Illustrative Teaching Case
Section Editors: Daniel Strbian, MD, PhD, and Sophia Sundararajan, MD, PhD

Early Onset Seizures in Stroke
Ashish Kulhari, MD; Daniel Strbian, MD, PhD; Sophia Sundararajan, MD, PhD

Case Description
A 43-year-old woman with a medical history of hypertension, myocardial infarction, ischemic cardiomyopathy, and systolic heart failure with an ejection fraction of 20% to 25% on a recent echocardiogram developed sudden onset of left hemiparesis, left hypoesthesia, left gaze deviation, and mutism. Two hours after symptom onset her initial National Institutes of Health Stroke Scale score was 25. A computed tomography of the head was unremarkable, but a computed tomography angiogram showed a distal right middle cerebral artery occlusion. She was given intravenous tissue-type plasminogen activator, but soon after tissue-type plasminogen activator administration, the patient had a generalized tonic clonic seizure. A repeat computed tomography of the head immediately after the seizure showed no hemorrhage, and the patient received mechanical thrombectomy for a right middle cerebral artery occlusion. She was started on levetiracetam for secondary seizure prevention. MRI showed multiple areas of diffusion restriction involving all vascular territories consistent with a cardioembolic source and her history of dilated cardiomyopathy. She was started on anticoagulation. Importantly there were both cortical and subcortical areas with diffusion positive signal. Electroencephalography showed severe diffuse encephalopathy without epileptiform discharges. She made a good recovery and her discharge National Institutes of Health Stroke Scale score was only 4. She had no more seizures and was discharged home on warfarin, statin, and levetiracetam with seizure restrictions. Two months later she had a minimal hemiparesis and returned to work. She had no further seizures. Although it was explained that the plan had only been to continue anticonvulsants for 3 months, she wanted to drive as soon as possible and elected to continue anticonvulsants indefinitely.

Discussion
Stroke is the most common cause of seizures in the elderly, and seizures are the most common neurological sequelae of stroke. In the Seizure after Stroke Study, 8.6% of ischemic stroke patients and 10.6% of hemorrhagic stroke patients had seizures. Seizures after stroke can be divided into 2 broad categories depending on their time of onset. Although definitions vary depending on the series, many groups define early onset seizures as occurring within 2 weeks of stroke onset and late onset seizures as occurring after 2 weeks. More than half of stroke-related seizures occur in the early period. Among the 8.6% of patients with ischemic stroke who had seizures in the Seizure after Stroke Study, 56% were early onset seizures and 44% were late onset seizures. Among the 10.6% of patients with hemorrhagic stroke who had seizures, 75% were early onset and 25% were late onset seizures. Most early onset seizures occur during the first 24 hours. The incidence of seizures after stroke is also increased with cortical location and larger volumes. The CA VE score has recently been developed to stratify patients more likely to develop late onset seizures after intracerebral hemorrhage. The score gives points for cortical location (1), age <65 years (1), volume >10 mL (1), and the presence of an early onset seizure (1). The risk of late onset seizures is ≈0.6%, 3.6%, 9.8%, 34.8%, and 46.2% for CA VE scores 0 to 4, respectively. The development of epilepsy, or recurrent seizures, after stroke occurs at varying rates, but it is higher after late onset seizures than early onset seizures. In patients with ischemic or hemorrhagic stroke, epilepsy developed in ≈30% of patients with early onset seizures and in 90% of patients with late onset seizures. The risk of epilepsy is higher in patients who experience an early onset seizure (30%) than in patients with stroke in general (5%–20%). Interestingly, patients with intracerebral hemorrhage tend to have a higher risk of developing epilepsy than those with ischemic stroke (10%–15% versus 6%–9%). The explanation for higher rates of late onset seizures progressing to epilepsy is likely because of the differing pathophysiology of early and late onset seizures. Early poststroke seizures are thought to be secondary to regional metabolic dysfunction and excitotoxic neurotransmitter (largely glutamate) production because of ischemia. This metabolic dysfunction is self-limited. However, late onset seizures are thought to be because of gliosis and meningocerebral scar, which is permanent.

Management
There are no specific guidelines on optimal timing and type of antiepileptic drugs after poststroke seizure and little...
data exist to guide management. However, there is general agreement that the use of antiepileptic drugs in patients with poststroke seizure should be dependent on the probability of recurrent seizures after stroke.4 Most patients with early onset seizures do not go on to develop epilepsy and do not require indefinite anticonvulsant therapy.2,3 However, many patients with early onset seizures are started on anticonvulsants during their hospitalization, and it can be difficult to withdraw them later because of driving restrictions. Many neurologists agree that multiple early onset seizures or status epilepticus should be treated with antiepileptic drugs for ≥3 months, but anticonvulsant treatment of a single early onset seizure after stroke is controversial. One approach would be to treat early seizures with an anticonvulsant initially but to discontinue the drug in patients without epileptiform discharges on electroencephalography at the time of hospital discharge. These patients may be less likely to have recurrent seizures and can begin their period of driving restriction, while they are recovering from their stroke, and in many cases already not driving. However, late onset seizures after stroke have a much higher incidence of recurrent seizures (90%) and are generally treated with lifelong anticonvulsants.

Potential Side Effects of Anticonvulsants

Anticonvulsants can have serious side effects; therefore, their use should be limited to those who are likely to require them. Previous studies have shown that patients on antiepileptic drugs for secondary seizure prevention after stroke have worse cognitive outcome, slower motor recovery, and less independence with activities of daily living when compared with patients not treated with antiepileptic drugs.5,6 Although many patients in these studies were treated with older antiepileptic drugs, newer antiepileptic drugs have a lower risk of cognitive impairment7 but may still have serious side effects (Table).

Side effects from antiepileptics can be an economic burden on society. A recent study published in The Netherlands8 found that the cost of common side effects to society in 2012 was estimated to be US $26675 per patient per year. These costs include healthcare costs and lost productivity for both the patient and the family. Cost estimates per year include behavioral costs (mean € 9689; US $12455), general healthcare costs (mean € 7454; US $9582), cognitive costs (mean € 7285; US $9365), and cosmetic side effect costs (mean € 2845; US $3657).

Driving Restrictions After Seizures and Effect on Return to Normal Activity

Duration of driving restrictions vary from region to region, state to state, and country to country. In the United States, driving restrictions vary from 3 to 18 months. In some states, the duration of driving restriction is at the physician’s discretion. There are many countries, such as Australia, Austria, Japan, and Italy, that restrict driving for 2 to 3 years. Seizure restrictions for >3 months have not been proven to reduce the rate of motor vehicle accidents.9 An Arizona, study failed to show any statistical reduction in seizure-related car crashes and deaths in patients with a 3-month driving restriction when compared with patients with a 12-month driving restriction.10

In areas where public transport is limited or nonexistent, driving restrictions can be devastating. Patients become dependent on family and friends and many face loss of employment. Because many patients already face financial loss because of their hospitalization and recovery from their stroke, they are unwilling to extend their driving restriction to stop anticonvulsants started for early onset seizures. Continuation of anticonvulsant medication at the time of discharge after stroke should be carefully considered.

Table. Selected Anticonvulsant Drugs and Their Side Effects

<table>
<thead>
<tr>
<th>Anticonvulsant Drugs</th>
<th>Selected Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Hyponatremia because of water retention, severe bone marrow suppression/pancytopenia, and severe hypersensitivity reactions, especially in Asians, hepatotoxicity</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Insomnia, irritability, aplastic anemia, and hepatitis</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Skin rashes, which can be not only mild but also serious reactions, such as Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Mood and behavioral changes, including irritability, agitation, depression, hallucinations, and psychosis</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Sedation, motor and cognitive impairment, megaloblastic anemia, osteomalacia, and mild hypersensitivity reactions</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Vertigo, nystagmus, hirsutism, gum hyperplasia, megaloblastic anemia, fetal malformations such as including cleft palate, hepatitis and neoplastic lymphocytic disorders, osteoporosis, and hepatic toxicity</td>
</tr>
<tr>
<td>Valproate</td>
<td>Hepatotoxicity, pancreatitis, fetal malformations, such as especially neural tube defects, thinning and curling of hair, weight gain, and tremor</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Peripheral visual field defects, depression, psychosis, and hallucinations</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Paresthesias, kidney stones, cognitive dysfunction, weight loss, and glaucoma</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Severe appetite suppression and weight loss</td>
</tr>
</tbody>
</table>

Data derived from Rang et al.4

TAKE-HOME POINTS

- Seizures are common after stroke.
- Early and late onset seizures differ in terms of the mechanism of seizure and the likelihood of developing epilepsy.
- Anticonvulsants can have serious side effects both during rehabilitation and long-term therapy.
- Withdrawal of anticonvulsants after recovery from stroke may be difficult because of restrictions placed on patients after withdrawal, especially driving restrictions.
Disclosures
None.

References

Key Words: antiepileptic agents ■ epilepsy ■ seizures ■ stroke