Abstract

Clinical trials conducted during the last 2 decades have consistently reported high rates of seizure recurrence following a first seizure. Although these studies have varied in the ways that they define a first seizure, the patient populations enrolled, and other methodologic details, they have consistently identified family history, severe head trauma, and the presence of other lesions of the central nervous system as factors associated with a high likelihood of recurrent seizure. A thorough physical and neurological examination is required to distinguish epilepsy from nonepileptic causes of seizures or seizure-like conditions. Magnetic resonance imaging using specific epilepsy protocols, electroencephalogram (EEG) recording within 24 hours of initial presentation, and extended ambulatory EEG recordings are particularly useful in the identification of patients with epilepsy. Treatment should be considered for patients with a first seizure that had clear focal manifestations, or who have a family history of seizures or who have clinical, radiographic, or electrophysiologic evidence of a brain abnormality. Treatment may also be considered for patients whose quality of life would be significantly diminished by a single recurrent seizure.

and neurological examinations should be performed to identify potential nonepileptic causes of seizures. The clinical expression of epilepsy is a function of the location of the seizure focus and the anatomic pathways by which seizure activity is projected through the brain. Because these features tend to be relatively fixed, the clinical presentation of epilepsy is usually quite consistent over time. This may help to distinguish seizures that are caused by epilepsy from seizures that are the result of other causes (eg, metabolic disturbances, fever).

Although a computed tomography scan may be performed on a patient presenting to the ED if there is concern about acute injury, a magnetic resonance imaging (MRI) scan should be considered the standard for all patients who require brain imaging for seizure diagnosis. The use of an epilepsy protocol to obtain MRI images has been shown to significantly increase the number of patients with identifiable CNS abnormalities. For patients undergoing seizure evaluation in the ED, a protocol-based MRI should be scheduled in the ED so that the results are available for the patient’s follow-up evaluation. EEG evaluation performed within the first 24 hours is more likely to identify abnormalities than EEG evaluation performed after a longer delay. In a prospective study of 300 patients over the age of 5 years with a first unprovoked seizure, epileptiform abnormalities were identified in 51% of patients who underwent EEG evaluation within 24 hours of a first seizure and in 34% of patients who underwent EEG evaluation after the first 24 hours.

The differential diagnosis of a seizure disorder can be extensive and complicated. Seizures may be caused by a large number of medical conditions, and epileptic seizures are often incorrectly attributed to other medical causes, such as a transient ischemic attack. Some nonepileptic causes that can produce seizures or confusional states include cardiovascular or cerebrovascular diseases, drug toxicity or withdrawal, fever, tics, sleep disorders, psychiatric disorders, and breath holding (primarily in pediatric patients).

Several psychiatric conditions can produce states that strongly resemble epileptic seizures (Table 1). Depression is one of the most common psychiatric causes of seizure-like episodes, and should be considered if the patient has a clearly depressed mood. Panic attacks may present as paroxysmal events and also be misdiagnosed as treatment-resistant seizures.

Consultation with a psychiatrist may be required to obtain a history that is adequate to identify a psychiatric cause of apparent seizures. There is a strong relationship between seizure disorders and migraine headache. Seizures and migraine may coexist in some conditions, such as convulsive migraine (migraine headaches that culminate in seizures). In some cases, a seizure disorder (eg, occipital epilepsy) may resemble migraine headache as the seizure starts with visual symptoms of flashing or an enlarging ball of light. Seizures are also associated with sleep disorders (Table 2). One of the most common seizure-related sleep disorders is paroxysmal nocturnal dystonia, a syndrome characterized by recurrent motor attacks with dystonic–dyskinetic features that occur during non-rapid eye movement sleep. Recent research suggests that paroxysmal nocturnal dystonia is often an expression of nocturnal frontal lobe seizures.

### Table 1. Psychiatric Disorders that May Resemble Epilepsy

- Depression
- Conversion reaction
- Anxiety/panic attacks
- Somatoform disorder
- Dyscontrol syndrome
- Munchausen syndrome
- Psychosis
- Schizophrenia
- Manic-depressive illness
- Malingering

### Table 2. Sleep Disorders Associated with or Resembling Seizures

- Paroxysmal nocturnal dystonia
- Nocturnal myoclonus
- Pavor nocturnus (night terrors)
- Parasomnias
- Narcolepsy
- Cataplexy
(sleep-onset myoclonus) is a normal occurrence and does not require treatment with anticonvulsant drugs.

A number of metabolic conditions can produce seizures (Table 3). Metabolic conditions typically cause generalized seizures, although a nonketonic hyperosmolar state can produce focal motor seizures. Metabolic causes of seizures are usually readily identified by standard diagnostic laboratory screening tests used in the ED.

Cardiovascular diseases are also a common cause of seizures or seizure-like events (Table 4). One particularly important cause of these events is neurocardiogenic syncope (also referred to as convulsive, vasovagal, or neurally mediated syncope). Although the precise mechanism is poorly understood, patients with neurocardiogenic syncope develop reflex bradycardia or peripheral vasodilation in response to standing or emotional reaction, resulting in a drop in blood pressure. The patient becomes pale, loses consciousness, and may experience a brief (5-10 second) interval of myoclonus, or rarely, a tonic-clonic activity. Neurocardiogenic syncope may strongly resemble epilepsy, and the definitive test that could identify it (the head-up tilt-table test) is often not performed. In patients without neurocardiogenic syncope, tilting produces a reduction in venous blood return that stimulates a compensatory increase in alpha- and beta-adrenergic activation. In patients with neurocardiogenic syncope, tilting produces an abnormal reflex stimulation of the vasodepressor region of the medulla, which causes an abrupt decrease in sympathetic nervous system activity (producing vasodilation), and stimulation of acetylcholine release by the vagus nerve (producing bradycardia). Pacemakers are usually not effective for the prevention of neurocardiogenic syncope because the drop in blood pressure typically precedes bradycardia.

**THE LONG-TERM COURSE FOLLOWING A FIRST SEIZURE**

Many studies have examined the long-term prognosis of patients with new-onset seizures. These results have varied considerably depending on the patient populations studied. Patient populations will also vary depending upon the referral sources (eg, EDs, primary care physicians, etc). For example, new-onset single-seizure patients identified in the ED are more likely to have a second seizure than those identified from an EEG lab. Patients initially diagnosed by primary care physicians tend to have a lower incidence of repeat convulsions. Studies also vary in the duration of follow-up (6 months to 5 years) and whether patients had only a single seizure or were diagnosed with epilepsy. In many instances, the investigators relied upon the history obtained by other physicians and did not personally determine that the seizure was truly a first seizure.

Despite these inconsistencies, most clinical studies have demonstrated that recurrent seizures are common following a first seizure. For example, Hauser and colleagues examined seizure recurrence rates in 244 newly identified patients with seizure of unknown cause, or following a putative causative event (eg, stroke, trauma). Patients with seizures within the first week following the precipitating event and those treated with an antiepileptic drug were excluded from the study. During 2 years of follow-up, 21% of the patients experienced at least one

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**Table 3. Metabolic Causes of Seizures**

- Uremia
- Diabetes
- Thyroid storm
- Hepatic failure
- Hypoglycemia
- Electrolyte disturbance
- Dysequilibrium syndrome
- Nonketonic hyperosmolar state

**Table 4. Cardiovascular Conditions that Cause or Resemble Seizures**

- Anemia
- Hypovolemia
- Neurocardiogenic syncope
- Arrhythmias
- Cardiomyopathies
- Mitral valve prolapse
recurrent seizure. Elwes and colleagues examined seizure recurrence in patients newly referred for epilepsy who had a history of 2 or more generalized tonic-clonic or partial seizures during the previous year. Patients with seizures caused by drugs, alcohol, or progressive neurologic disease were excluded. The investigators reported a recurrence rate of 82% over a median follow-up period of 64 months. In a study of 133 patients identified within 1 day following a first-ever tonic-clonic seizure, recurrent seizures were noted in 20% of patients after 1 month, 46% after 6 months, and 71% after 3 to 4 years. Matsson and colleagues found that even in a study population in which 100% of patients received treatment with antiepileptic drugs, a recurrence rate of 55% was observed after 1 year. Several factors have been associated with significantly elevated rates of seizure recurrence (Figure 1). Some of the most important are a family history of epilepsy, significant neurologic injury, evidence of CNS lesions (eg, brain tumor, stroke, neurodegenerative disorders) and presence of epileptiform activity on the EEG. The incidence of seizure following head injury depends on the extent of the injury. Severe injury (intracranial mass lesion or unconsciousness for more than 24 hours) is associated with a 20- to 30-fold increase in seizure risk; moderate injury (loss of consciousness of 30 minutes to 24 hours) is associated with approximately a 5-fold increase; and mild injury is not associated with a significant increase in seizure risk. In severe military head injuries (which are typically penetrating head wounds), the risk of seizures is as high as 50%, representing a 580-fold increase in seizure risk compared with the normal population. In a long-term community-based study, Annegers and colleagues examined seizure occurrence following head injury in patients who were evaluated initially between 1935 through 1984, with additional follow-up through 1994, in Olmstead County, Minn. Patients with a known history of epilepsy before head injury were excluded. In a total of 4541 patients, the 30-year cumulative incidence of posttraumatic unprovoked seizures following trauma was greater among those with severe injury (16.7%) than with moderate injury (4.2%) or mild injury (2.1%; Figure 2). Prophylactic treatment with antiepileptic medications has been shown to reduce the occurrence of seizures following trauma during the first 2 weeks, but not over the long term. The effects of phenytoin on late and early seizures were examined in a double-blind, randomized trial of 404 patients who...
began treatment within 24 hours of serious head injury. The incidence of early seizures (during the 2 weeks after injury) was significantly lower among patients who received phenytoin (3.6%) than placebo (14.2%; \( P < .0001 \)). However, the incidence of late seizures (after the 2 weeks, through a total of 2 years of follow-up) was similar for the phenytoin and placebo groups (27.5% vs 21.0%, respectively [not statistically significant; Figure 3]).

In a subsequent study, patients with traumatic brain injury who were considered to be at risk of developing seizures were randomized to one of three treatments: phenytoin for 1 week, valproate for 1 month, or valproate for 6 months. A total of 379 patients were enrolled and evaluated periodically for up to 2 years. The rates of seizures were similar for the 3 treatment groups. During the first 7 days, seizures were reported for 1.5% of patients with phenytoin and 4.5% of patients who received valproate (\( P = .14 \)). Late seizures (seizures that occurred after the first 8 days) were reported for 15% of patients who received phenytoin, 16% with 1-month valproate, and 24% with 6-month valproate (\( P = .19 \); Figure 4).

EEG findings provide important prognostic information about seizure recurrence and possibly response to prophylactic treatment. A study conducted in patients in the military examined EEG findings associated with new-onset seizures in patients who were evaluated but were not treated. Many patients with spike or sharp waves on the EEG did not develop subsequent seizures; although some of these EEG findings may have been normal EEG variant patterns such as phantom spike waves or benign epileptiform transients of sleep, which were not well defined until after this study was completed. However, the presence of spike activity was predictive of future epilepsy, and spike waves were rarely observed in patients who did not experience subsequent seizures.

Camfield and colleagues examined the relationship between EEG findings and seizure recurrence in 168 pediatric patients (between the ages of 28 days and 16 years) who underwent EEG testing after a single definite unprovoked seizure. Overall, 51.8% had a second seizure. Seizure recurrence was noted for 37% of patients with normal EEG findings, 45% of those with abnormal epileptiform findings, 58% of those with generalized spike-wave patterns, 63% with generalized atypical spike waves, and 68% of those with focal epileptic findings. In elderly patients, an analysis of data from a Veterans Affairs cooperative study com-

**Figure 3. Cumulative Fraction of Patients with Late Seizures (Occurring More than 8 Days After Injury)**

![Graph showing cumulative fraction of patients with late seizures.](image)

**Figure 4. Cumulative Fraction of Patients with Late Seizures Among Patients Assigned to Treatment with Phenytoin for 1 Week or Valproate for Either 1 Month or 6 Months**

![Graph showing cumulative fraction of patients with late seizures.](image)
pared routine EEG findings with EEG results obtained during long-term continuous EEG recording. Of 9 patients with normal routine EEG readings, one patient had slow waves and 2 patients had epileptiform patterns during long-term monitoring. Of 14 patients with slow waves during routine EEG, 10 patients had epileptiform discharges during long-term EEG recording (Spitz M, unpublished observations). In a treatment trial that compared valproate versus phenytoin in primary generalized seizures in patients age 5 years and older, no difference was observed between the treatment groups in the seizure recurrence rate for the study as a whole.18 When the data were analyzed on the basis of EEG evaluations, patients with generalized slow-wave EEG patterns were more likely to have recurrent seizures with phenytoin treatment (63% of patients) than with valproate (42%), although the number of patients in each group was relatively small and the difference was not statistically significant.

In patients who have recurrent seizures, there is often a considerable amount of time between the first and second seizures. Elwes and colleagues examined the time interval between the first and second seizure in 183 patients who had a total of 2 to 5 untreated tonic-clonic seizures.19 The median interval between the first and second seizure, in the absence of treatment, was 12 weeks (95% confidence interval, 10 to 18 weeks). Thus, when evaluating a patient with a first seizure, there is usually a considerable delay before seizure recurrence, and it may not be necessary to begin immediate treatment or to “load” a patient with an antiepileptic drug in the ED.

**SEIZURE FOLLOWING STROKE**

An increased risk of epilepsy in patients with stroke has been reported by several studies. So and colleagues performed a community-based study of seizure disorders after ischemic stroke in Rochester, Minn.20 The authors examined the incidence of early and late seizures following a first cerebral infarction for all patients who lived in the community between 1960 and 1969, with follow-up continuing until 1992 for patients who remained alive and were living within the Rochester area. Patients with ischemic strokes, with no previous history of seizures, were included in the study. A total of 535 patients were studied, with a mean duration of follow-up of 5.5 years. Early seizures (within 1 week of cerebral infarction) occurred in 6% of patients, usually within the first 24 hours, and were associated with a 16-fold increase in the risk of developing epilepsy. The cumulative probability of a late seizure (past 1 week) increased from 3.0% after 1 year to 4.7% after 2 years, 7.5% after 5 years, and 8.9% after 10 years, a 6-fold increase in seizure rate compared with the general population. Overall, 9.6% of the patients developed epilepsy. Early seizure occurrence (as well as recurrent stroke) was predictive of the subsequent development of epilepsy.

**FIRST SEIZURE: TREATMENT RECOMMENDATIONS**

Treatment of new-onset seizures should be considered if: (a) no acute precipitating factor is identified; (b) epileptiform patterns are identified on EEG; (c) the patient has a clear family history of epilepsy in a first-degree relative; (d) the neurological examination is clearly abnormal indicating cerebral cortical injury; (e) an imaging study shows a significant and pertinent abnormality; or (f) there is no evidence of a benign syndrome (eg, Rolandic epilepsy). Treatment may also be considered for a patient after a single seizure where one or more risk factors for recurrence are present and recurrent seizures could have a detrimental effect on their employment or quality of life.

**SUMMARY AND CONCLUSIONS**

Epilepsy (recurrent seizures) following a first seizure in the setting of significant risk factors is common. Seizures or seizure-like symptoms may result from a large number of medical and psychiatric conditions. A thorough clinical, radiological, and electrophysiological evaluation is required to identify the cause of new-onset seizures. MRI evaluation using specific epilepsy protocols, and EEG evaluations performed within 24 hours of a seizure or an extended ambulatory EEG, is particularly helpful in identifying brain abnormalities and patients at risk for the development of epilepsy.

**DISCUSSION**

*Dr Kaplan:* On what basis do you treat after the first unprovoked seizure?

*Dr Ramsay:* I would not treat a patient if a precipitating factor was found and everything else was normal.
If they had significant sleep loss, alcohol consumption, systemic metabolic disturbance, or something that we know is associated with seizures but not epilepsy.

**Dr Kaplan:** So you are in effect saying you would treat after all situations in which there is a first epileptic seizure, patient considerations aside.

**Dr Ramsay:** If after a first seizure, we find an appropriate abnormality on an imaging study or an epileptiform abnormality on EEG, I would strongly recommend treatment.

**Dr Glauser:** That is very different than in kids.

**Dr Ramsay:** Children are in a different situation in that they do not drive. You have syndromes which have a known outcome. For example, benign Rolandic epilepsy has a time-limited occurrence and will spontaneously go away. The consideration is different for complex partial seizures in adults; the evidence that we have now is that partial onset epilepsy does not go away on its own. I have some patients who were having one seizure a year, and some of those elect not to remain on therapy. Unfortunately, most of these patients experience recurrent seizures and usually an increase in seizure frequency. Spontaneous remissions are unusual in adults.

**Dr Dlugos:** In younger patients where driving is not an issue, many of us would not treat after the first seizure.

**Dr Glauser:** Clearly it is a risk-benefit assessment, and the evidence gives you what the risks are and then the risk is weighed in the context of the patient's situation.

**Dr Crane:** Another factor is, 5 years from now, when you still have not had another seizure, you are going to want to come off the medicine because you are tired of being on this medicine. At that point, should we keep you from driving? Should you refrain from driving while we are taking you off the medicine? And the second question is how long driving should be restricted?

**Dr Montours:** Another point is if they are waiting 6 months, if that is what your state regulation is, and they have another seizure at 5 and a half months, the clock starts ticking again. So that now becomes a year without driving. And a lot of people—I have seen it post-op, you know, 2 years after surgery, no seizures. Then you say: “Okay, if I am going to start withdrawing medicine, there is no driving.” And they say to me: “Forget it, I will stay on the medicine.” I am finding more and more people want to stay on medicine than come off, whereas in the past, it was the opposite.

**Dr Dlugos:** I think it is complicated, but we can also clarify this in a way that makes sense. There is the medical risk of a second seizure, there are the psychosocial consequences of a second seizure, and then there is the risk of treatment. The medical risks of the second seizure, whether you are a kid or an adult, are rather low. The psychosocial consequences are very different between pediatrics and adults. The risk of treatment is probably similar. So where we differ is on the psychosocial consequences of a second seizure. Devastating in an adult, perhaps, because of driving and employment; probably not that bad in kids if you are only going to wait for the second one. So I think that is where the difference comes and it all gets back to risk/benefit.

**REFERENCES**