

Post-stroke epilepsy

This article discusses the current understanding of epidemiology, pathogenesis, clinical features, differential diagnoses and diagnostic studies of post-stroke seizures and epilepsies with an emphasis on the current recommended treatments, prophylaxis and important considerations when using different medications for seizure control.

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A stroke is the most common cause of seizures in the elderly population.^{1,2} Age itself is an independent risk factor of stroke.³ With the continuation of the long-running trend of an ageing population, the incidence and prevalence of post-stroke seizure and post-stroke epilepsy is expected to increase.

There is no distinct pathophysiological explanation for post-stroke seizures; however, current evidence suggests that post-stroke seizures are triggered by cerebral irritation by biochemical dysfunction and products of blood deposition in ischaemic strokes and haemorrhagic strokes, respectively.

As there is no single diagnostic investigation for post-stroke seizures, it is not always easy to distinguish true seizures from seizure-like conditions, and it is also challenging to diagnose atypical seizures, particularly in older people. Efforts should be made to avoid delaying the diagnosis of post-stroke seizures because they generally respond

well to antiepileptic medication (AED) monotherapy.

Definitions

Post-stroke seizure

Single or multiple convulsive episode(s) after a stroke and thought to be related to reversible or irreversible cerebral damage due to a stroke, regardless of the time of onset following the stroke.⁴

Post-stroke epilepsy

Recurrent seizures following a stroke with a confirmed diagnosis of epilepsy.⁵ The most commonly used definition of post-stroke epilepsy (PSE) has been identified as two or more unprovoked seizure occurring ≥ 1 week after the stroke.

In general, seizures after a stroke are classified as early or late onset. The first seizure occurring within 24 to 48 hours,⁶⁻⁸ one week,⁹⁻¹¹ two weeks¹²⁻¹⁸ or one month¹⁹ after a stroke has been identified as an early seizure. Late seizures have most commonly

been described as those occurring at least two weeks after a stroke.²⁰

Prevalence and incidence

Approximately 5–10% patients who have a stroke develop seizures and stroke is the most commonly identified cause of epilepsy in patients over 35 years. Box 1 summarises the current evidence on epidemiology of post-stroke seizures.

Prevalence

The prevalence is 0.7% in males above 65 years of age increasing to 1.5% after 80 years, whereas in females it is 0.5% above 65 years of age and there is a threefold increase (1.5%) after 80 years.²¹

Incidence

The incidence is 4.7% in males older than 75 years of age and 3.7% in females older than 75 years and all other incidences are about 4.4–9.8%.²² Cardiovascular disease accounts for half of seizures in elderly patients. The incidence of

Box 1: Prevalence and incidence of post-stroke seizures

	Prevalence		Incidence	
	Male	Female	Male	Female
Overall				4.4–9.8%
Age				
65 years	0.7%	0.5%		
>75 years			4.7%	3.7%
>80 years	1.5%	1.5%		
Lesion				
Intracerebral haemorrhage				10.6–15.4%
TIA				3.7%
SAH				5.5–8.5%
Ischaemic				6.5–8.6%
Time of onset				
Early				14%
Late				86%
Seizure type				
Simple partial				
+/- secondary generalisation				50%
Complex partial				
+/- secondary generalisation				25%
Primary generalised				25%
Status epilepticus				1.5–2.8%

epilepsy in the elderly increases with cerebral infarcts, haemorrhages and vascular risk factors.

Early onset seizures are more likely to be partial, whereas late onset seizures are more likely to generalise. Status epilepticus is rare and is more common in patients with severe disability.

Pathophysiology

Many clinical studies make a distinction between early and late seizures based on various postulated pathophysiology. Different features and mechanisms of post-stroke seizures have been proposed, but no distinct pathophysiological basis exists.

Early onset of seizure

Ischaemic stroke

Cellular biochemical dysfunction leading to electrically irritable tissue is the main cause.^{23,24} During acute ischaemic brain injury, the accumulation of intracellular calcium and sodium may cause the depolarisation of the transmembrane potential and a lowered seizure threshold.^{12,25}

Excitotoxicity in acute ischaemia is another well-established mechanism. An increased extracellular concentration of glutamate, which is an excitatory neurotransmitter, is associated

with a secondary neuronal injury. Antiglutamatergic drugs may have a neuroprotective role in the settings of ischaemia, apart from the role of treating seizures.²⁶

In experimental studies of the post-ischaemic brain in animal models, altered membrane properties and increased excitability were noticed in neuronal populations in the neocortex²⁷ and hippocampus,²⁸ which may lower the threshold for seizure initiation. The region of viable tissues adjacent to the core of infarction in ischaemic strokes is called the “ischaemic penumbra,” and contains electrically irritable tissue, which may be a focus for seizure activity.

Box 2: Risk factors for development of seizures³¹

Stroke type	Risk factors for development of seizures
Haemorrhagic ³²	<ul style="list-style-type: none"> • Site <ul style="list-style-type: none"> • Lobar cortical structures 54% • Basal ganglia 19% • Thalamus 0%
Ischaemic ³³⁻³⁵	<ul style="list-style-type: none"> • Severity of initial neurological deficit • Severity of persistent disability • Involvement of multiple sites or a larger lesion • Cortical damage-associated with early-onset seizures • Hippocampal involvement
SAH ³³	<ul style="list-style-type: none"> • Middle cerebral artery aneurysm • Intraparenchymal haematoma • Cerebral infarct • Hypertension thickening of cisternal clot

Global hypoperfusion and a hyperperfusion injury, particularly after carotid endarterectomy, have been commonly accepted as the aetiologies of early onset seizures.

Haemorrhagic stroke

The exact mechanism of seizure initiated by a haemorrhagic stroke still remains uncertain. Focal cerebral irritation may be caused by products of blood metabolism such as haemosiderin, and seizures are thought to be the consequence.

This postulated mechanism is consistent with the findings of one animal model, which showed that focal epilepsy can be produced by iron deposition on the cerebral cortex.²⁹ The ischaemic area, secondary to a haemorrhage, has also been proposed in seizure aetiology.

Late onset of seizure**Ischaemic stroke**

Gliotic scarring has been implicated as the most probable underlying cause of late onset seizures.^{20,12} Persistent changes in neuronal excitability are found to be associated with late onset seizures. Healthy cell parenchyma appears to be replaced by neuroglia and immune cells, maintaining the abnormal neuronal excitability and leading to the late onset of seizures.²⁶

Haemorrhage

Similar to an early onset seizure in a haemorrhagic stroke, haemosiderin deposits are thought to cause focal cerebral irritation leading to a seizure.²⁶

Symptoms

Although the symptoms depend on the location of the lesion, about two thirds would present as a partial seizure and it is more common with early onset seizures. One third would develop generalised tonic clonic seizures, which is more common with late onset.^{4,26} Status epilepticus has been reported in about 9% of patients.^{4,30}

Atypical presentations

- Acute confusion
- Behaviour change
- Syncope.

Differential diagnosis

It is not always easy to distinguish whether or not the patient has had seizures. Apart from atypical presentations of post-stroke seizures, the apparent cause of a seizure (ie. a stroke) can become a mere cloak to hide the true underlying cause of a seizure, particularly in elderly patients. Such conditions include cardiac arrhythmia, cerebrovascular infections, and electrolytes imbalance, and abrupt drug withdrawal should not be overlooked.⁴ Syncope is another important condition which can mimic a seizure. It can be presented with features of seizures such as traumatic injury, incontinence and confusion with slow recovery. Migraine-related focal phenomena and transient ischaemia attacks can produce focal slowing on EEG findings.

The above entities should not be overlooked in order to avoid delays in appropriate diagnosis

and management, and it is worthwhile remembering that elderly patients can present with seizures atypically.

Risk factors

Which types of patients tend to develop post stroke epilepsy after stroke?

The highest incidence is with haemorrhagic lesions and the location of the lesion is an important determinant of post stroke seizures.

No single investigation is diagnostic. Using diagnostic modalities in combination can be useful in establishing the cause in many cases.

Investigations

EEG

Normal EEG can be found in about 5% of cases and therefore normal EEG does not exclude epileptogenicity or cerebral ischaemia definitively.

In a prospective study with mean follow up period of 15.9 months, no specific EEG pattern was found in those who developed post-stroke epilepsy as the total number of cases of recurrent seizures were too small (n=4) to be conclusive.³⁶

Focal slowing, diffuse slowing and normal findings on EEG were associated with relatively low risk of focal seizure. In contrast, patients who had EEG showing periodic lateralising and bilateral independent periodic lateralising epileptiform discharges were prone to a higher risk of post stroke seizures development. Patients with focal spikes on EEG

Box 3: Other measures important in the management of post stroke epilepsy

Other Measures

- Advice on driving
 - Must notify DVLA
 - May drive a motor vehicle if seizure-free for one year
 - Avoid if affected by drowsiness
 - Avoid during medication changes or withdrawal of AEDs and for six months after
- Advice on activity supervision
- Regular follow up to monitor for side effects
- Education and counselling for patient and family/carers
- Multidisciplinary team involvement
- Surgery may be beneficial for controlling seizures in intractable epilepsy after ischaemic strokes

were also associated with a high risk of seizures.³⁷

In selected patients, focal slowing of EEG may reflect a wide region of ischaemic or infarcted tissue involving the cerebral cortex or sub cortical territory. It may also be useful in the early evaluation of poorly defined post-stroke focal neurological symptoms.²⁶ Other works found that neuroanatomical imaging studies showing cortical involvement were more predictive of epilepsy than any single EEG finding.³⁸

CT

A study showed that focal features of seizures on neurological examination and/or in EEG, correlated significantly with CT abnormalities in 202 adult with newly diagnosed epileptic seizures and therefore CT can be a useful diagnostic when used in conjunction with EEG and other clinical findings.³⁹

The absence of these abnormalities did, however, not

exclude the possibility of brain lesions, which in many cases were treatable by surgery.

In the SASS studies, the majority of patients with a diagnosis of lacunar infarction have normal CT scan results, and seizures were reported in eight of 307 of those patients (2.6%). Brain MRI was not performed in these patients and therefore the possibility of cortical involvement cannot be excluded.¹²

MRI

MRI is another choice of imaging which will show a number of abnormalities that may be missed on CT such as cortical malformations, hippocampus sclerosis, small mass lesions, and cavernomas—particularly in the temporal lobes.⁴⁰

A recent study by Lansberg et al has described acute MRI findings in three patients with partial status epilepticus. Diffusion-weighted imaging and T2-weighted MRI studies of the brain showed cortical hyperintensity

and a corresponding area of low apparent diffusion coefficient. These findings were readily distinguished from typical ischaemic stroke in their nonvascular distributions, increased signals of the ipsilateral middle cerebral artery on MRI angiography and leptomeningeal enhancement on post-contrast MRI.⁴¹

Management

Antiepileptic medication (AED)

There is currently little evidence which compares different antiepileptic drugs in stroke patients however monotherapy controls seizures in 88% of patients.³⁸ Carbamazepine is commonly used. Lamotrigine is better tolerated in newly diagnosed epilepsy in elderly patients and may make patients seizure free for longer intervals than carbamazepine.⁴² Benzodiazepines, especially lorazepam, are useful in ongoing seizures.²⁶

Choice of monotherapy should be tailored to each patient and considerations include route, concurrent medications and comorbidities. Care must be taken when prescribing AEDs in the elderly population as they are more likely to be on multiple medications, eg. warfarin and digoxin, thus increasing the risk of drug interactions via hepatic enzyme induction or inhibition. Physiological changes in the elderly are likely to affect pharmacokinetics of AEDs and impair clearance of drugs. Patients with renal or hepatic impairment may require dosing adjustments. Drug choice may

also be limited by side effects, most commonly sedation.

There have been some studies which suggest a link between certain AEDs and impairment of post-stroke recovery and they recommend avoiding phenytoin, phenobarbital and benzodiazepines in the post-stroke recovery period if possible.^{20,43}

Management with AEDs is otherwise governed by the standard principles of epilepsy management.

- When monotherapy of a first-line AED has failed the diagnosis should be checked and monotherapy with a second-line AED should be trialled
- Medication changes require care—slow withdrawal of one drug only when the new regimen is established
- Combination therapy may be necessary but is less preferable as it increases the risk of side effects and drug interactions.

Prophylaxis

Prophylaxis is recommended in the acute phase for intracerebral and subarachnoid haemorrhages for one month after which it can be stopped if there has been no seizure activity.⁴⁴⁻⁴⁶ Long-term prophylaxis is recommended if seizure activity continues after two weeks of presenting.⁴⁷ It is not advised for cerebellar or deep sub-cortical lesions.⁴⁴⁻⁴⁶

Management of reperfusion syndrome involves aggressive control of systemic blood pressure.⁴⁸ The role of AEDs is unclear but current practice in patients with high-grade carotid stenosis is to give prophylaxis for one to two weeks after a carotid endarterectomy.²⁶

Prognosis

There is conflicting evidence regarding prognosis in patients with post-stroke seizures. Current studies concur that stroke severity is the most important factor in determining outcome in stroke patients.²⁰ It is suggested that patients with early-onset seizures have a poor outcome with a high in-hospital mortality rate, and that late-onset seizures are associated with higher levels of disability and vascular cognitive impairment.⁷

It is well established that epilepsy has a negative impact on health-related quality of life,⁴⁸ but this has not been extensively studied in post-stroke patients.²⁰

Conflict of interest: none

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