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Clinical Case Studies in Epilepsy

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Clinical Case Studies in Epilepsy

Tracey A. Milligan, MD

INTRODUCTION

A *seizure* is a temporary alteration in brain function due to excessive and/or hypersynchronous neuronal activity. *Epilepsy* is the tendency to have recurrent unprovoked seizures. Approximately 10% of individuals will have 1 seizure in his or her lifetime, and up to 3% will suffer from epilepsy.¹ However, the prevalence of active epilepsy is only 0.8%. In the United States, approximately 2 million people have epilepsy, with 100,000 new cases diagnosed per year. People of every background and age are affected. Epilepsy is associated with impaired quality of life, and its treatment can have serious consequences. Unfortunately, 20% to 40% of patients with epilepsy continue to experience occasional seizures despite treatment.^{2–5}

Epilepsy is not a single condition but a symptom of various disorders and reflects underlying brain dysfunction. The International League Against Epilepsy (ILAE) currently has 2 classification schemes for epilepsy that are designed to be used together. The first divides seizures into 3 types, with subtypes of each: partial (focal seizures involving only part of the brain), generalized (seizures involving both hemispheres of the brain), and unclassifiable (**Table 1**).⁶ This system allows for simple classification that may determine diagnostic evaluation, choice of medication, and prognosis. A supplement to this system, the ILAE Classification of Epilepsies and Epileptic Syndromes,⁷ divides epilepsies into 4 groups: localization-related (involves 1 or more focal areas of the brain), generalized (involves both hemispheres of the brain at the same time), undetermined, and special syndromes. The localized and generalized groups further divide into idiopathic (no identifiable cause and no associated neurologic abnormalities, although underlying genetic mutations are increasingly being discovered), symptomatic (cause is identified), or cryptogenic (presumed symptomatic, but the cause is unknown) epilepsy syndromes. Epilepsy syndromes are defined by the specific seizure type, clinical findings (including age of onset), and type of EEG abnormality. Epilepsy syndromes include the catastrophic epilepsy syndromes of infancy and childhood (eg, West syndrome, Lennox-

Gastaut syndrome, myoclonic epilepsies), idiopathic partial epilepsy syndromes (eg, benign epilepsy with centrotemporal spikes), idiopathic generalized syndromes (eg, benign neonatal convulsions, juvenile myoclonic epilepsy [JME]), and special syndromes such as febrile seizures. A specific epilepsy syndrome may require specific anticonvulsant drug treatment and is frequently associated with a predictable prognosis. The ILAE is currently developing a third diagnostic scheme aimed at providing a standardized description of individual patients rather than a fixed classification.⁸ This scheme uses 5 axes: ictal phenomenology (axis 1); seizure type (axis 2); syndrome, when known (axis 3); genetic defect or specific pathologic substrate for symptomatic focal epilepsies (axis 4); and impairment classification (axis 5).

This review presents 4 cases that evolve over the course of the discussion to encompass evaluation of a first seizure, diagnosis and management of epilepsy in the elderly, management of epilepsy during pregnancy, and evaluation and management of acute mental status change in a patient with epilepsy.

EVALUATION OF A FIRST SEIZURE

CASE 1 PRESENTATION

A 19-year-old woman is referred to a neurologist for evaluation after experiencing a convulsion while jogging. The patient is otherwise healthy and takes no medications besides oral contraceptives. Records from the emergency department (ED) visit document that a physician who was jogging behind the patient witnessed the event and did not notice any prodrome or focal findings. Evaluation in the ED showed a postictal period of confusion for 20 minutes followed by a normal examination. Electrolytes, renal function, complete blood count, and a computed tomography (CT) scan of the patient's head were normal.

DIAGNOSING EPILEPSY

- What is the differential diagnosis for a seizure?

Table 1. 1981 ILAE Classification of Epilepsy

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GTC = generalized tonic-clonic; ILAE = International League Against Epilepsy. (Adapted with permission from Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1981;22:489–501. Copyright © 1981 Blackwell Publishing Ltd.)

Distinguishing Between Epileptic and Nonepileptic Seizures

The first step in evaluating a seizure is to determine whether the event was an epileptic seizure or a paroxysmal event mimicking an epileptic convulsion (**Table 2**). Syncope is commonly mistaken for an epileptic seizure; however, certain features can help distinguish between the 2 types of events (**Table 3**). An electroencephalogram (EEG) during an event can be helpful. Convulsive syncope involves the release of brainstem and spinal activity from cortical influence, and the EEG shows slowing and flattening rather than seizure activity. An event that occurs while exercising may be more suspicious for a cardiac etiology. Psychogenic nonepileptic seizures (PNES, or pseudoseizures) are also frequently mistaken for epileptic seizures and represent up to 20% of referrals to an epilepsy center. Certain features aid in the diagnosis of PNES (**Table 4**), although inpatient video EEG monitoring may be required.

Once an event has been identified as a seizure, the next step is to determine whether the seizure was provoked. This distinction has important therapeutic and prognostic implications. A *provoked seizure* is one that

Table 2. Nonepileptic Disorders That Mimic Epilepsy

Syncope (vasovagal/neurocardiogenic, decreased cardiac output, volume depletion, arrhythmia)
Migraine (classic, basilar, confusional, acephalgic)
Cerebrovascular (transient ischemic attack, amyloid angiopathy)
Sleep disorders (REM behavior disorder, narcolepsy, parasomnias)
Movement disorders (tics, nonepileptic myoclonus, tremor)
Transient global amnesia
Psychiatric (panic, dissociation, conversion, malingering)

REM = rapid eye movement.

results from a recognizable cause. A seizure can be provoked by many factors (**Table 5**). Common causes include metabolic disturbances, medications, and alcohol withdrawal. If seizures recur only in the presence of this stimulus, they are not defined as epilepsy.

- **What are important historical questions to ask the patient and/or any witness to the event?**

Questions for the Patient

Asking the patient about events leading up to the seizure may reveal possible provoking factors (eg, stress, alcohol withdrawal, sleep deprivation, medication use, illicit drug use) or unusual stimuli (eg, hyperventilation, flickering lights). The patient should also be asked to identify, if possible, any activity that immediately preceded the event (eg, exercise, change in posture). A review of the early symptoms as well as postictal symptoms (eg, presence of a Todd's paralysis) may also help classify the event.

Obtaining a history of any prior events suspicious for seizures also is important and may lead to a diagnosis of previously unrecognized epilepsy. Suspicious events include episodes of lost time, frequent déjà vu, transient neurologic symptoms, morning myoclonus, awakening with a tongue bite or incontinence, nocturnal convulsions, and reports of unusual movement that the patient was unaware of performing, such as staring with eye fluttering, lip smacking, or hand automatisms.

Questions for a Witness

Obtaining a history from any witness to the event is also critical in making the diagnosis. Key questions to ask a witness include: Where in the body did the movements begin? Did the patient's head or eyes deviate to one side? Were there automatisms of the face or hands? Did incontinence or tongue biting occur? What were the

Table 3. Features That Distinguish Syncope from Seizure

Clinical Feature	Syncope	Seizure
Loss of consciousness	Typical	Common
Episode duration	Seconds	Minutes
Involuntary movements	Common	Typical
Triggers	Frequent	Rare
Preceding symptoms	Nausea, blurred vision, feeling hot, tinnitus, palpitations	Sensory, motor, psychic auras
Postictal features	Amnesia for event, somnolence, headache	Amnesia for event plus confusion, somnolence, headache
EEG findings	Slow waves, flattening	Focal or generalized spike-wave

EEG = electroencephalogram.

Table 4. Features That Distinguish Psychogenic Nonepileptic Seizures (PNES) from Tonic-Clonic Epileptic Seizures (ES)

Clinical Feature	PNES	ES
Trigger	Frequent	Rare
Onset	Often gradual	Usually sudden
Movements	May stop and start, pelvic thrusting, back arching, erratic movements, absence of stereotypy	Usually synchronized and stereotyped
Eyes	Closed	Open
Lateral tongue bite	Rare	Common
Self-injury	Rare	Common
Incontinence	Rare	Common
Postictal confusion	Rare	Common
Duration	Lengthy (hours)	1–2 min
Serum prolactin	Usually normal	Usually elevated

Table 5. Common Causes of Provoked Seizures

Metabolic (hyponatremia, hypoglycemia, hyperthyroidism, nonketotic hyperglycemia, hypocalcemia, hypomagnesemia, renal failure, porphyria)

Hypoxia

Medications (benzodiazepine withdrawal, barbiturate withdrawal, phenothiazines, bupropion, tramadol)

Substance abuse (alcohol withdrawal, cocaine, amphetamine, phencyclidine, methylenedioxymethamphetamine [“ecstasy”])

features of the postictal state? The patient’s level of responsiveness and awareness will also help classify the seizure and has important implications for possible etiologies, diagnostic work-up, treatment, and prognosis.

- **What historical features are considered risk factors for the development of epilepsy?**

RISK FACTORS FOR EPILEPSY

There are well-recognized risk factors for the development of epilepsy (**Figure 1**).⁹ Febrile seizures occur in 2% to 4% of otherwise healthy children younger than age 5 years; however, a history of a complex febrile seizure or a neurodevelopmental abnormality or a family history of epilepsy may increase the risk of developing epilepsy to 2% to 4%.¹⁰ A history of significant head trauma also is a risk factor. Studies of Vietnam War veterans show a risk of 50% after a penetrating head trauma.¹¹ Head trauma with loss of consciousness, amnesia, or a skull fracture increases the 5-year risk to approximately 2%; however, the risk is increased with severe head injuries, with 12% of survivors developing epilepsy.¹² Vascular lesions are a significant cause of epilepsy. Epilepsy develops in 6% to 44% of individuals with arteriovenous malformations.¹³ Cavernous malformations commonly present as seizures,¹⁴ and cerebrovascular disease is the major cause of epilepsy in the elderly.¹ Brain tumors account for approximately 4% of cases of epilepsy,¹⁰ and seizures are often the presenting feature of brain tumors. Central nervous system (CNS) infections can also increase the risk of developing epilepsy, particularly in children and the elderly. This risk is further increased with certain types of infections and if there are symptomatic seizures early in the course of infection. For example, in patients with viral encephalitis and early seizures, the risk of epilepsy is 10% by 5 years and 22% by 20 years.¹⁵ Degenerative CNS diseases are associated with an increased risk of epilepsy. Alzheimer’s disease increases the risk tenfold, and 10% of long-term Alzheimer’s disease survivors eventually develop epilepsy.¹ Up to 5% of patients with multiple sclerosis develop epilepsy.¹⁶ Mental

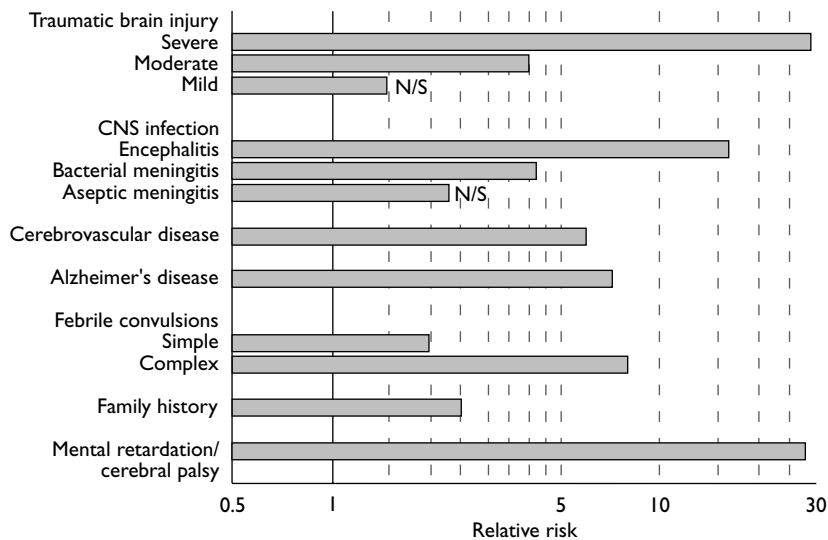


Figure 1. Relative risk of epilepsy (log scale), shown by cause. CNS = central nervous system; N/S = not statistically significant. (Adapted with permission from Annegers JF, Rocca WA, Hauser WA. Causes of epilepsy: contributions of the Rochester epidemiology project. *Mayo Clin Proc* 1996;71:572.)

retardation (MR) and cerebral palsy (CP) are important risk factors for the development of epilepsy in children and young adults. Prematurity and birth complications are risk factors for both CP and MR, but pre- or perinatal events themselves are not independent risk factors for epilepsy when children with CP or MR are excluded.¹⁷ Finally, patients with a first-degree relative with epilepsy have a twofold to fourfold risk of developing epilepsy.¹⁸

Risk of a Recurrent Seizure

Assessing risk of seizure recurrence is important in the counseling and management of patients (Table 6). After a single tonic-clonic seizure, the 5-year recurrence rates vary from 16% to 62%, depending on the presence of other risk factors. The greatest risk of recurrence is within the first 6 months.¹⁹ A family history of seizure, a spike-and-wave pattern on EEG, and a history of prior neurologic insult increase the risk of recurrence after a first unprovoked seizure.²⁰ An abnormal EEG may be a significant risk factor for recurrence (58%–75% versus 16%–27% in cases of a normal EEG).^{21–24} However, a single EEG is normal in approximately 50% of persons with epilepsy.²⁵ Other risk factors for recurrence may include a family history of epilepsy (46% versus 27%), Todd's paralysis (75% versus 39%), partial seizures, and an abnormal neurologic examination.²⁶

CASE 1 CONTINUED

The patient reports that for as long as she can remember flashing lights (eg, riding in the car and seeing the lights flash through the trees) have caused her to lose short periods of time. As a result, she avoids jogging through areas with leafy trees on sunny days. She also notes that in the morning her hands occasionally jerk

and she may drop what she is holding. The patient reports that her father has had 2 unprovoked convulsions during adulthood and is currently taking phenytoin. She has no other known risk factors for epilepsy. In consideration of the patient's history of photosensitive absence seizures, morning myoclonic seizures, and 1 convulsive seizure, the neurologist make a presumptive diagnosis of JME.

• What are characteristic features of JME?

JME is an idiopathic generalized epilepsy (IGE) syndrome characterized by myoclonic jerks (particularly in the morning) and generalized tonic-clonic seizures; 28% of affected persons also have *absence seizures*—a type of generalized seizure that can occur in both idiopathic and symptomatic, generalized epilepsy. IGEs make up approximately one third of all epilepsies, and different IGE syndromes frequently cluster within a family. They are considered to be primarily genetic in origin. JME is an inherited disorder, although in most cases the exact mode of inheritance is unclear. Between 17% and 49% of patients with JME have a relative with epilepsy. The genetics of IGEs was recently reviewed.²⁷ Mendelian or monogenic IGEs are often ion channel disorders. The more common familial IGEs are complex and nonmendelian. There has been considerable progress in identifying many of the genetic mutations responsible for epilepsy that can result in a similar electroclinical syndrome.

CASE 1 CONTINUED

The patient's physical and neurologic examinations are normal. An EEG is performed, which shows occasional 4- to 6-Hz spike-wave discharges. Results of magnetic resonance imaging (MRI) are normal.

Table 6. Risk Assessment After a First Seizure

History: Previously undiagnosed seizures, possible provoking factors, focal onset or aura, risk factors for epilepsy

Examination: Presence of focal neurologic signs, cognitive or developmental disorder, unrecognized medical disease

Laboratory tests: Tailored depending on patient's age and presenting scenario: glucose, sodium, calcium, magnesium, liver and kidney function, complete blood count, blood and urine toxicology, thyroid function tests; also, lumbar puncture if suspicion of meningitis or encephalitis or cancer known to metastasize to the meninges

Magnetic resonance imaging: Coronal cuts through the mesial temporal lobe structures to assess for mesial temporal sclerosis, gradient echo sequence to assess for cavernous malformations

Electroencephalogram: Should include both a sleep and waking recording; a sleep-deprived or ambulatory recording may increase the yield in assessing for epileptiform abnormalities

- **Based on the patient's EEG reading, how should she be managed?**

An EEG showing generalized fast spike-wave discharges confirms the diagnosis of JME. The diagnosis of generalized versus focal epilepsy is important, as some AEDs that are helpful in focal epilepsies may worsen aspects of IGE. The efficacy of AEDs also differs depending on the type of generalized seizure. Most seizures respond well to appropriate AEDs, but treatment is often life-long. Commonly used AEDs are listed in **Table 7**.

For JME, valproate is effective at fairly low doses. Lamotrigine may be preferable in women of childbearing age, given the birth defects associated with valproate. Many AEDs, including benzodiazepines, carbamazepine, phenobarbital, primidone, oxcarbazepine, and topiramate, affect oral contraceptives. Lower serum levels of lamotrigine are associated with concomitant use of oral contraceptives. Thus, if lamotrigine therapy is chosen for the case patient, a higher dose than otherwise is required may be necessary.

DIAGNOSIS AND TREATMENT OF EPILEPSY IN THE ELDERLY

CASE 2 PRESENTATION

A 70-year-old woman is referred to a neurologist for evaluation of recurrent episodes of loss of consciousness. According to the patient's daughter, the episodes

Table 7. Commonly Used Antiepileptic Drugs

Partial seizures (± secondary generalization)

Carbamazepine	Levetiracetam
Phenytoin	Oxcarbazepine
Primidone	Topiramate
Felbamate	Tiagabine
Lamotrigine	Zonisamide
Gabapentin	

Generalized seizures

Absence	Tonic-clonic
Ethosuximide	Valproate
Valproate	Phenytoin
Lamotrigine	Carbamazepine
Topiramate	Felbamate*
Levetiracetam	Lamotrigine
Myoclonic	Topiramate
Valproate	Levetiracetam
Clonazepam	Zonisamide
Lamotrigine	
Topiramate	
Levetiracetam	
Zonisamide	

Adapted with permission from American Epilepsy Society. Clinical epilepsy. Available at www.aesnet.org/visitors/professionaldevelopment/meded/newppt/clinical/clinical13-20.pdf. Accessed 4 Jan 2006.

*For tonic-clonic seizures associated with Lennox-Gastaut syndrome.

begin with the patient suddenly stiffening, falling to the ground, and shaking for 1 to 2 minutes, after which she is confused for 10 to 45 minutes. The daughter reports that these episodes occur 1 to 2 times a week. On evaluation today, the patient's neurologic examination is normal, but her blood pressure is 190/90 mm Hg.

- **What is the differential diagnosis of transient spells in elderly patients?**

DIFFERENTIAL DIAGNOSIS

The basic differential diagnosis of transient spells of neurologic dysfunction or loss of consciousness in the elderly includes cardiac events, transient ischemic attacks (TIAs), amyloid angiopathy, migraine, and seizures. Other etiologies to consider include parasomnias, movement disorders, metabolic dysfunction, and psychogenic events.

Cardiovascular disorders that may impair cerebral

blood flow and cause spells include arrhythmias, congestive heart failure, and aortic stenosis. Orthostatic hypotension, precipitated by volume depletion and/or antihypertensive or diuretic medications, can also lead to syncope. TIAs have characteristic symptoms and signs consistent with known vascular territories. They typically have negative symptoms (eg, weakness, sensory loss), whereas seizures are associated with positive phenomena (eg, stiffening, shaking, positive sensory disturbances, hallucinations). Limb shaking TIAs are an exception, with shaking of an arm, leg, or both caused by severe carotid stenosis. The underlying pathophysiology of cerebral amyloid angiopathy spells has not been definitively established, but their presentation is similar to that of TIAs. Migraine auras and other migraine symptoms may precede the headache by more than an hour, and “migraine equivalents” without headache are common in the elderly. Migraine auras are more gradual in onset and of longer duration than seizures.

CASE 2 CONTINUED

Further history reveals that several times a week the patient experiences episodes during which she smacks her lips, picks at her clothes and hair, and is not responsive. Her medical history is significant for hypercholesterolemia, hypertension, and anxiety. She takes atorvastatin and hydrochlorothiazide. Family history is significant for a brother who developed seizures in his 60s and then had a stroke. The patient has no other known risk factors for epilepsy.

- How common are seizures in the elderly?
- What are the common causes of seizures in this population?

INCIDENCE AND ETIOLOGY OF SEIZURES IN THE ELDERLY

The incidence of epilepsy is highest in those aged 75 years or older (**Figure 2**). Nearly 25% of all persons with epilepsy are elderly, and of all new seizures, 25% to 50% occur in the elderly.^{28,29} Up to 18% of elderly nursing home residents have epilepsy.³⁰ Status epilepticus is more common in the elderly and can carry a fatal prognosis (30%–40% among those aged ≥ 60 years).³¹ New-onset epilepsy in the elderly should generally be considered either cryptogenic or symptomatic. If a seizure is generalized tonic-clonic, it was probably of focal onset with rapid secondary generalization, although there have been rare case reports of newly diagnosed primary generalized epilepsy in the elderly.

Major causes of newly diagnosed epilepsy in patients

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Figure 2. Age-specific incidence of seizures in Rochester, MN, between 1935 and 1984. (Adapted with permission from Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. *Epilepsia* 1993;34:456. Copyright © 1993 Blackwell Publishing Ltd.)

older than age 60 years include cerebral infarction (33% of cases), arteriosclerosis (15%), head trauma (7%), and hemorrhage (2%); other causes (eg, brain tumor, trauma, Alzheimer’s disease) account for 19% of cases, and in 24% of cases the cause is unknown.²⁸ The risk factors for development of post-stroke epilepsy are similar to those for acute symptomatic seizures in stroke (eg, hemorrhage, cortical involvement, size of infarct).³² An acute symptomatic seizure increases the risk of developing post-stroke epilepsy; 35% of individuals with acute seizures will develop post-stroke epilepsy.³³ Most cases of cryptogenic seizures are probably related to cerebrovascular disease, given the increased incidence of stroke risk factors (particularly hypertension but also hypercholesterolemia), coronary artery disease, and peripheral vascular disease.²¹ After a cryptogenic seizure, even in the absence of a history of stroke, there is an increased risk for a subsequent stroke, with a relative risk of 2.89.³⁴

- Is epilepsy easily diagnosed in the elderly?
- What diagnostic studies are helpful?

DIAGNOSING EPILEPSY IN THE ELDERLY

The diagnosis of epilepsy in the elderly is often delayed. Most seizures are complex partial seizures with episodic periods of unresponsiveness or staring spells. However, clinical features may differ compared with younger patients; the primary presentation may consist of altered mental status, memory lapses, episodes of confusion, or sudden loss of consciousness, and postictal confusion may be prolonged.²⁸

Routine interictal EEGs are unlikely to reveal epileptic discharges. In 1 study, the first EEG showed interictal discharges in 35% of patients with pre-existing epilepsy

and only 26% of patients with seizure onset after age 60 years.³⁵ However, ambulatory EEG or video EEG monitoring may increase the diagnostic yield by as much as 50%, particularly when combined with electrocardiogram monitoring.^{36,37} Several studies have shown the utility of inpatient video EEG monitoring. In a study of 94 patients, 46 had documented epileptic events and 27 had documented nonepileptic events that included syncope, cerebrovascular events, sleep disorders, and psychogenic events.³⁸

Neuroimaging is essential in the evaluation of most new-onset seizures and is crucial in the work-up of a new seizure in an elderly patient. Head CT should be used in the acute emergency setting to exclude hemorrhage or a large mass. Otherwise, an MRI with gadolinium is the imaging modality of choice and should be performed expeditiously in patients older than 40 years.³⁹ MRI with coronal cuts through the mesial temporal structures is helpful in assessing for mesial temporal sclerosis, and gradient echo sequences may identify microbleeds associated with cerebral amyloid angiopathy, cavernous angiomas, and post-traumatic changes. In the VA Cooperative Study, only 18% of patients were found to have normal head CT scans; common findings were stroke (42.6%) and encephalomalacia (9.1%).²⁸ Other findings included tumors (1.5%), atrophy, small-vessel disease, and hydrocephalus. Cerebral and cervical vascular studies may be indicated in the work-up as well.

CASE 2 CONTINUED

The patient undergoes an MRI, which reveals mild diffuse atrophy and white matter changes consistent with small-vessel ischemic disease. Laboratory test results and a routine EEG are normal. A 24-hour ambulatory EEG shows multifocal epileptiform discharges, particularly in the right frontal region.

- **What are important treatment considerations for this patient?**

ANTIPILEPSY DRUGS IN THE ELDERLY

New-onset seizures in the elderly have a higher risk for recurrence (up to 90%), in part because the seizures are symptomatic or cryptogenic. Even if the MRI and EEG are unrevealing, initiation of AED therapy should be strongly considered and treatment will likely be long-term.

The average community-dwelling elderly person takes 5 medications daily, and the average nursing home resident takes 5 to 10.⁴⁰ Elderly patients are also more sensitive to drug interactions and adverse events because they have reduced hepatic and renal clearance, reduced pro-

tein binding, and altered gastrointestinal absorption. Phenytoin and valproate are highly protein bound and may lead to a higher free fraction in the elderly, contributing to adverse events. Cognitive changes and gait dysfunction are common side effects of many AEDs. These symptoms may be attributed to other known problems, and the patient may not be able to recognize these side effects.

As new-onset seizures in this age-group are readily controlled with modest dosages, the selection of an initial AED for an elderly patient should consider tolerability and potential drug-drug interactions and side effects as much as efficacy of the agent. The VA Cooperative Study assessed the efficacy and tolerability of 3 AEDs (gabapentin [up to 1500 mg], lamotrigine [up to 150 mg], and carbamazepine [up to 600 mg]) for new-onset seizures in patients older than 60 years.²⁸ There was no significant difference in efficacy among these agents. However, trial retention was a critical criterion by which the AEDs were evaluated; carbamazepine was associated with significantly more adverse events (27.3%) compared with gabapentin (17.4%) or lamotrigine (10%). Several agents are recently recognized as being associated with an increased risk of osteoporosis (carbamazepine, phenobarbital, primidone, phenytoin). The selection of an AED in the elderly has been recently reviewed.⁴¹

Given the high risk of stroke in elderly patients with cryptogenic seizures, careful assessment and treatment of risk factors for stroke should be part of the overall care. Thus, the management of the case patient should involve treatment and close monitoring of her blood pressure.

MANAGEMENT OF EPILEPSY IN PREGNANCY

CASE 3 PRESENTATION

A 35-year-old woman with a seizure history presents to a neurologist for advice on becoming pregnant. At age 20 years, the patient had a secondarily generalized seizure and was diagnosed with a right parietal region meningioma. She took carbamazepine for 5 years and then was tapered off the medication. She had a second convulsive seizure 3 months later. She again tapered off carbamazepine 4 months ago and had her third unprovoked seizure. She has resumed taking carbamazepine.

The patient would like to become pregnant within the next year. She wants to know the risks of having a seizure versus taking carbamazepine during pregnancy, if she can safely discontinue taking carbamazepine, and if there are other methods for managing her epilepsy.

- **What are important treatment considerations for women with epilepsy who wish to become pregnant?**

PREGNANCY AND EPILEPSY

Approximately 1 million women of childbearing age in the United States have epilepsy, and 200,000 give birth each year. Women with epilepsy appear to have a greater baseline risk of fetal malformations, which is further increased by the use of AEDs. There is also an increased seizure frequency in 17% to 33% of pregnancies. Nevertheless, 90% of women with epilepsy have a normal pregnancy and a healthy baby, and although the incidence of congenital malformations is increased, the actual incidence of major malformations remains low (ie, 4%–6% versus 2%–3% in the general population).

Risk of Seizures During Pregnancy

The increased frequency of seizures during pregnancy is due to several factors. During pregnancy, the volume of distribution increases, and hepatic and renal metabolism of AEDs are increased. Changes in serum-binding proteins also affect the free component of medications. The increased levels of both estrogen and progesterone also may influence seizure frequency during pregnancy. Estrogen, which peaks during the third trimester, has been shown to be epileptogenic, decreasing the seizure threshold. Conversely, progesterone has antiepileptic effects; many women have fewer seizures during the luteal phase of the menstrual cycle. In addition to hormonal changes, increased stress and decreased sleep during pregnancy are also likely to lower the seizure threshold. Finally, patient compliance with AEDs may be decreased because of concerns about medication effects on the fetus.

The risks of having a seizure during pregnancy include fetal hypoxia as a result of decreased placental blood flow or apnea during a seizure. The fetal heart rate may also decelerate, which may persist for up to 30 minutes after the seizure.⁴² If there is maternal trauma during a seizure, the fetus is at risk of injury and there is a risk of placental abruption or miscarriage. One prospective study found no association between first trimester seizure and major malformations, but the 95% confidence intervals (CI) were wide (0.1–2.9).⁴³

Risk of AED Use During Pregnancy

Older evidence indicates that women with epilepsy have an increased risk of fetal malformations, even without AED use. Specific congenital abnormalities include cleft lip and palate and cardiac anomalies. First trimester use of a single AED may be associated with a twofold to

fivefold increase in major malformations, depending on the agent. Polytherapy is associated with an even greater risk of fetal malformations, although the main offender appears to be valproate.⁴⁴ All the older AEDs are class C or D. Valproate is particularly teratogenic and associated with an increased risk of neural tube defects. Higher peak levels may be more teratogenic, and use of the extended release preparation is preferable. Neural tube defects are associated with exposure to valproate and carbamazepine at a frequency of 1% to 2% and 0.5% to 1%, respectively. Minor congenital anomalies affect 7% to 15% of infants exposed to AEDs, which represents a twofold increase over that in the general population. These anomalies principally involve the face and digits and include hypertelorism, epicanthal folds, broad nasal bridge, elongated philtrum, and distal digital and nail bed hypoplasia. Recent studies have shown a much higher risk with valproate versus carbamazepine.^{43,45} The North American Pregnancy Registry (www.massgeneral.org/aed) is an ongoing study with a primary goal of determining the frequency of major malformations in infants exposed to AEDs during pregnancy. Recently released data show an increased risk of major malformations with phenobarbital (relative risk, 4.2; 95% CI, 1.5–9.4).⁴⁶ Phenytoin has increased the risk of fetal cleft palate and heart disease. It also is associated with the fetal hydantoin syndrome (ie, growth deficiency, small head size, abnormalities of the nails and fingers, other minor malformations); intelligence is usually normal. However, longer-term studies of neurodevelopment show higher rates of developmental delay and lower IQ scores in children with in utero exposure to valproate⁴⁷ and phenobarbital.⁴⁸

Information is gradually being acquired for the newer AEDs, and it has been proposed that there is a lower risk of teratogenicity as pregnancy outcomes have generally been favorable and no consistent pattern of malformations has been observed. However, animal studies on all the agents show fetal toxicities, and there is less known about the teratogenicity of the newer AEDs in humans. The International Lamotrigine Pregnancy Registry has reported a very low incidence of major malformations,⁴⁹ but this low incidence may be in part related to the significant decline in lamotrigine serum levels during pregnancy.

Patient-Specific Decisions Regarding AED Use

Despite the known risks of many AEDs, treatment is better than uncontrolled seizure activity. Prior to conception, an evaluation of the clinical necessity of an AED and optimization of therapy is ideal. If continued AED therapy is required, achieving monotherapy at the lowest effective dose reduces the risks of teratogenicity. An AED can

often be discontinued safely. However, there is a continued risk of seizures in the presence of a structural lesion. The case patient, who has a structural cerebral lesion and whose previous attempt to taper off carbamazepine was unsuccessful, is at increased risk for having a seizure. After 2 unprovoked seizures, the risk of a recurrent seizure is 57% over 1 year and 73% over a 4-year period.⁵⁰

- **What options besides AEDs are available to treat epilepsy?**

NONPHARMACOLOGIC TREATMENT OPTIONS

Surgery

Candidates for resective surgery include those with a structural lesion and those with medically refractory partial epilepsy (ie, persistent and disabling seizures despite use of 2 or more appropriate first-line anti-seizure medications at appropriate doses) who have seizures from a region of the brain that can be resected without neurologic morbidity. For medically intractable partial epilepsy, surgical resection of the focal cortex is often the most effective treatment for both adults and children; anterior temporal lobectomy is the most common surgical procedure performed and renders approximately 60% to 80% of patients seizure-free. Other types of brain surgery include multiple subpial transections (used for eloquent areas of cortex) and corpus callosotomy (used to reduce drop attacks).

Vagal Nerve Stimulation

The vagal nerve stimulator was developed based on the observation that intermittent vagal nerve stimulation reduced seizures in experimental animals. The vagal nerve stimulator is approved by the U.S. Food and Drug Administration for the treatment of medically refractory epilepsy in individuals older than 12 years. Approximately one third of those treated with vagal nerve stimulation have a greater than 50% reduction in their seizure frequency.⁵¹ Use of the vagal nerve stimulator can be considered equally efficacious as the addition of a second or third AED, with minor side effects of neck pain, hoarseness, and a brief cough associated with activation of the stimulator.⁵¹

Other Therapies

The ketogenic diet is a high-fat, low-carbohydrate diet developed to mimic the anticonvulsant effect of fasting known since biblical times. Diet modification, through the ketogenic or low glycemic index diet, can be helpful in reducing seizure frequency, particularly in children, but is very restrictive and too onerous for most adults. Other therapies under clinical investigation in-

clude supplementation with polyunsaturated fatty acids, progesterone therapy, transcranial magnetic stimulation, neurostimulator devices, and gamma knife surgery.

CASE 3 CONTINUED

The patient decides to remain on carbamazepine and not pursue surgical options. She is concerned about whether epilepsy will make it more difficult for her to become pregnant, and she asks whether she should do anything in particular while trying to become pregnant.

- **What are fertility issues in women with epilepsy?**

Overall, women with epilepsy have fewer children than women in the general population; they also have a higher rate of menstrual cycle irregularities (including anovulatory cycles), hormonal abnormalities, polycystic ovary syndrome, infertility, weight gain, hirsutism, and galactorrhea.⁵² Fertility rates may be 33% lower in women with epilepsy.⁵³ Folate has been shown to decrease the incidence of neural tube defects. Women of child-bearing age with epilepsy should take folate daily regardless of their desire to become pregnant because the neural tube is formed before most women realize they are pregnant. Screening for a family history of birth defects may be helpful in leading to a recommendation for prenatal genetic counseling.

CASE 3 CONTINUED

The patient returns to the neurologist's office 3 months later after just learning that she is pregnant. She is feeling well and has had no seizures. She asks what special management will occur during her pregnancy. She also wants to know if her baby is at risk for having seizures and if she can breastfeed while on carbamazepine.

- **How should this patient be counseled at this time?**

EPILEPSY MANAGEMENT IN PREGNANCY

Table 8 summarizes principles of epilepsy management in pregnancy. It is recommended that women who become pregnant continue folate supplementation and begin to take prenatal vitamins and calcium supplements. If the patient is on AED therapy, it may be necessary to increase the dosage; some AEDs require up to a two- to threefold increase in dosage during pregnancy to maintain the same serum levels. Monthly monitoring of free and total AED levels also is recommended. Because of the increased risk of anomalies, a level II fetal survey should be performed at 18 to 20 weeks' gestation, with careful attention to the face, CNS, and heart. Because of the increased risk of neural tube defects, offering a

maternal serum α -fetoprotein (MSAP) screening test is also recommended. Performing an amniocentesis routinely for α -fetoprotein is controversial, but it is more sensitive than MSAP. In the setting of a family history of neural tube defects or with the use of valproate or carbamazepine, it may be recommended.

There is an increased risk of spontaneous hemorrhage in newborns that was historically described in women taking phenobarbital or primidone. This risk may be due to AEDs causing a decrease in vitamin K-dependent clotting factors and/or inhibiting placental transport of vitamin K. Although a recent study of 204 neonates born to mothers taking AEDs who did not receive vitamin K supplementation showed no evidence of coagulopathy,⁵⁴ the general practice is to administer oral vitamin K (10 mg/day) during the last month of pregnancy and to administer 1 mg of vitamin K to the infant at birth.

SEIZURE RISK IN CHILDREN

Children born to mothers with epilepsy have a greater risk of developing a seizure disorder. In 1 study of 687 children of parents with epilepsy, the cumulative incidence of unprovoked seizures up to age 25 years was about fourfold higher in the offspring of affected mothers than in the offspring of affected fathers (9% versus 2%).⁵⁵ However, maternal seizures during pregnancy do not lead to an increased risk of epilepsy in the offspring.

BREASTFEEDING

Breastfeeding while taking AEDs is generally encouraged and safe in term infants and is endorsed by the American Academy of Neurology and the American Academy of Pediatrics. The infant has already been exposed to the AED for 9 months in utero. There is an increased risk of infant sedation in women taking phenobarbital or primidone. Infant serum levels may be helpful for monitoring toxicity.

ACUTE MENTAL STATUS CHANGE IN A PATIENT WITH EPILEPSY

CASE 4 PRESENTATION

A 40-year-old man with a history of focal epilepsy is brought by ambulance to the ED. The man is unconscious and is accompanied by his wife, who notes a change in mental status in her husband over the past few days culminating this morning in the inability to wake up. The wife reports that her husband recently went on a 3-day camping trip and forgot to take his

Table 8. Epilepsy Management in Pregnancy

Preconception

- Evaluate need for continued AED therapy
- Attempt to decrease pharmacotherapy to monotherapy
- Taper AEDs to the lowest possible dose(s)
- Establish the level of total and free AEDs necessary for achieving good clinical control
- Review family history for birth defects and consider genetic counseling
- Begin folate supplementation (4 mg/day)

During pregnancy

- Do not switch to an alternate AED solely to reduce teratogenic risk
- Check total and free levels of AEDs monthly (many AEDs will require significant increases during pregnancy)
- Consider early genetic counseling
- Check maternal serum AFP levels at 16 weeks' gestation
- Perform a level II fetal survey and ultrasonography at 18–20 weeks' gestation
- Consider amniocentesis for AFP and acetylcholinesterase
- Administer vitamin K during the last month of pregnancy

Postpartum

- Encourage breastfeeding but counsel about avoiding sleep deprivation
- Continue to monitor AED blood concentrations closely; anticipate adjustments over the next several months
- Counsel about extra safety tips for infant care as appropriate (eg, changing clothing and diapers on the floor)
- Monitor for development of postpartum depression

AED = antiepileptic drug; AFP = α -fetoprotein. (Adapted with permission from Delgado-Escueta AV, Janz, D. Consensus guidelines: preconception counseling, management, and care of the pregnant woman with epilepsy. *Neurology* 1992;45:149.)

phenytoin with him. For several days after his return, he has been occasionally confused and complaining of a headache. This morning, after trying unsuccessfully to wake her husband, she witnessed a 2-minute convulsion. The patient's examination is significant for being stuporous but is otherwise unremarkable.

- **What is the differential diagnosis for a change in mental status in a patient with epilepsy?**

A change in mental status is one of the most common reasons for neurologic consultation, and the differential diagnosis is extensive. In the patient with epilepsy, special attention should be paid to medication toxicity,

drug-induced metabolic abnormalities, and the possibility of status epilepticus including nonconvulsive status epilepticus. There may be a common pathophysiology of the change in mental status and epilepsy, such as in cases of progressive epilepsies, mitochondrial disorders, and porphyria.

CASE CONTINUED

While evaluating the patient, his eyes and head deviate to the left. He then experiences a tonic-clonic seizure that lasts 5 minutes.

- **How is status epilepticus defined clinically?**
- **What are the steps in management of patients with status epilepticus?**

STATUS EPILEPTICUS

The most frequently used definition of status epilepticus, from the Epilepsy Foundation of America, is 30 minutes of either continuous seizure activity or repetitive seizures without recovery between them.⁵⁶ This definition was based on animal studies that have shown neuronal death after 30 minutes of seizure activity, with recovery seen in shorter time periods. The working definition has been broadened by some to 2 seizures over any interval with no interval recovery or 1 seizure lasting 5 minutes or longer.⁵⁷ Most seizures last less than 2 minutes⁵⁸; therefore, any seizure lasting 5 minutes or longer is of greater severity. DeLorenzo et al⁵⁹ studied several hundred cases of prolonged seizures and found that more than half of all seizures lasting 10 to 29 minutes eventually required treatment for status epilepticus.

Estimates of the incidence of status epilepticus in the United States range from 20 to 57 per 100,000 (higher incidence in non-whites) or about 150,000 cases each year.^{60–62} In adults, about 22% of cases are related to AED withdrawal or insufficient AED levels.⁶³ Alcohol withdrawal, stroke, and anoxia are also common causes. Other etiologies to consider include toxic-metabolic conditions, CNS infections, tumor, and trauma.

Initial Management

The initial management of the patient with status epilepticus consists of assessing the airway, assessing and monitoring cardiorespiratory status, providing oxygen and suctioning, obtaining intravenous (IV) access, administering an AED, and sending blood for laboratory tests (**Figure 3**). Thiamine and glucose are administered unless the patient has a documented normal glucose level. A focused history from any available family members, friends, or witnesses to the events and a neurologic examination are performed to assess for a

known seizure disorder or other illnesses, trauma, focal neurologic signs, and signs of medical illness (eg, infection, substance abuse). After a convulsion has ended, the patient should be carefully assessed for the possibility of nonconvulsive or subtle ongoing seizures.

Benzodiazepines are used as first-line agents in the acute management of seizures but are generally followed in quick succession by a longer acting AED, most commonly phenytoin. Lorazepam is the preferred benzodiazepine due to a longer duration of antiseizure action. Phenytoin (or fosphenytoin) is administered immediately following lorazepam. If the patient is already taking phenytoin, a dose of at least 10 mg/kg can be given while awaiting the serum level.

Further Work-up

Once the patient is stabilized, a further diagnostic work-up may include head CT, lumbar puncture (LP), EEG, and brain MRI. Immediate EEG assessment is required if there is use of a long-acting paralytic agent, when there is no improvement or return to baseline mental status after controlling overt convulsive movements, when the diagnosis is in doubt, or in cases of refractory status epilepticus. In a prospective study, 164 patients who presented with convulsive status epilepticus were monitored by EEG for 24 hours following control of the presenting status epilepticus; 49% of the patients continued to have seizures, and in 14%, there were no clinical signs of the seizure activity.⁶⁴

CASE CONTINUED

The patient is given IV lorazepam, and IV phenytoin is started. The patient's phenytoin level returns at 2 µg/mL, and he is given the full 20 mg/kg loading dose of phenytoin. His head CT and LP are normal. No further seizure activity is observed and his vital signs stabilize. However, the patient does not regain consciousness and 30 minutes later has a second generalized seizure lasting 5 minutes.

- **How should this patient be treated at this point?**

Management of Persistent Seizures

An additional phenytoin bolus of 10 mg/kg can be administered if seizures continue. Phenytoin is associated with the risk of hypotension and bradycardia. These side effects are less frequently seen with fosphenytoin, but the increased cost of fosphenytoin limits its availability. Other agents that may be used instead of phenytoin or may follow phenytoin infusion if seizures continue include IV valproate or phenobarbital. Phenobarbital is also associated with a risk of hypotension.

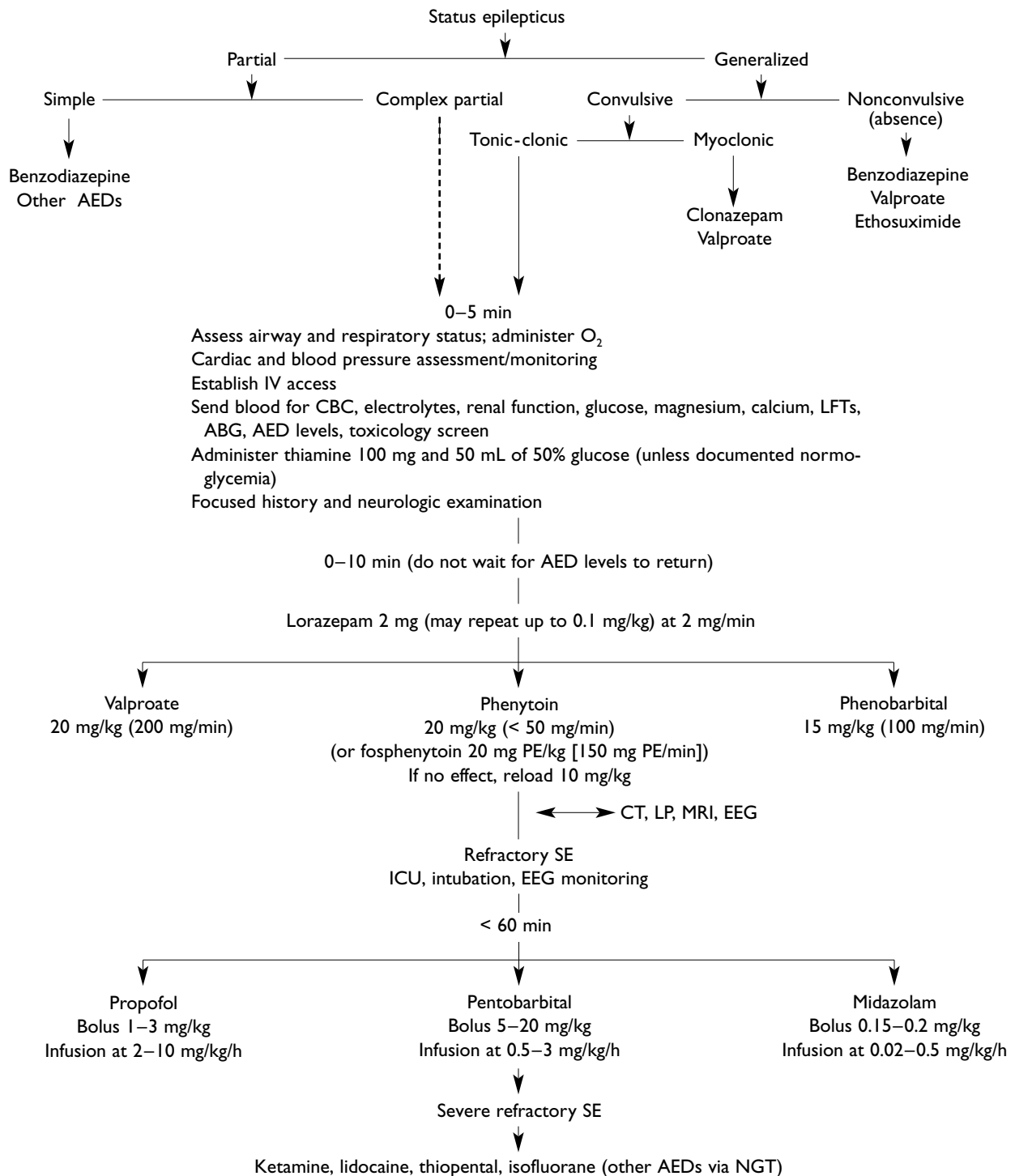


Figure 3. Algorithm for the treatment of status epilepticus (SE). AED = antiseizure drug; ABG = arterial blood gas analysis; CBC = complete blood count; CT = computed tomography; EEG = electroencephalogram; LFTs = liver function tests; LP = lumbar puncture; MRI = magnetic resonance imaging; NGT = nasogastric tube.

If seizures persist despite benzodiazepines and a second AED, status epilepticus is considered refractory and will likely require drug-induced coma with intubation (if not already performed), intensive care unit admission, and continuous EEG monitoring. The medication is titrated to a burst-suppression pattern on EEG or suppression of epileptiform activity. Medication-induced hypotension is to be expected and can be treated by slowing or stopping the infusion, giving fluid boluses, and using vasopressors as necessary. Historically, pentobarbital has been the agent most widely used. More recently, midazolam and propofol have been used with success. All these agents are thought to exert their anti-seizure action by increased GABA-ergic activity.

If the patient fails to respond to these treatments, the status epilepticus is considered severely refractory and carries with it an even higher risk of mortality. Further treatment options include ketamine, lidocaine, thiopental, and isoflurane. Other AEDs, such as topiramate and levetiracetam, can be administered via a nasogastric tube and have been successful in some cases.

- **What physiologic changes occur in convulsive status epilepticus?**

Initially there is a compensation phase. Cerebral metabolism is greatly increased because of seizure activity, but physiologic mechanisms are sufficient to meet the metabolic demands, and cerebral tissue is protected from hypoxia or metabolic damage. Catecholamines are released, there is tachycardia, hypertension, increased cardiac output, increased blood glucose, and increased cerebral blood flow as the body attempts to meet the increased oxygen and perfusion requirements. After about 30 minutes, decompensation and homeostatic failure begin. Cerebral blood flow, brain glucose, and oxygenation all decrease as the seizure goes on, the system can no longer keep up, and there is a decompensation phase. At this point, blood pressure falls, cerebral blood flow does not keep up with demand, and neuronal damage occurs.

- **What are the medical complications and mortality risk of convulsive status epilepticus?**

COMPLICATIONS AND MORTALITY RISK

The medical complications of convulsive status epilepticus include neurologic, cardiac, respiratory, autonomic, and metabolic derangements and damage.⁶⁵ Many patients have a profound acidosis (with an arterial pH < 7) that rapidly reverses with control of seizures. The acidosis is generally metabolic due to increased lactate, but respiratory acidosis can be seen as well. The

acidosis usually spontaneously corrects and does not require use of sodium bicarbonate. Fever occurs in 28% to 79% of patients and, based on evidence from the stroke literature, may be associated with a worse prognosis for neurologic recovery because it increases cerebral demand. Therefore, fever should be treated aggressively. Transient leukocytosis also may occur. With prolonged seizures, a mild elevation in cerebrospinal fluid white blood cells may be seen, although other etiologies should be considered as well. Muscle creatine phosphokinase is released and can lead to rhabdomyolysis. Neurologic complications include cerebral edema, worsening of epilepsy, and residual cognitive and neurologic deficits.

Mortality rates range from 3% to 50% and are related to the underlying condition,⁶⁶ with status epilepticus due to anoxia having the highest mortality. Mortality is highest in the elderly. Other factors influencing mortality risk may include level of consciousness at presentation, seizure duration, and whether status epilepticus is refractory.

CONCLUSION

Seizures and epilepsy are heterogeneous phenomena with varied etiologies, clinical courses, and outcomes, but the unifying principle is the presence of cortical injury and/or dysfunction. The cases discussed involve common issues facing a neurologist. Once epilepsy has been diagnosed, a thorough assessment for an underlying cause should follow and include a detailed history and physical examination, laboratory testing, neuroimaging, and an EEG. The classification of epilepsy as well as any medical comorbidities will guide selection of the appropriate AED. Status epilepticus is a neurologic emergency. It is important to consider nonconvulsive status epilepticus in patients whose mental status is not recovering appropriately following a seizure and in hospitalized patients with unexplained coma or change in mental status. Use of AEDs in status epilepticus is guided by a protocol. Overall, a neurologist can have a meaningful impact on the medical care and quality of life of individuals with epilepsy at a variety of life stages.

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