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Post-stroke epilepsy

CLINICAL REVIEW

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Epilepsy as a result of stroke is currently the most rapidly increasing form of epilepsy. The risk of post-stroke epileptogenesis is higher after haemorrhagic stroke than after ischemic stroke. We provide here a brief clinical review of the topic to highlight the misinterpretation and undertreatment of focal epileptic seizures in stroke patients. Correct diagnosis and treatment are important because recurrent epileptic seizures can reduce quality of life and hinder rehabilitation.

Every year, around 10 000 people in Norway suffer a stroke (1). The incidence of stroke is decreasing (2), and due to improved treatment options, more people are surviving strokes. These people often experience sequelae such as epilepsy (3).

Based on a literature search and our own clinical experiences, we aim to highlight post-stroke epilepsy in this clinical review. We discuss its definition, incidence, pathophysiology, manifestation, diagnosis and possible predictors, and suggest possible treatments.

We published an article on this topic in the Journal of the Norwegian Medical Association in 2004. The definition of 'post-stroke epilepsy' has changed since then, as have the treatment options, and we have therefore written an updated article.

Definition and incidence

In the week after a stroke, some people experience epileptic seizures known as 'provoked seizures' or 'acute symptomatic seizures'. These patients only have about a 30 % risk of having subsequent seizures, and do not therefore meet the criteria for an epilepsy diagnosis (4). For a diagnosis of epilepsy, at least two *unprovoked* seizures occurring at least 24 hours apart are required, or *one* unprovoked seizure and a probability of further seizures that is at least as high (60 % or more) as after two unprovoked seizures (4).

'Unprovoked seizures' are epileptic seizures that start more than one week after the stroke. Because the risk of further seizures is now more than 60 % (5), the criteria for epilepsy diagnosis are met after just *one* seizure (4).

Post-stroke epilepsy is the most common form of epilepsy with a morphological substrate, and in Rochester, Minnesota it accounts for 11 % of all epilepsy cases (6), 22 % of status epilepticus cases and 50 % of epilepsy cases among the older population (7). Around 1.5 % of the US population over the age of 70 currently have epilepsy (8).

Results from studies on the incidence of acute symptomatic seizures are inconsistent, but broadly speaking, the incidence is 3–5 %, and significantly higher after a haemorrhagic stroke (10–18 %) than an ischemic stroke (2–4 %) (9).

A registry study in Sweden found that the cumulative incidence of post-stroke epilepsy was 6.4 % after ischemic stroke and 12.4 % after haemorrhagic stroke. This was observed over a follow-up period of almost five years (10).

Pathophysiology and manifestation

The pathophysiology of acute symptomatic seizures differs from that of late seizures, and is thought to represent a neuronal response to acute cerebrovascular injury. This involves transient biochemical and metabolic dysfunction, including increased release of glutamate (11).

Late seizures in post-stroke epilepsy are thought to be due to permanent structural and functional changes in the damaged neural network. Neuroinflammation is likely involved in the development of an epileptogenic network, leading to increased neuronal excitability, which in turn makes the brain susceptible to epileptic seizures (11).

Post-stroke epilepsy is a focal form of epilepsy, and seizure manifestation depends on which parts of the brain are affected by the stroke. In many older people, brief focal epileptic seizures are either overlooked or misinterpreted (12). This is particularly the case when seizures manifest as brief episodes of confusion, visual disturbances, dizziness or speech difficulties. Tonic-clonic seizure onset following focal onset seizure is somewhat less common in older adults compared to younger adults, but a tonic-clonic seizure is, nevertheless,

the presenting symptom in around 30 % of cases (13). Some people experience focal twitching followed by transient paresis (Todd's paresis), which *can* be misinterpreted as another stroke.

Conversely, fainting episodes in older adults such as those due to heart disease or while urinating during the night (micturition syncope), can be misinterpreted as epilepsy.

Diagnosis

Post-stroke epilepsy is a purely clinical diagnosis that is primarily based on a detailed medical history, often supplemented with information from the patient's family. What form did the seizures take? What about the frequency, duration and risk of injury? Diagnostics also include EEG, ECG and brain MRI, but there is no urgency for these. Epileptic abnormalities on the EEG can support a suspected diagnosis but are *not* a diagnostic criterion. Blood tests to detect conditions like diabetes or electrolyte imbalances should also be included. If there is uncertainty about the nature of the seizures, a wait-and-see approach should be permissible.

Possible predictors

Major ischaemic stroke or haemorrhage affecting the supply region of the middle cerebral artery, particularly in cases of cerebral cortex involvement, increases the risk of post-stroke epileptogenesis. Younger stroke patients (< 65 years) and those who experienced acute symptomatic seizures or who abuse alcohol are at greater risk of post-stroke epilepsy. Cerebral venous thrombosis and cerebral amyloid angiopathy can also predispose to epilepsy onset (11, 14, 15).

Scoring systems have been devised to calculate patients' risk of post-stroke epileptogenesis: CAVE score for intracerebral haemorrhage and SeLECT score for ischaemic stroke (16, 17). In our experience, these scoring systems are rarely used in clinical practice.

We recommend an EEG for all patients with suspected post-stroke epileptic seizures. However, the utility of EEG in predicting the later development of post-stroke epilepsy is uncertain for people who have *not* experienced such seizures.

The search is on for blood biomarkers that may be predictors of epilepsy. A slightly increased risk of post-stroke epileptogenesis has been found in those with a first-degree relative with epilepsy. Although some polymorphisms associated with post-stroke epilepsy have been identified (18), genetic testing in this patient group has so far shown little clinical utility.

The glymphatic system, including perivascular spaces, serves as the brain's drainage system. Evidence has been found of glymphatic system dysfunction after ischemic stroke. One hypothesis suggests that changes in such functions

play a role in the pathogenesis of various neurological conditions, including epileptogenesis after ischemic stroke. Advanced MRI modalities can detect enlargement or asymmetry of perivascular spaces as a potential biomarker for post-stroke epileptogenesis (19).

Epileptic seizures in older adults can sometimes be a precursor to stroke. A UK study showed that people over the age of 60 with a recent diagnosis of epilepsy faced a 2.89 times higher risk of stroke at any point than the control group (20).

Treatment

Although some clinicians prescribe anti-seizure medication for patients with acute symptomatic seizures, we do not recommend primary or secondary prophylaxis for such seizures.

However, such medications should be considered for treating late seizures. If the seizures are seldom and not particularly problematic, medication is not always needed, but in the vast majority of cases, it is appropriate to initiate treatment.

When choosing medication for this patient group, numerous factors need to be considered. Many older patients have impaired liver and kidney function as well as low levels of serum albumin, which necessitates a low dosage rate and low initial target dose. The reference ranges for these medications are not as valid for this patient group as for younger adults.

Although there are no fundamental differences in seizure-reducing effect between the old and new medications, the results of clinical trials favour the new ones (21), mainly due to better tolerance and a lower risk of drug interactions. The latter is particularly important in older patients given the high prevalence of multimorbidity.

The choice of medication should be tailored to the individual, taking account of age, sex, weight, co-morbidity and other treatment. Lamotrigine, levetiracetam and lacosamide are the preferred medications for this patient group (22, 23). Valproate can also be a good alternative, but not as a first choice in our opinion. Table 1 shows the initial dose, dose escalation rate, initial target dose and the most common adverse effects of these medications. Further dosing depends on efficacy and adverse effects.

Table 1

Suggested medications for post-stroke epilepsy, including initial doses, dose escalation rates, initial target doses and the most common adverse effects. The suggestions are based on our own clinical experience.

Medication	Initial dose	Dose escalation rate	Initial target dose	Common adverse effects
Lamotrigine	25 mg daily (monodose)	Up-titrate with 25 mg daily every 2 weeks (monodose)	100 mg daily (monodose)1	Skin rash, insomnia, headache

Medication	Initial dose	Dose escalation rate	Initial target dose	Common adverse effects
Levetiracetam	500 mg daily (250 mg × 2)	Up-titrate to 1000 mg daily after 2 weeks	1000 mg daily (500 mg × 2)	Fatigue, irritability
Lacosamide	50 mg daily	Up-titrate to 100 mg daily after 1 week	100 mg daily (50 mg × 2)	Fatigue, dizziness

[1]Lower dose when combined with valproate, higher dose when combined with enzyme inducers (e.g. carbamazepine).

Old liver enzyme-inducing drugs such as carbamazepine, phenytoin and phenobarbital are best avoided for this patient group as they can cause numerous pharmacokinetic drug interactions and have a tendency to increase markers of vascular risk and lead to bone loss (24, 25). Oxcarbazepine, which is a less potent enzyme inducer than carbamazepine, should also be avoided due to its tendency to cause hyponatraemia, particularly in older patients (26).

Initial follow-up should entail frequent outpatient check-ups. Blood analyses should be performed in cases of inefficacy or suspected adverse effects, drug interactions or poor treatment adherence. If the patient stops having seizures and has no problematic adverse effects, annual check-ups with a neurologist or general practitioner will suffice.

Prognosis

Post-stroke epilepsy can reduce quality of life, hinder rehabilitation and increase the risk of death in this patient group (27). Driving licence revocation can lead to isolation and loneliness. In our experience, it is a myth that most people with post-stroke epilepsy are able to control their seizures with medication. As with other types of epilepsy, around 30 % of these patients are drug-resistant (28).

The article has been peer-reviewed.

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