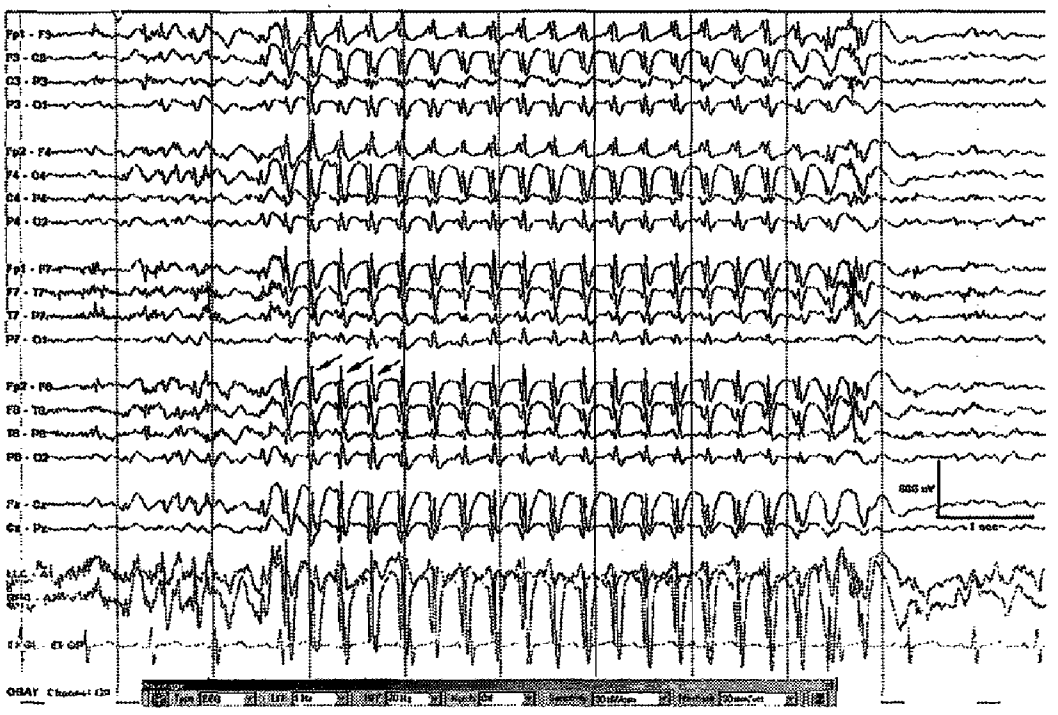

FIGURE 9-2 Typical 3-Hz spike wave run lasting 8 seconds associated with behavioral pause, diagnostic of an absence seizure. This 13-year-old patient also had polyspikes during sleep and generalized convulsions. Arrows points 3-spikes in 1 second.

and mood changes. Valproate is again the gold standard, but other broad-spectrum agents are now often tried first. A minimum of 2 years of seizure freedom is generally thought to be required prior to discontinuation of medication. Remission, when it occurs, is typically by mid-adolescence.

There is significant overlap between CAE and juvenile absence epilepsy. Distinguishing features include the later onset near puberty (10 to 17 years of age) and rarer absence events that may be less impairing, but with GTCs in 80%. The EEG may show slightly faster spike-wave discharge frequency with less regularity and polyspike activity. Patients may also have myoclonic seizures, suggesting phenotypic overlap with JME as well.

The patient described in the case fit many of the descriptors of JME, though she adamantly denied having myoclonus or clumsiness, she does not appear to have ever had absence seizures, and her age of symptom onset was much later in life. She falls into the category of "epilepsy with GTCs only," with peak onset closer to 20, with a range of 5 to 50 years of age. Like all IGEs, there is a broad spectrum of severity, EEG findings, and prognosis. The abnormal EEG (Fig. 9.3) and history of GTCs prompted the decision

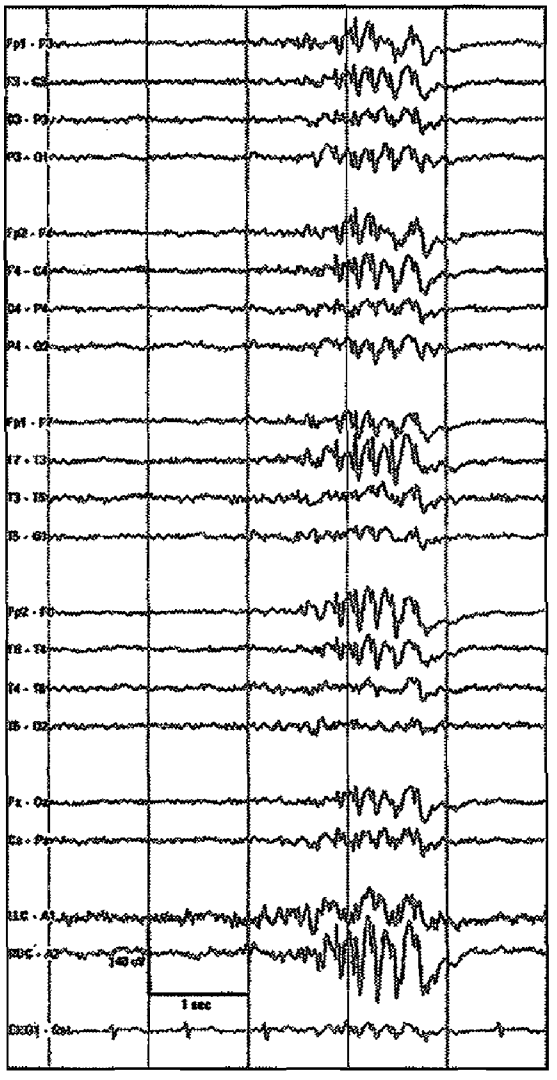

FIGURE 9-3 The EEG from the patient in the case showed irregular polyspike-wave runs of varying frequencies, from 2 to 4 Hz.

to start medications, though it is arguable that despite her EEG, her seizure threshold was only mildly lowered such that provocations were necessary for a seizure to occur. Because she could not predict when she would next be sleep-deprived, and she worried about driving with her children in the car, the risk of treatment was considered lower than the risks involved with a recurrence. The medication choice is similar to that of JME. Lamotrigine was chosen, as her syndrome can be considered mild and would likely not require VPA.

It is also notable that prolonged monitoring, either ambulatory or as an inpatient, increases the yield to identify abnormalities as it not only includes

sleep and drowsy states but offers a greater period of time for capture. This is recommended in cases where routine studies are normal yet there is a clinical suspicion for epilepsy. Abnormalities on EEG in IGE can often be elicited with hyperventilation, even on a routine outpatient EEGs. Medications may suppress the abnormalities. The MRI of the head was arguably unnecessary based on this diagnosis, although generalized-appearing discharges can be seen with focal lesions, and her history was only retrospectively fitting for an IGE.

Her family history was negative for seizures, but it is clear there is a risk that her children may have inherited the trait from her. Due to the spectrum and overlap of IGE presentations, families may have members with various syndromes, with one child having CAE, another JME, and another with EEG findings but no definite clinical seizures.

KEY POINTS TO REMEMBER

- Idiopathic generalized epilepsies (IGEs) occur in patients with presumed or documented genetically-reduced seizure thresholds and are expressed in a spectrum of disorders with overlap in symptoms and EEG findings.
- Valproic acid (VPA) is the gold standard medication for all IGEs. It has proven to be most effective but also has the greatest chance of side effects compared with newer agents that may also be effective. Lamotrigine, levetiracetam, zonisamide, and topiramate may be able to treat all of the various seizure types of IGE.
- Ethosuximide is effective only against absence seizures; acetazolamide is mainly effective against generalized tonic-clonic seizures (GTCs); clonazepam suppresses myoclonus but may not control GTCs.
- Carbamazepine, phenytoin, and other partial agents may worsen idiopathic generalized epilepsy and may even precipitate atypical absence status epilepticus.
- Routine EEG with hyperventilation may be sufficient to make the initial diagnosis; medications suppress epileptiform activity and some believe full suppression reduces the risk of seizure activity.

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10 Initial Treatment of Localization-Related Epilepsy

A 28-year-old right-handed schoolteacher was brought to the ER by ambulance after what appeared to be his third seizure. This was the first time he had some type of warning. He was about to ask his students a question when thoughts came racing through his mind but he was unable to speak. He walked around his desk, where he ultimately blacked out. Witnesses indicated that he fell to the ground, became stiff, and made gurgling noises. The principal reported that he thought the entire event lasted 10 minutes. The patient did not return to his baseline cognitive function until midway through the ambulance ride, per his report. There was no tongue bite or incontinence.

His first seizure occurred 6 months ago on a train in the evening. A witness reported his eyes rolling up and having drooling. The second seizure occurred at home in front of the computer. His brother noticed that his arms moved a bit erratically for several seconds prior to his

head arching back and eyes rolling back before shaking all over. He had not yet been seen by a neurologist or started on medications. He has no significant medical or family history otherwise and no known allergies.

What do you do now?

The semiology of the events is in keeping with partial or focal seizures, and the fact that they are unprovoked and recurrent leads to the presumptive diagnosis of a localization-related epilepsy. After three seizures, there is no question that he requires medication in an effort to reduce the risk of further seizures.

Once seizure type has been taken into account, drug selection primarily involves choosing medications with properties and side-effect profiles that are least likely to cause additional problems for patients, or using the positive secondary properties of certain AEDs to help comorbidities. This is because there have not been large variations in the proven efficacy of AEDs, and although we all have biases about which may be more effective than others, few head-to-head trials have shown differences in efficacy alone; instead, they are an amalgamation of efficacy and tolerability. It is also clear from clinical practice that there are no good predictors as to whether a specific AED will be efficacious in any individual patient; one may be effective when another is not.

Some obvious comorbidities that may guide treatment include using topiramate in patients who also have chronic headache, or lamotrigine in patients with a tendency for depression or bipolar fluctuations. Essentially, finding a medication with the "personality" to match that of the patient will lead to best long-term tolerability and compliance, and thus the greatest chance of immediate success.

Another factor to consider is the speed of titration. Because this patient has had three seizures and does not wish for another to occur in front of his students, he preferred immediate protection from seizures. AEDs that can be rapidly titrated include levetiracetam, zonisamide, phenytoin, valproic acid, and to a certain extent carbamazepine and oxcarbazepine. In each of these, there would be some effectiveness of the medication that same night. Topiramate, pregabalin, gabapentin, and lacosamide take 2 to 4 weeks for patients to adjust to the potential side effects before they are thought to become therapeutic.

On the other end of the spectrum is lamotrigine, which has a serious rash risk that limits its titration over 5 weeks, and doses are not considered therapeutic until then. While carbamazepine and oxcarbazepine also have high rash risks, they may be at least partly effective at starting doses. There is some cross-reactivity with rash risks, so if patients have had many rashes

in the past, AEDs with high rash potential should be avoided. There is a specific polymorphism, HLA-B*1502, that predisposes to Stevens-Johnson syndrome with carbamazepine, particularly in the Han Chinese and Thai population, but not in Japanese or caucasian populations.

Benzodiazepines work rapidly but are not ideal for long-term use due to their tendency for tachyphylaxis, though some patients manage to maintain seizure freedom on them for years. Clobazam is a 1,5-benzodiazepine with fewer sedative side effects that has been used for over a decade in Europe and Canada and may be approved for use in the United States shortly. Felbamate and vigabatrin are restricted for use in highly refractory cases due to their substantial known risks.

The pharmacokinetic properties of some AEDs, such as once-daily dosing, can be particularly helpful for some college students or others in whom compliance is predicted to be difficult. Zonisamide, phenytoin, and extended-release formulations of lamotrigine, levetiracetam, and valproic acid can be dosed once daily. Another pharmacokinetic issue is with drug–drug interactions. Experts recommend against using enzyme-inducing agents for multiple reasons. Finally, costs are a reality for many patients. With the majority of the AEDs now having multiple generic versions, insurance companies place a premium on non-generics, and this may alter the decision to stay with the brand-name version or higher-tier medication.

Specific AEDs may have more published data to support monotherapy use, although most have been used successfully in clinical practice in this off-label application. Surprisingly, of 470 new-onset epilepsy patients, only 47% achieved seizure freedom with their first agent attempted, with the chance precipitously decreasing with subsequent trials, though this includes withdrawals due to intolerability. In that study, 27% of patients on carbamazepine withdrew for this reason, compared to only 10% of patients on lamotrigine. This emphasizes the importance of medication choice to optimal treatment.

Plasma drug levels have been commonly used with older agents, and levels are available for most of the newer drugs as well. Most older antiseizure medications (phenytoin, carbamazepine, phenobarbital) have a narrow, well-defined therapeutic range, although specific patients vary in terms of a level that is effective and one that causes toxic symptoms. Plasma levels, however, are not required "routinely," particularly for the newer drugs.

Situations in which levels may be useful include: establishing a baseline level when seizure-free and without adverse events (in case of worsening later); suspected noncompliance; lack or loss of therapeutic effect; suspected toxicity; suspected alteration of metabolism by a secondary disease, changing physiological state, drug–drug interaction; need for medicolegal verification of treatment; or verification of increased absorption when this is dose-dependent (gabapentin).

KEY POINTS TO REMEMBER

- **There is a wide choice of medications, all with presumably similar efficacy, so the practitioner should take attempt to match the "personality" of the AED with the "personality" of the patient.**
- **Factors that play a role in the decision include potential effects on mood and weight, rapidity of titration, dosing schedule, and rash risks.**
- **Obtaining a baseline AED level when the patient is doing well is reasonable and may help decide whether to change the AED if the patient begins to have breakthrough seizures.**

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11 Status Epilepticus

The patient is a 23-year-old woman with no significant past medical history who was transferred to the neurological intensive care unit for treatment of status epilepticus. Several days prior to admission, she complained to her family of a slight headache, fever, and malaise. The following day, the family noted that she was confused and forgetful. That evening, her family came into her room to find her convulsing on the floor. She was taken to the local emergency room where she was given 4 mg lorazepam. A head CT was normal and she underwent a lumbar puncture that demonstrated 42 white blood cells per mm^3, majority lymphocytes, 2 red blood cells per mm^3, protein of 50 mg/dL (normal), and glucose of 42 mg/dL (normal). She was treated with empiric antibiotics and antiviral medications. She continued to have twitching movements of the left side of the face. She was given an additional 2 mg lorazepam and underwent endotracheal intubation. She was loaded with 20 mg/kg fosphenytoin intravenously. An emergent EEG revealed frequent right frontal-temporal onset seizures, often associated with subtle left face and arm

clonic movements. She was transferred to the neurological intensive care unit for further management, where the nurses note frequent rhythmic facial movements on arrival.

What do you do now?

Convulsive status epilepticus (SE) is a neurologic emergency with an annual incidence of 3.6 to 44 per 100,000; the highest rates are in the very young and elderly. The traditional definition of SE is continuous or intermittent seizures without recovery of consciousness for over 30 minutes. This definition is based on studies in animals that demonstrated irreversible neuronal injury after 30 minutes of continuous seizures. Many experts currently define SE as more than 5 minutes of ongoing seizure activity, based on the fact that generalized tonic-clonic seizures are unlikely to stop spontaneously if they last longer than this period.

SE is associated with a significant mortality, reported to be 3% to 33% depending on the population studied. SE due to hypoxic/anoxia has the highest mortality (approximately 60%), and SE due to low antiepileptic drug levels in patients with known epilepsy has the lowest mortality rates (less than 3%). SE can be the result of an acute brain injury such as stroke, traumatic brain injury, or infection or a systemic toxic or metabolic derangement such as sepsis, drug overdose, or metabolic derangement. SE may also be the initial presentation of epilepsy due to a remote symptomatic or idiopathic etiology.

In one prospective treatment study, approximately 35% to 45% of patients failed to respond to initial therapy and had refractory SE (RSE). RSE is associated with a significantly elevated mortality rate of 30% to 50%, and less than one third of survivors return to their premorbid condition. Risk factors for RSE include CNS infection, hypoxic-ischemic injury, delayed diagnosis and treatment, subtle or nonconvulsive seizures, focal motor seizures at onset, and young age.

There is evidence from animal models of SE that the duration of seizures predicts treatment responsiveness. Therefore, the diagnosis of SE should be made quickly and treatment instituted rapidly and aggressively with the goal to abort clinical and electrographic seizures.

An urgent EEG is important in the management of SE. It is needed to determine if there is ongoing electrographic seizure activity once convulsive activity has ceased. Ongoing nonconvulsive seizures after generalized convulsive SE are associated with increased mortality. It is also necessary to determine titration of treatments and to assess for seizure recurrence after drug withdrawal, especially in the case of continuous intravenous infusions.

The initial treatment of SE has been studied in several well-designed randomized controlled trials. Initial treatment with lorazepam 0.1 mg/kg was more effective than treatment with diazepam with phenytoin or phenobarbital in terminating SE in the VA Cooperative Trial of treatment for SE. Studies have also shown that lorazepam is safe and effective for prehospital treatment of SE by paramedics or emergency medical technicians when compared to diazepam or placebo. If seizures persist, the recommended next treatment is phenytoin 18 to 20 mg/kg given intravenously or an equivalent fosphenytoin dose. Phenytoin infusions should be given with concurrent blood pressure and EKG monitoring at a maximal rate of 50 mg/min (150 mg/min for fosphenytoin). If available, fosphenytoin is the preferred agent for rapid infusions to avoid cardiac and infusion-site reactions associated with the propylene glycol vehicle within intravenous phenytoin. Some evidence suggests that intravenous valproic acid may be safe and effective for the treatment of SE and can be given as a 30- to 40-mg/kg intravenous bolus, especially in patients with a history of phenytoin allergy or with cardiovascular instability.

If SE persists after first- and second-line treatment, options for treatment include continuous intravenous infusions of anesthetic agents such as propofol, midazolam, or pentobarbital. At this point, endotracheal intubation is necessary if it has not been performed already. In some centers, boluses of phenobarbital are often used prior to continuous intravenous treatments, though it also carries a risk of respiratory depression. In all cases, EEG monitoring is necessary to determine if the treatment has effectively stopped all seizure activity. Typical loading doses and infusion rates are listed in the example protocol shown in Fig. 11.1. As there is a theoretical increased risk of neuronal injury with more prolonged SE, all anesthetic agents should be given rapidly and in bolus doses until seizure activity has stopped or there is an adverse reaction such as hypotension. Once seizures have stopped, a maintenance infusion rate is set and titrated to maintain continued seizure suppression for at least 24 hours. Pentobarbital is a continuous intravenous medication that is considered more effective in preventing breakthrough seizures, but is often associated with significant complications such as hypotension. Therefore, a trial of midazolam or propofol is typically used prior. Once seizures are suppressed with a continuous intravenous agent, other AEDs should be maximized before

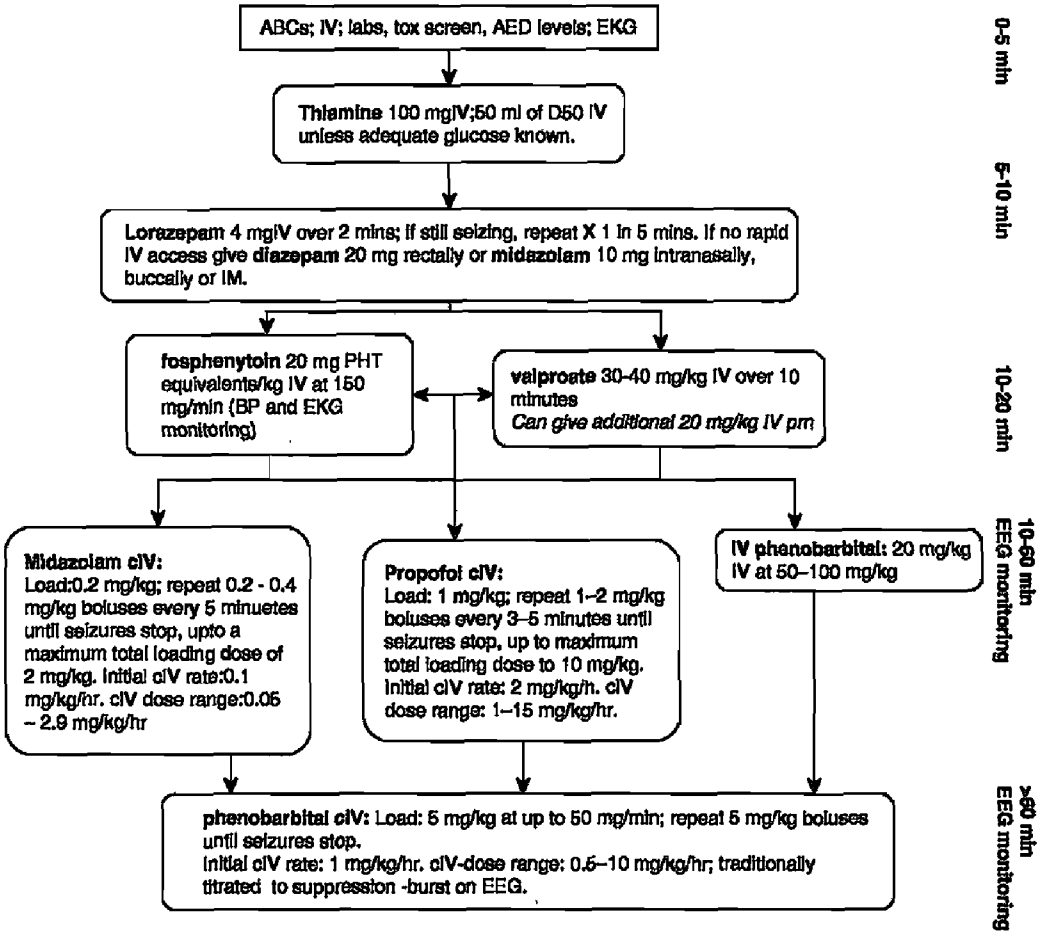

FIGURE 11-1 A sample treatment protocol for generalized convulsive SE. Protocols may vary by institution based on practice preference and availability of medications on the hospital formulary. ABCs: airway/breathing/circulation; cIV: continuous intravenous infusion.

the continuous intravenous agent is tapered off to prevent seizure recurrence.

Needless to say, careful examination for treatable causes of SE should be carried out contemporaneously with its treatment. Common treatable etiologies of RSE include metabolic abnormalities, toxic ingestions, herpes encephalitis, or autoimmune limbic encephalitis.

In some cases, SE continues to be refractory despite the above treatments and attempts at weaning continuous intravenous therapy result in seizure recurrence. There have been reports of successful seizure treatment in RSE with the addition of other intravenous or oral antiepileptic drugs such as levetiracetam, lacosamide, topiramate, zonisamide, gabapentin, and pregabalin. In the case presented here, SE was refractory to phenytoin, valproate,

and midazolam at maximal doses/levels. Continuous intravenous pentobarbital was used and titrated to a burst-suppression pattern on EEG but could not be weaned without seizure recurrence despite the addition of levetiracetam and topiramate. Ultimately, the patient developed bowel ischemia, a complication of prolonged pentobarbital use, and her family elected to withdraw supportive care.

KEY POINTS TO REMEMBER

- Convulsive SE is a neurologic emergency that requires prompt identification and treatment.
- Electrographic seizures may persist even if motor activity has stopped. An EEG is necessary if a patient does not regain consciousness after a seizure.
- Lorazepam is the preferred first-line treatment for SE if intravenous access is available; alternatives may include rectal diazepam or intranasal, buccal, or intramuscular midazolam.
- Refractory SE carries a high mortality rate.
- Stepwise approaches to SE treatment are useful in stopping the seizures as quickly as possible with the least potential for harm to the patient; anesthetic agents that are associated with significant complications should be reserved for patients who do not respond to benzodiazepines and AEDs.

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12 Adverse Effects of AEDs-Rash

A 66-year-old right-handed man began feeling an abnormal sensation rushing up his body and towards his head. The next day the events occurred almost every hour, often with thoughts racing in his head and an indescribable taste. He was initially misdiagnosed with panic disorder but video-EEG monitoring revealed frequent left temporal partial seizures. MRI of the brain revealed a non-enhancing mass in the left mesial temporal lobe suggestive of low-grade glioma. He was started on oxcarbazepine with significant improvement in his seizure frequency and discharged on a dose of 600 mg twice daily. One week later, he presented to the local emergency room with fever, malaise, and a maculopapular rash on his trunk. There was no involvement of his mucous membranes or evidence of desquamation. He had eosinophilia and mild elevation in his transaminases. He was seen by a dermatologist who diagnosed anticonvulsant hypersensitivity syndrome.

What do you do now?

Drug rashes are common idiosyncratic reactions to anticonvulsant medications. While the majority of rashes are benign, some cutaneous reactions, such as the drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), can be life-threatening, with mortality rates of 5% to 35%. Outcomes in these severe, immune-mediated reactions are often related to the duration of symptoms and signs; therefore, prompt identification of the rash, discontinuation of the offending drug, and treatment are critical. Furthermore, certain drugs and patient characteristics are associated with a higher risk of drug rashes and should factor into the selection of anticonvulsants. Finally, abrupt discontinuation of an anticonvulsant can place patients at risk for seizures, and neurologists should have a strategy for seizure control during this critical period.

Most drug rashes are nonconfluent and nontender maculopapular or morbilliform (measles-like macular rash) eruptions on the trunk and limbs, usually sparing the face. They typically occur between 5 days and 2 months of starting a medication. Approximately 5% to 17% of patients starting older anticonvulsants such as carbamazepine, phenytoin, and phenobarbital will have a rash. In initial trials, lamotrigine was associated with a 5% to 10% risk of rash. This was likely due to rapid titration or co-administration with valproate, an inhibitor of lamotrigine metabolism, and in current clinical practice rates of rash are closer to 5%. Oxcarbazepine and zonisamide have also been associated with a low but significant risk of rash in clinical trials. Most rashes are benign, but they may rarely herald the onset of more serious immunologic reaction and warrant prompt evaluation. If the patient's seizures are well controlled and there is a question about the nature of the skin eruption, urgent evaluation by a dermatologist may help the neurologist decide whether the risks of continued use of the anticonvulsant outweigh the risks of possible seizures on an unproven alternative drug.

More ominous forms of cutaneous reactions such as DRESS, SJS, and TEN often require inpatient evaluation and care. DRESS is characterized by fever, rash, and eosinophilia, with additional organ involvement such as arthralgias, lymphadenopathy, hepatitis, nephritis, encephalitis, pharyngitis, and hematologic abnormalities. Angioedema of the face can herald a very severe reaction. The rash may or may not be itchy and is sometimes pustular. Often DRESS occurs 1 to 8 weeks after starting a medication or

dosage change. The syndrome is thought to be due to aberrant activation of antigen presenting cells in the skin, and the majority of cases are due to anticonvulsants, typically phenytoin, phenobarbital, or carbamazepine and rarely lamotrigine. The incidence for DRESS is 1 to 4.1 in 10,000 for carbamazepine and 2.3 to 4.5 in 10,000 for phenytoin. The incidence is unknown for other drugs. The treatment is prompt identification and withdrawal of the causative drug. Most skin and systemic abnormalities will return to normal over several weeks, but supportive care may be necessary. The role of corticosteroids in this syndrome is controversial.

SJS and TEN are cutaneous reactions characterized by blister formation. They are distinguished by the degree of skin detachment: SJS has less than 10% whereas TEN has greater than 30%. There is often mucosal and gastrointestinal involvement. Mortality is related to the degree of skin involvement, the patient's age, and how soon the offending drug is stopped. The incidence of SJS and TEN is 1 to 10 per 10,000 for carbamazepine, phenytoin, and phenobarbital. Initial reports suggested a higher rate of SJS, especially in children, with lamotrigine. However, this appeared to be due to the rapid titration rates used in early clinical trials, especially in the presence of valproate. More recent studies using the recommended slow titration rate found SJS and rash rates similar to the other aromatic anticonvulsants.

In this patient with a mild case of DRESS syndrome, the offending drug was stopped and his fever improved over several days. His rash cleared over the next 2 weeks. Once a drug reaction is identified, the neurologist must determine how to best protect the patient from both seizures and a similar reaction. Many agents demonstrate cross-reactivity, and the biggest predictor that a patient will develop a rash with a new anticonvulsant is a history of rash with a prior drug. In a large anticonvulsant database, Hirsch and colleagues found that prior drug rash increased the risk of rash fivefold. Some drugs have a high cross-sensitivity with other anticonvulsants. For instance, 42% to 58% of patients who had a rash with phenytoin develop a rash when exposed to carbamazepine. Approximately 40% to 57% of patient with a rash on carbamazepine will develop a rash on phenytoin. A milder degree of cross-sensitivity occurs with oxcarbazepine, zonisamide, lamotrigine, and phenobarbital. Levetiracetam, gabapentin, pregabalin, vigabatrin, felbamate, valproate, and topiramate have not demonstrated

significant cross-reactivity with other anticonvulsants, and all have very low rates of rash. Levetiracetam, gabapentin, or pregabalin would be a reasonable choice for the next AED for this patient as oxcarbazepine is discontinued; all can be started at or near therapeutic doses and titrated quickly to give the patient the best protection against seizures. Levetiracetam and valproate can be loaded and given intravenously if the patient is unable to take medications orally due to extensive gastrointestinal system involvement. If necessary, a brief course of benzodiazepines can be used to "bridge" patients to the next agent.

Some susceptibility to drug reactions may have a genetic component. Having a family member with a history of an anticonvulsant reaction can increase the patient's risk. This may be due to genetic variation in the metabolism of drugs into their potentially immunogenic metabolites via the P450 system or variability in immune system–drug interactions. The human leukocyte antigen, HLA-B, is thought to be involved in the pathophysiology of SJS and TEN. Certain polymorphisms in the drug are highly associated with risks of SJS and TEN upon exposure to specific drugs. For instance, the HLA-B*1502 allele, common in the Han Chinese ethnic group, is highly associated with SJS following exposure to carbamazepine. The FDA now recommends genetic testing for the HLA-B*1502 allele in all patients with Asian ancestry prior to starting carbamazepine. The prevalence of this allele in other ethnic groups is not fully known. It is also not clear if carrying this allele increases the risk of SJS or TEN following exposure to other anticonvulsants.

KEY POINTS TO REMEMBER

- **Drug rash is common in patients taking anticonvulsants.**
- **While most rashes are benign, some patients will have a potentially life-threatening reaction such as DRESS, SJS, or TEN.**
- **Prompt identification and discontinuation of the offending drug is key to treatment.**
- **The greatest risk for having a drug reaction is a history of prior drug reaction.**

Continued

- **Aromatic anticonvulsants such as carbamazepine, phenytoin, and phenobarbital as well as lamotrigine carry the greatest risk of rash and cross-reactivity.**
- **The HLA-B*1502 allele, common in patients with Han Chinese ancestry, is highly associated with SJS in response to carbamazepine, so patients with Asian ancestry should undergo genetic testing prior to starting the medication.**

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13 Adverse Effects of AEDs–Idiosyncratic Reactions

You are asked to see a 54-year-old woman in consultation on the orthopedic service. She was diagnosed with a right parasagittal meningioma in her mid-20s. Shortly after it was resected she began having focal motor seizures involving her left leg. She was treated with carbamazepine and lorazepam as needed with good seizure control. At age 49, her meningioma recurred and she was treated with resection and gamma knife therapy. At that time, her physician noted that she had hyponatremia that was attributed to carbamazepine. She was switched to divalproex and after several dose increases she became seizure-free. However, several years ago, she began having some difficulty walking and noticed a tremor in her hands. More recently, she has been falling at home and now is admitted after a fall and compression fracture of her spine. On examination, she has masked facies, cogwheel rigidity of both arms, and significant galt instability with retropulsion.

What do you do now?

All medications have side effects, and AEDs are no exceptions. Some side effects can be expected of drugs that act on central nervous system neurons. Somnolence, dizziness, and ataxia are common side effects of many AEDs and are often dose-dependent. Some side effects, such as low vitamin D levels and other endocrinopathies associated with phenytoin, carbamazepine, and phenobarbital use, can be predicted by their known effects of hepatic metabolism. Other side effects cannot necessarily be predicted by the medication's main mechanism of action or metabolism and are often not related to the medication dose. These are called idiosyncratic reactions. Drug rashes are a common idiosyncratic reaction and are addressed in Chapter 12.

The woman described in this case has parkinsonism, a complication of chronic valproate use. Other idiosyncratic reactions include liver, hematologic, neurologic, or immunologic dysfunction (Table 13.1).

Liver dysfunction, which may be fatal, is a rare reaction to several AEDs. It can occur due to direct hepatotoxicity of the AED or its metabolites or by immune-mediated mechanisms. Valproate and felbamate have the greatest risk for fatal hepatic failure, with rates of 1:12,000 to 1:37,000 and 1:26,000 to 1:34,000, respectively. The rate of valproate-associated hepatotoxicity is highest in children under age 2, especially if there is an associated inborn error of metabolism. Valproate should be used with caution in this age group. Patients on these AEDs should have frequent monitoring of liver function tests, especially in the first 6 months of therapy, and new nausea, vomiting, lethargy, abdominal pain, or jaundice should prompt urgent evaluation. Other drugs, such as phenytoin, carbamazepine, phenobarbital, and lamotrigine, can cause liver dysfunction primarily through immunologic mechanisms. This can occur as part of a systemic reaction such as drug eruption with systemic symptoms (DRESS syndrome, see Chapter 12) or in isolation. The role of frequent laboratory monitoring in asymptomatic patients for these AEDs is less clear.

Hematologic reactions are also seen with several AEDs and can be life-threatening. The reactions can affect all cell lines. Aplastic anemia is most commonly associated with felbamate, occurring in 1:10,000 exposed patients, but can also be seen with carbamazepine (1:50,000 to 1:200,000) and, more rarely, with ethosuximide, phenytoin, and valproate. Agranulocytosis can be seen with carbamazepine and phenytoin. Thrombocytopenia, platelet

TABLE 13-1 Potentially Life-Threatening and Other Serious Idiosyncratic Effects of Commonly Used Antiepileptic Drugs

Drug	Potentially Life-Threatening Idiopathic Reactions	Others
Carbamazepine	Aplastic anemia, agranulocytosis, hepatotoxicity, SJS/TEN, SLE	Hyponatremia
Ethosuximide	Aplastic anemia, agranulocytosis, hepatotoxicity, SJS/TEN, SLE	
Felbamate	Hepatotoxicity, aplastic anemia, agranulocytosis, SJS/TEN, SLE	
Gabapentin	SJS/TEN, hepatotoxicity	Myoclonus
Lacosamide*		
Lamotrigine	SJS/TEN, hepatotoxicity, aplastic anemia	Aseptic meningitis
Levetiracetam	Hepatotoxicity, thrombocytopenia	
Oxcarbazepine	SJS/TEN, hepatotoxicity, aplastic anemia, agranulocytosis, SLE	Hyponatremia
Phenobarbital	SJS/TEN, hepatotoxicity, agranulocytosis, SLE	Shoulder-hand syndrome
Phenytoin	SJS/TEN, hepatotoxicity, aplastic anemia, agranulocytosis, SLE	Cerebellar atrophy, peripheral neuropathy, Dupuytren's contractures
Pregabalin		Myoclonus
Rufinamide*	SJS/TEN, aplastic anemia, agranulocytosis	
Tiagabine	SJS/TEN	
Topiramate	SJS/TEN, hepatotoxicity, pancreatitis	Acute glaucoma

TABLE 13-1 (Cont'd) Potentially Life-Threatening and Other Serious Idiosyncratic Effects of Commonly Used Antiepileptic Drugs

Drug	Potentially Life-Threatening Idiopathic Reactions	Others
Valproate and derivatives	Hepatotoxicity, pancreatitis, SJS/TEN, SLE, thrombocytopenia	Tremor, parkinsonism, encephalopathy, alopecia
Vigabatrin	Hepatotoxicity	Visual field defects
Zonisamide	SJS/TEN, hepatotoxicity, aplastic anemia, agranulocytosis	

*Newly approved drugs such as rufinamide and lacosamide likely do not have sufficient post-marketing surveillance data to identify all possible adverse reactions.
SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis; SLE: drug-induced systemic lupus erythematosus.

dysfunction, and clotting factor depletion are common with valproate use, especially with high serum levels. Patients on valproate are thought to be at higher risk for perioperative bleeding and may require platelet transfusion. Some epileptologists discontinue valproate prior to resective epilepsy surgery, especially if there is evidence of quantitative or qualitative platelet dysfunction. Thrombocytopenia can occur with carbamazepine, phenytoin, lamotrigine, felbamate, primidone, and levetiracetam use.

Pancreatitis is a rare but serious reaction to valproate therapy and can occur at any time. Patients with developmental delay and cerebral palsy are particularly at risk. Clinicians should be highly suspicious for pancreatitis when patients on valproate complain of abdominal pain, nausea, and vomiting and should check serum amylase and lipase levels.

Unexpected neurologic reactions can be seen with some AEDs. Irreversible visual field constriction has been reported in about 40% of patients taking vigabatrin through presumably retinotoxic mechanisms. Peripheral visual field loss may be progressive and seen as early as 1 month of treatment. The majority of patients are asymptomatic, with deficits noted primarily on formal visual field testing. Currently, patients taking vigabatrin in the United States must have formal visual field testing every 3 months to obtain the medication from a central pharmacy. Encephalopathy, parkinsonism, tremor, and dyskinesias can be seen with valproate use. Nonepileptic myoclonus has

been reported with gabapentin and pregabalin. Chronic phenytoin use has been associated with peripheral neuropathy and cerebellar atrophy.

Immunologic disorders can be associated with AEDs apart from DRESS syndrome. Drug-induced systemic lupus erythematosus can be seen with carbamazepine and, less frequently, with phenytoin, ethosuximide, and lamotrigine use. Manifestations of drug-induced SLE are similar to the idiopathic form and can involve any organ system but typically remit after stopping the offending drug. Other idiosyncratic reactions include acute secondary angle closure glaucoma and hypohidrosis due to topiramate, Dupuytren's contractures due to phenytoin use, shoulder–hand syndrome due to phenobarbital use, and alopecia due to valproate use.

The management of idiosyncratic reactions depends on the manifestations and severity. Potentially life-threatening reactions warrant rapid drug discontinuation, often with the addition of a benzodiazepine or AED with little cross-reactivity to prevent seizures. Other reactions can be managed with slower substitutions or with the addition of other drugs. For instance, L-carnitine can be used to treat mild forms of valproate-induced encephalopathy if that AED has been particularly effective for the patient. This patient was switched to levetiracetam monotherapy over several weeks. She remained seizure-free and had significant improvement in her gait when she was seen in the office several months later.

KEY POINTS TO REMEMBER

- **Idiosyncratic drug reactions are those that cannot be predicted by the drug's mechanisms of action or metabolism.**
- **Some idiosyncratic reactions are mediated by immunologic mechanisms while others are due to direct cytotoxic effects of the drug or its metabolites.**
- **While laboratory monitoring is recommended with some high-risk drugs such as felbamate and valproic acid, the utility of frequent laboratory monitoring in preventing serious adverse reactions is unknown.**
- **Prompt discontinuation of the offending AED is necessary for all life-threatening adverse effects.**

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14 Generic AED Substitutions

A 35-year-old man with primary generalized epilepsy returns for an annual follow-up. He has been doing well on brand-name levetiracetam (Keppra) for the past 3 years, with no seizures. He tolerates this medication without obvious side effects. He is happy with the medication, but he learned from his insurer that his out-of-pocket costs per month would decrease from $50 to $10 per month if he changes to a generic equivalent.

What do you do now?

Generic equivalents have recently been approved for lamotrigine, topiramate, oxcarbazepine, and levetiracetam. At this point, there are generic equivalents for the majority of commonly used anticonvulsant drugs. With increasing pressure on insurers and physicians to control costs, the use of generic equivalents in medicine has become an important topic. As with any medication or treatment change, the physician must always weigh the benefits versus the cost of such a change.

The U.S. Food and Drug Administration sets strict standards for the approval of generic equivalents in any class, and the rules do not differ for AEDs. Each must be compared to the approved brand-name drug in normal volunteers to ensure that two measures, area under the curve (AUC, a measure of total drug absorbed) and C_{max} (the peak concentration), are comparable. To do this, single doses of the proposed generic are tested against the brand-name drug. The 95% confidence interval for each of these measures must fall between 80% and 125% of the branded drug. Usually, that translates into an average variability of 3% to 5%. For most conditions, this would be an insignificant amount. Think of a headache: if a 600-mg generic ibuprofen actually delivers only 570 mg, that probably doesn't translate into a major problem for the patient; at worst, the headache may last a bit longer, or another dose would be needed.

In epilepsy, there is a relatively narrow therapeutic window that must be maintained for extended periods of time. Too much, and the patient experiences toxicity; too little, and a seizure may occur. So the consequences of a slight fall in delivered dose may be severe: a patient who was seizure-free may have a sudden seizure, potentially resulting in injury, loss of driver's license, or even death. Under most circumstances we wouldn't expect a 5% change to cause this, but there are other, at least theoretical reasons that that variability could be greater. First, generic equivalents are tested in normal volunteers. Epilepsy patients may have greater differences in absorption or metabolism due to their condition or to concurrently administered drugs. Second, generic agents are not tested against each other; they are tested only against the brand-name equivalent. There are actually multiple, sometimes dozens, of approved generic manufacturers for each epilepsy drug, and pharmacists frequently change manufacturer based on price. Therefore, each time the patient returns to the pharmacy, a generic equivalent from a different manufacturer may be dispensed. The roughly 5% variability

compared to the brand could then become a 10% swing from one generic to another. A handful of states (including Hawaii and North Carolina) have limited changes in generic manufacturers dispensed to a given epilepsy patient. Several others (Florida, Kentucky, Maine, Maryland, Minnesota, Missouri, and Rhode Island) limit substitution for drugs; however, the practice of substitution is still the norm.

Most neurologists have anecdotes of a problem resulting from a generic AED switch, a sudden seizure in a previously controlled patient being most common. However, unexplained seizures also occur in patients remaining on a brand-name drug, so it is often difficult to prove it is due to the generic substitution. There are a few cases where the time course and documented changes in levels make generic change the likely culprit, but these are rare.

A few studies suggest that costs actually increase overall in epilepsy patients when changed to generics, particularly when more than one generic manufacturer is used. The reasons seen are increases in other prescriptions, increased outpatient visits (presumably due to complications or perceived complications of change), and increased injury (presumably due to injuries related to adverse effects and/or seizures). However, none of these studies are randomized and controlled, so it remains difficult to be certain whether the change itself was the culprit.

Generic equivalents in epilepsy are not unreasonable, but they should be used more cautiously than in other conditions. How can we best protect our patients? First is with education: when a generic is available, alert the patient that a change in the appearance of the drug likely means generic substitution. Possible changes should be discussed with a patient, whether from brand to generic, from generic to brand, or between different generics, though the latter may be the most difficult to control. Get baseline levels on all anticonvulsant drugs when the patient is stable; this way if a problem arises it will be easier to know if it was a result of a brand change. And when generic equivalents are used, ask the patient to work with a pharmacist to stay with a single manufacturer. Some will be willing to do this, further reducing the potential for variability. Finally, when a suspected problem arises, physicians should report it to the FDA's MedWatch: www.fda.gov/medwatch/. Going forward, this will help the FDA, and us, to better understand the scope of the problem.

KEY POINTS TO REMEMBER

- Generic equivalents are available for most AEDs, and pharmacists can substitute in most states unless the prescriber clearly specifies that the brand-name drug be dispensed.
- Changes between a brand and a generic equivalent, or between different generic equivalents, introduce a small potential variability in the total amount of drug delivered and in the peak concentration. In most patients this should not be significant, but it could result in toxicity (if the peak is higher) or seizures (if the trough is lower).
- Minimizing changes between manufacturers, including staying with the same generic manufacturer, helps to limit variability.
- Obtaining blood levels before and after any change can help to ensure that large changes in delivered dose have not occurred.

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15 Withdrawal of AEDs

A 41-year-old, right-handed man had his first recognized seizure 2 years previously. This occurred during sleep and he has no memory of it. His wife reported that she awoke with bed shaking and found the patient stiff with his eyes opened. This was followed by drooling, confusion, and agitation. He suffered a rotator cuff injury during the seizure that required surgery. In retrospect, he had had an episode of nocturnal tongue biting 6 weeks earlier, accompanied by diffuse muscle soreness; however, this event was not witnessed and medical attention was not sought. An EEG showed right temporal slowing and epileptiform spikes. He was started on oxcarbazepine and subsequently changed to lamotrigine (Lamictal), 150 mg BID (level 4.2). He has had no further seizures since that time.

Since then, he reports that he sometimes has a feeling of unsteadiness when he stands up suddenly or when he is walking quickly for a period of time. This goes away immediately if he sits. He also reports longstanding

difficulties with focus; it has neither improved nor worsened since this seizure and medication.

There were no known risk factors for epilepsy. Physical examination was normal. The patient asked whether it was reasonable to stop his medications.

What do you do now?

By history, he had two probable unprovoked generalized tonic-clonic seizures. Workup was unremarkable except for right temporal spikes on the EEG. Many clinicians prefer to wait for a definite second event before starting medications. In this case, the treating physician was no doubt influenced by an apparently clear epileptiform abnormality on the EEG in addition to the probable prior seizure and initiated seizure prophylaxis.

Most research involving stopping anticonvulsant medication looks at patients who have been seizure-free for at least 2 years, as in this case. A review of 28 studies including over 4,000 patients with all types of seizures suggested that the number continuing to be seizure-free in adults was 35% to 57%; in children the rate was 61% to 91%. A meta-analysis of 25 studies showed the overall risk of recurrence to be 2% to 34% at 2 years. Patients with remote symptomatic epilepsy and patients with abnormal EEG (at the time of withdrawal) were more likely to relapse. A prospective study of 84 patients with partial seizures, who were seizure-free for over 2 years, showed that relapse following AED withdrawal was more common in patients with atrophy or increased signal of the hippocampus. Most available information therefore suggests that the risk of recurrence with AED withdrawal, after 2 years of seizure freedom, is in the neighborhood of 30%.

The best information comes from one randomized trial of 1,013 patients. The average age of onset was about 13 years, and the average duration of epilepsy was about 5 years. About half had tonic-clonic seizures that were either generalized or unclassifiable; the majority of the remainder had partial seizures with or without secondary generalization. Within 2 years of randomization, 78% of patients randomized to continued treatment remained seizure-free, while 59% randomized to drug withdrawal remained seizure-free. It is important to note that 22% of subjects had a seizure recurrence while remaining on medication; as clinicians we often don't think about that. Nearly half of the seizure recurrences in the drug withdrawal group occurred during the withdrawal period, so patients should remain particularly cautious during this time. Perhaps most importantly, this study showed an inverse relationship between the duration of seizure freedom and the risk of recurrence at 2 years, with the relative risk decreasing from 0.67 after 3 to 5 years to 0.27 after more than 10 years seizure-free. It also showed a higher rate of recurrence in patients with generalized tonic-clonic seizures

and generalized spike-wave discharges on EEG, but not with focal spikes or nonspecific EEG abnormalities.

Juvenile myoclonic epilepsy (JME) has been thought to be a lifelong condition, and many clinicians feel that these patients should continue AED treatment indefinitely even if seizure-free. There are no randomized studies of this, but a recent, very-long-term follow-up on a small number of patients suggested that about one third of patients with JME may ultimately be able to stop medications. However, seizures in JME remain more likely to recur than in other epilepsies.

Given these numbers, there is a reasonably good chance that patients who are seizure-free for 2 or more years on medication can remain seizure-free after medication withdrawal. On the other hand, the risk of recurrence is never zero, so the decision must be made with regard to the patient's individual circumstances and aversion to risk. A good perspective on this comes from the randomized study mentioned above: after 4 years, there is no appreciable difference in seizure recurrence whether the patient was randomized to drug withdrawal or not. Factors that may influence a patient to accept that risk may be women who are attempting to conceive, in which case medication withdrawal should be attempted before pregnancy to minimize the risk of seizures during pregnancy. Questions of acute or long-term toxicity may also influence a recommendation to withdraw medication.

Withdrawal to monotherapy in patients seizure-free on two or more medications may be an easier decision. While there are no published trials of the rate of recurrence in patients controlled on two or more drugs when an agent is withdrawn, the rates are almost certainly lower than those with complete withdrawal of anticonvulsant treatment.

KEY POINTS TO REMEMBER

- **Withdrawal from anticonvulsant drugs can be considered after 2 years of seizure freedom.**
- **The chance of remaining seizure-free off medications increases between 2 and 6 years of seizure freedom prior to AED withdrawal.**

Continued

- The EEG should be considered before a recommendation to withdraw is made, as some evidence suggests that abnormalities make recurrence following AED withdrawal more likely.
- Certain syndromes, particularly juvenile myoclonic epilepsy, may have a somewhat higher potential for recurrence.

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