

Seizures As a Consequence of Stroke

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Disclosure

- I have the following financial relationship to report:
 - UCB Speakers Bureau

Learning Objectives

1. Identify patients at risk for post stroke seizure.
2. Identify seizure type and describe proper work up.
3. Describe treatment options for acute seizure post stroke.

Impact of Stroke

- Stroke is the 5th leading cause of death in men and the 3rd leading cause of death for women.
- It remains among the top 10 causes of death in children.
- Stroke is on the rise among younger adults – 15% of ischemic strokes occur in young adults and adolescents.
- Stroke is the leading cause of adult disability.

Stroke Types

- Ischemic Stroke
 - Thrombotic - large vessel is the most common
 - Embolic - 15% of embolic strokes occur in people with atrial fibrillation
- Hemorrhagic strokes are less common, only 15% of all strokes are hemorrhagic, but they are responsible for about 40% of all stroke deaths.

Seizures Post-Stroke

- In the first few weeks following a stroke some stroke survivors will experience a seizure.
- Seizures occur due to sudden disorganized electrical activity in the brain.
- Stroke is the most common cause of seizures in older people.

- Around 5% of people will have a seizure within a few weeks of having a stroke.
- It is difficult to predict which stroke survivors will have a seizure.
- Acute seizures normally happen within 24 hours of the stroke.
- Increased risk is associated with hemorrhagic stroke or large cortical stroke.

- Many clinical studies make a distinction between early and late seizures based on differences in their presumed pathophysiology.



Early Onset

- Early poststroke seizures are thought to result from cellular biochemical dysfunction leading to electrically irritable tissue.
- Acute ischemia leads to increased extracellular concentrations of *glutamate*, an excitatory neurotransmitter that has been associated with secondary neuronal injury.
- Experimental data also suggest that epileptogenesis is enhanced by *hyperglycemia* at the time of ischemia.

Luhmann HJ. Ischemia and lesion induced imbalances in cortical function. *Prog Neurobiol.* 1996; **48**:131–166.

Uchino H, Smith ML, Bengzon J, Lundgren J, Siesjö BK. Characteristics of postischemic seizures in hyperglycemic rats. *J Neurol Sci.* 1996; **139**:21–

Late Onset

- Late-onset seizures (at least 2 weeks after stroke) are thought to be caused by gliosis and the development of a meningocerebral scar.
- Changes in membrane properties, deafferentation, selective neuronal loss, and collateral sprouting may result in hyperexcitability and neuronal synchrony sufficient to cause seizures.

Epidemiology

- In a large epidemiological project, cerebrovascular diseases represented the most commonly identified etiology of secondary epilepsy (11%).
- The frequency of early postischemic seizures ranged from 2- 33%, with 50-78% occurring within the first 24 hours after stroke.
- The frequency of late postischemic stroke seizures varies from 3- 67%.

Epidemiology

- One population-based study found that patients with early postischemic seizures were approximately 16 times (95% CI) more likely to develop epilepsy as compared with patients without early seizures.
- A prospective study found seizure recurrences in 55% (34 of 62) of patients with late postischemic seizures, this is higher than that reported for the general population experiencing a first unprovoked seizure.
- These types of epidemiological studies can be confounded by the use (or lack of use) of anticonvulsant drugs.

Status Epilepticus

- >5 minutes of continuous seizure activity
- OR
- >2 discrete seizures between which there is incomplete recovery of consciousness.
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- 2 Types: Convulsive and Nonconvulsive
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- Convulsive > Non may have long-term consequences including neuronal death, neuronal injury, and alteration of neuronal networks.

- Stroke accounts for up to 25% of cases of status epilepticus in some series.
- A single institution study found that 17 of 1174 patients with ischemic or hemorrhagic strokes (0.14%) developed status epilepticus.
- A second single institution study reported that 22 of 2742 patients with ischemic stroke (0.8%) had status epilepticus (0.1% within the first 14 days).
- This compares with a 0.9% rate from a population-based study.
- Therefore, it appears that <1% of patients with ischemic stroke develop status epilepticus.

Embolic Stroke

- In the Seizures After Stroke Study (SASS), the largest prospective, multicenter study conducted to date, patients who had a probable cardioembolic stroke were not at elevated risk of a first seizure (HR, 1.00; 95% CI, 0.67 to 1.50; $P=0.99$) or recurrent seizures (HR, 0.68; 95% CI, 0.31 to 1.48; $P=0.33$).
- None of the 137 patients with presumed embolism had seizures in the Lausanne Stroke Registry.
- Similarly, there was no association between seizure at onset and the presence of a cardiac source of embolism in the National Institute of Neurological Disorders and Stroke (NINDS) Stroke Data Bank study.
- Therefore, clinical data showing a clear relationship between cardiogenic embolism and seizures are lacking.

TIA

- Available studies report a low frequency (1.8% to 3.7%) of seizures associated with transient ischemic attack.
- Distinguishing a TIA from a focal seizure can sometimes be difficult. This is particularly true in cases of so-called limb-shaking TIAs.
- Limb-shaking TIAs are thought to result from focal cerebral hypo-perfusion due to carotid artery occlusive disease.
- Because of diagnostic uncertainty, the true frequency of seizures associated with TIA remains uncertain.

Stroke Location

- **Cortical** location is the best-characterized risk factor for early seizures after ischemic stroke and is supported by studies with widely differing designs; these results have been repeated in numerous studies.
- In the setting of subcortical ischemic stroke, seizure is a possible consequence of a substantial release of **glutamate** from axonal terminals arising from injured thalamocortical neurons.

Impact of Poststroke Seizures on Outcome

- It is plausible that early seizures in penumbral areas might be harmful because of the additional metabolic stress they may cause in already vulnerable tissue.
- After accounting for stroke severity, population-based studies have not found an association between early postischemic seizures and mortality.

- More recently, a large population-based study found that new onset postischemic seizures were independent predictors of mortality; unfortunately, the impact of early- and late-occurring seizures was not analyzed separately.
- None of the available studies include a multivariable analysis of the effect of early or late seizures on functional outcome after ischemic stroke

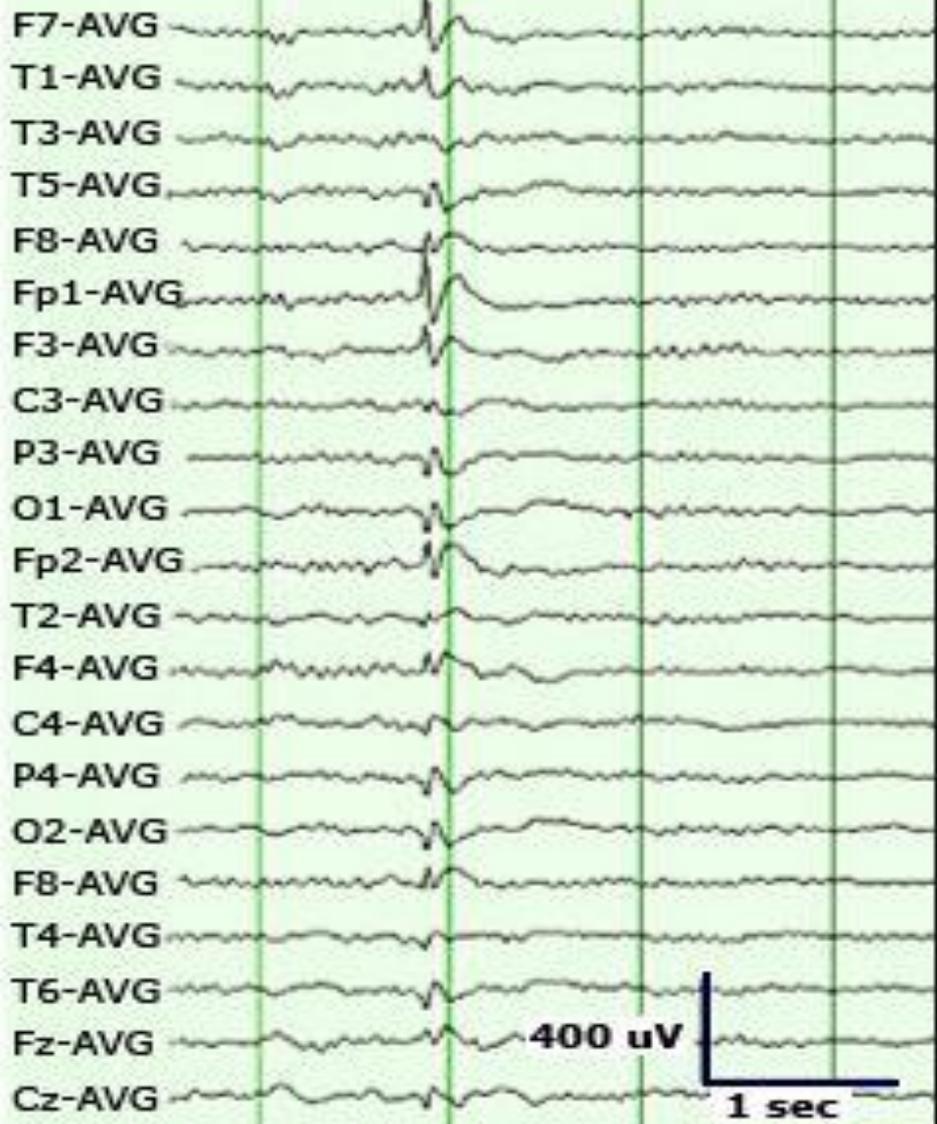
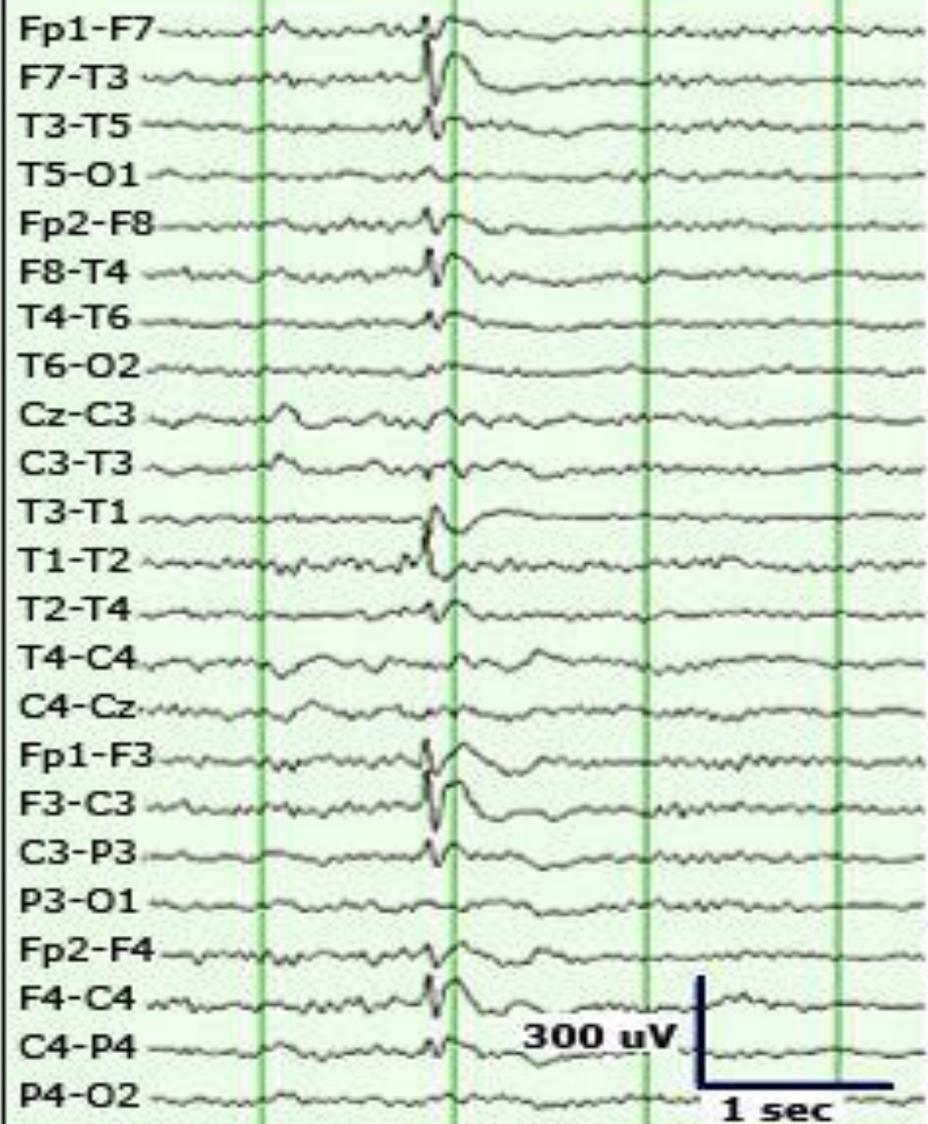
- Although mortality rates in stroke patients with status epilepticus can be high, data reflecting the independent affect of postischemic status epilepticus on outcome is limited because it is confounded by other factors related to the stroke, particularly stroke severity.
- Whether or not nonconvulsive status epilepticus affects outcome after ischemic stroke is largely unknown.

Work UP

- Convulsive seizures/status are clinical diagnosis, confirmed by the presence on exam of sustained and rhythmic tonic-clonic motor activity.
- Clinically obvious seizures should be treated immediately; there is no need to wait for an EEG.

Work Up

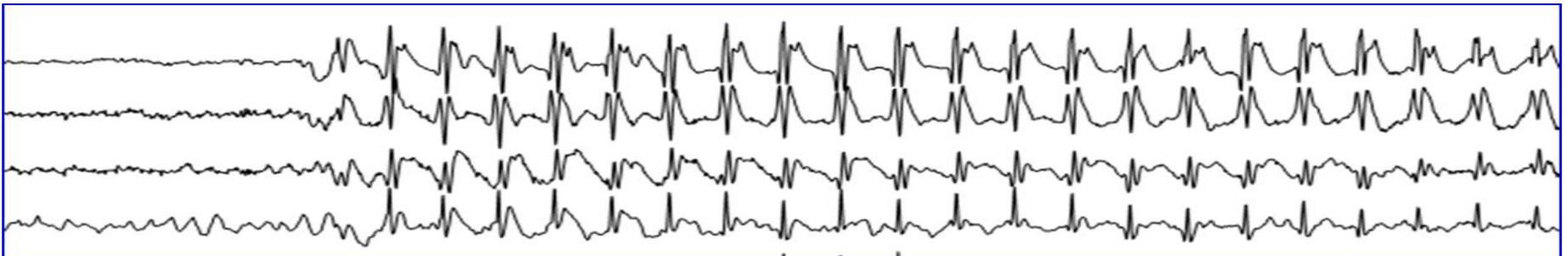
- Routine EEG can be normal in about 5% of cases and, therefore, normal EEG result does not exclude epileptogenicity.
- Focal slowing or diffuse slowing activities are associated with a low risk of seizures whereas ***focal spikes, periodic lateralizing, or periodic bilateral discharges*** are associated with a higher risk.





Work Up

- EEG may help distinguish myoclonic status epilepticus from non-epileptic myoclonus.
- In the aftermath of convulsive status epilepticus, and EEG may help exclude ongoing non-convulsive seizures.



Treatment of Status

- **Lorazepam** 0.1mg/kg at max rate of 2mg/min allowing 1 minute to assess its effect before administering additional doses.
- **Fosphenytoin** 20mg/kg/PE max rate of 100-150mg PE/min.
 - Additional 5mg/kg/PE can be given 10min after loading dose if seizures persist.
- **Valproic Acid** IV 20-40mg/kg rate 5mg/kg/min
- **Levetiracetam** IV 1-3g over 15 minutes

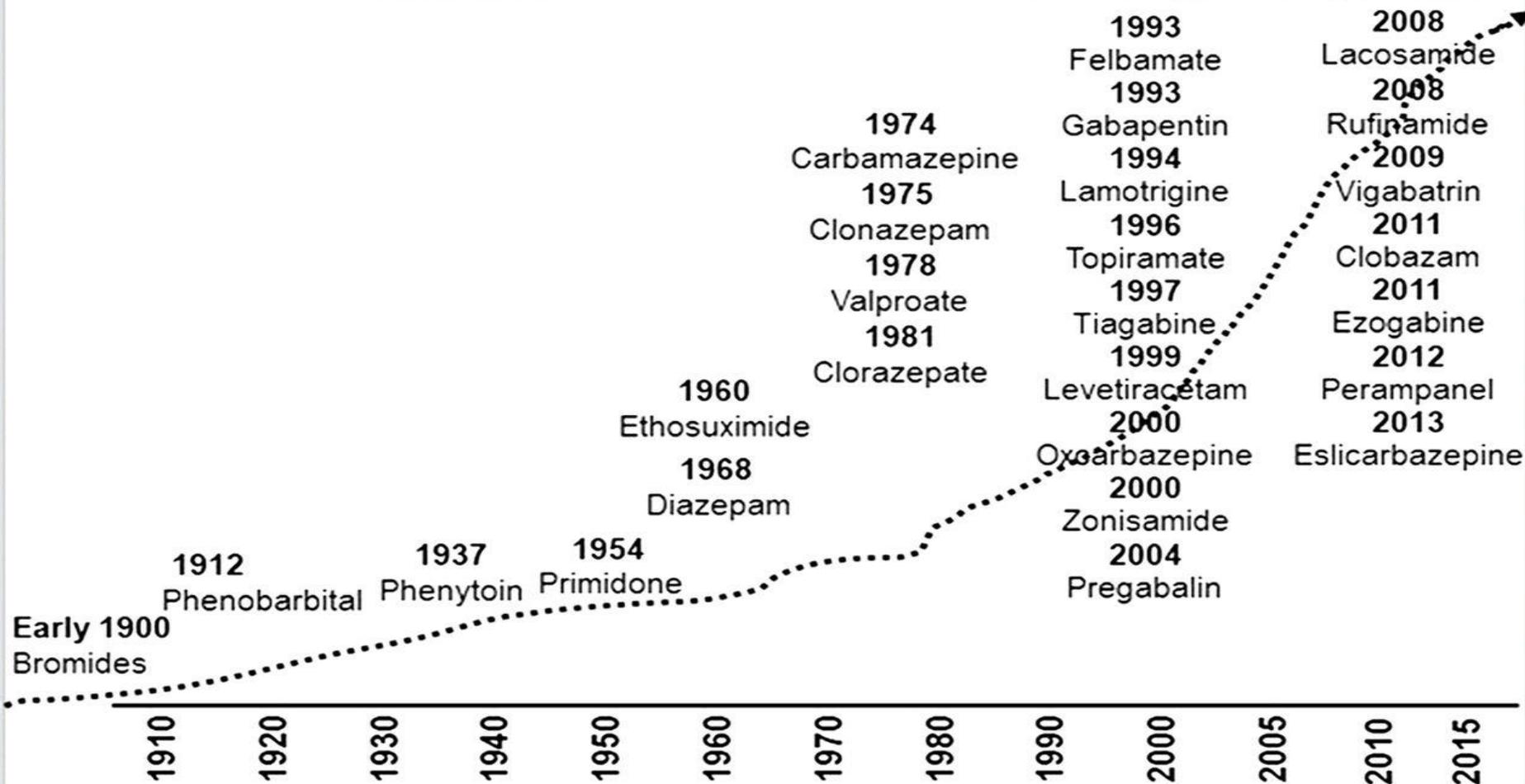
Treatment

- The dilemmas facing the clinician are whether to treat an isolated seizure and what antiepileptic drug to use in patients who have had single or recurrent seizures.
- Unfortunately, studies addressing these questions generally do not distinguish between the treatment of early and late seizures, do not include seizure recurrence or epilepsy as an end point, and do not provide data regarding dosages or patient compliance.
- Observational studies with small numbers of patients suggest that an isolated early seizure after cerebral infarction does not require treatment or can be easily controlled with a single drug.

Introduction of Major Antiepileptic Drugs in the US

1st Generation

2nd Generation 3rd Generation



Treatment

- Patients who develop recurrent early or late postischemic stroke seizures require pharmacological treatment.
- An observational hospital-based study and a prospective cohort study showed that 54% and 67% of patients with cerebral infarction and subsequent post-stroke epilepsy were seizure-free for at least 1 year with the majority of patients being treated with a single drug.

Treatment

- The Stroke Council of American Heart Association recommends prophylactic seizure treatment in the acute phase for intracerebral and subarachnoid hemorrhages.
- Patients with cerebellar or deep subcortical lesions are less likely to develop recurrent seizures and treatment is not recommended routinely.
- Pragmatically, early onset seizures need treatment for one month and drug treatment can be stopped if no seizure activity occurred during treatment.

Epileptic seizures in intracerebral hemorrhage: a clinical and prognostic study of 55 cases. *Cervoni L, Artico M, Salvati M, Bristot R, Franco C, Delfini R Neurosurg Rev. 1994; 17(3):185-8.* Guidelines for the management of spontaneous intracerebral hemorrhage: A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Broderick JP, Adams HP Jr, Barsan W, Feinberg W, Feldmann E, Grotta J, Kase C, Krieger D, Mayberg M, Tilley B, Zabramski JM, Zuccarello M Stroke. 1999 Apr; 30(4):905-15.*

There remain no data showing that administration of anticonvulsant drugs after stroke, or other acute brain injuries, prevents the later development of epilepsy.

Figure 1: Anticonvulsant Adverse Events

	Phenytoin	Carbamazepine	Phenobarbital	Valproic Acid	Gabapentin	Levetiracetam	Tiagabine	Lamotrigine	Oxcarbazepine	Topiramate	Zonisamide
Osteoporosis	X	X	X								
Platelet function				X							
Rash	X	X					X				
Renal Stones									X	X	
Sedation	X		X			X			X		
Slowed Thinking			X		X	X	X	X			
Tiredness				X							
Tremor											

Unanswered Questions

- Current understanding of the pathophysiology, epidemiology, risk factors, and treatment of poststroke seizures remains incomplete.
- Better definition of factors placing patients at very high risk for the development of postischemic stroke epilepsy might help identify a population that could benefit from therapies aimed at reducing epileptogenesis.
- Data regarding the relative effects of the various anticonvulsants on clinical outcome when given during the acute and recovery periods would help physicians make more rational drug treatment choices.