Epilepsy in stroke

Seizure after stroke is common and late-onset seizures have higher recurrence rate and poorer prognosis. Patients with post-stroke epilepsy are difficult to rehabilitate and are more likely to be hospitalised for an extended period of time. Second generation antiepileptic drugs have emerged as a favoured drug in post-stroke epilepsy in older patients.

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It has been known for quite some time that epilepsy is a recognised complication of cerebrovascular disease and that stroke is the commonest cause of epilepsy in older people.1 Post-stroke epilepsy may represent up to 11% of all adult epilepsies and 45% of seizures starting after 60 years of age.2,3

Patients with post-stroke epilepsy are difficult to rehabilitate and are more likely to be hospitalised for an extended period of time. The condition has implications on social and mental health as well as on quality of life such as driving eligibility. Because of lack of consensus, relevant and comparable studies, clinical guidelines are difficult to formulate and clinicians often find it difficult to manage this problem. The decision to initiate antiepileptic drug (AED) treatment after a first or a second seizure should be individualised, primarily based on functional impact of the first seizure episode and the patient’s preference.4

The aim of this review article is to highlight epidemiology, pathophysiology, risk predictors and, in particular, the management strategy of epilepsy in stroke.

Definition and classification

Seizure is defined as abnormal uncontrolled electrical activity in the brain that may lead to convulsions, loss of consciousness, thought disturbances or a constellation of signs and symptoms. It can be either provoked or unprovoked. Provoked seizures are mostly due to fever, metabolic disturbances, drugs or alcohol.

Epilepsy is characterised by recurrent unprovoked seizures. Post-stroke seizure is defined as single or multiple convulsive episode/s after stroke. It is thought to be related to reversible or irreversible damage due to stroke regardless of time of onset of seizures following the stroke. It may also be defined as recurrent seizures following stroke with confirmed diagnosis of epilepsy.5

In 1981, the International League against Epilepsy (ILAE) divided it into two major classes (Table 1). Partial-onset seizures begin in a focal area of the cerebral cortex, whereas generalised-onset seizures have an onset recorded simultaneously in both cerebral hemispheres. Some seizures are difficult to fit into a single class and they are considered unclassified seizures.

Early and late onset seizures

According to time of onset, early seizures are defined as seizures within 24 hours—1 month in various studies.6,7,8 A cut off time of 2 weeks seems to be widely accepted, but up to 45% of post-stroke seizures occur within the first 24 hours. Late-onset seizure is described as seizure occurring 2 weeks after the stroke.7 Epilepsy develops in about one third of early onset and half of late-onset seizures. The differentiation is important because early seizures may have other causes such as acid–based balance, electrolyte imbalance, hypoxia etc. Late seizures may be regarded as real post-stroke seizures.

Epidemiology

Stroke is one of the commonest causes of epilepsy accounting for about 11% of all aetiologies.2,4 In the elderly population, more than 40% of seizures are related to stroke.2,3 These seizures have also been reported as a predictor of future stroke and are secondary to small
vessel disease. Seizure occurring after the age of 60 years with no past history of stroke had a 2.89 relative hazard of a subsequent stroke compared with a control group (p<0.0001). Risk of epilepsy in stroke is 17-fold higher than the age-matched general population.

Diagnostic challenges

Mostly post-stroke seizures are focal (simple partial) or focal seizure with secondary generalisation. In about one third of cases they can present as generalised tonic clonic seizures. Often patients are unable to recognise symptoms or even after recognition are unable to convey it to the clinician because of reasons such as expressive dysphasia. It is often difficult to get an eye witness account because most of the patients are elderly individuals living in isolation.

For clinicians it becomes difficult to differentiate between transient ischaemic attacks and seizures or vice-versa. Todd’s paralysis after seizure can also be perceived as stroke recurrence. The presentation can be atypical such as behavioural change, acute confusional state and syncope. The key to diagnosis is a high degree of suspicion with careful history taking.

Limited role of EEG

Electroencephalography (EEG) has a very limited value in the setting of post-stroke epilepsy. In a study, EEG abnormalities were found in 17% of stroke patients, among these only 2% eventually suffered a post-stroke seizure. The picture gets further complicated by the finding that 12–38% of healthy individuals develop EEG abnormalities with increasing age.

Management

The general principles of management and investigations are similar to other causes of epilepsy. Hypoglycaemia and metabolic abnormalities should be excluded. DVLA guidelines should be followed for driving issues and patients should avoid swimming, water sports and fire hazards. There is huge psychosocial distress on patients and families; therefore, patient education and multidisciplinary input has a paramount role.

AEDs are the mainstay of treatment, but the current available evidence does not support prophylactic use of AED in stroke patients including haemorrhagic strokes.

First generation antiepileptics

Valproate

This drug is mostly well tolerated and has a broad spectrum of activity and is drug of choice for generalised seizure.

Box 1: ILAE classification of seizures

**Partial seizures**
- a. Simple partial seizures
- b. Complex partial seizures (associated loss of consciousness)
- c. Partial seizures with secondary generalisation

**Primary generalised seizures**
- a. Absence seizure (petit mal)
- b. Tonic-clonic (grand mal)
- c. Tonic
- d. Atonic
- e. Myoclonic

Box 2: The risk predictors for likely seizure

- **Stroke subtype**: haemorrhagic stroke and cerebral venous thrombosis are associated with higher incidence of seizures than ischaemic stroke.
- **Stroke location**: cortical location makes patients more prone for stroke than sub-cortical locations.
- **Stroke severity**: total anterior circulation stroke (TACI) is more likely to result in seizures and lacunar stroke is least likely to give rise to this complication.
- **Early and late onset seizures**: late onset seizure is associated with a higher risk of developing epilepsy. Late onset seizure has a peak within 6 to 12 months after the stroke and has a higher incidence of recurrence rate of up to 90% in both ischaemic and haemorrhagic stroke.
In the NICE guidelines. It was indicated in a survey that it was the preferred drug by physicians for the elderly in the UK.15

Phenytoin
Phenytoin should be avoided in post-stroke epilepsy because of its pharmacokinetics and interaction with warfarin and antiplatelet agents. There are some concerns that it might hamper functional outcome in ischaemic stroke.16

Carbamazepine
It has been considered drug of first choice for partial seizures by NICE. Extended release carbamazepine appears to be a better tolerated drug than intermediate-release form.17

Treatment of first seizure?
There is no study to date answering the question conclusively. NICE guidance suggests that AEDs should be given when an individual has a history of more than one seizure,18 but there is a high risk of seizure recurrence in elderly people and underlying structural disease.19 The Scottish Intercollegiate Guidelines Network (SIGN) 2003 favours that after a clearly documented seizure, following a full and frank discussion about the risks and benefits of treatment, AED therapy can be commenced.20 Few clinicians follow a pragmatic approach to treat early-onset seizures for 1 month and to stop treatment if no further seizure activity.16

Start low, go slow
Pharmacotherapy aims to achieve complete seizure control on the lowest possible dose to avoid side effects. Therefore, it is essential to start low and go slow. The important issues to consider during drug selection are:

- Possible drug interactions, especially with warfarin and other antiepileptic drugs. Phenytoin and carbamazepine are hepatic enzyme inducers and mutually interact with warfarin. It is difficult to keep plasma therapeutic ranges of each drug leading to poor seizure control and bleeding risk
- Knowledge of pharmacokinetics and adverse drug reactions due to physiological/pathological decline in elderly people
- Osteoporosis and osteopenia secondary to first line AED, including phenytoin, valproate and carbamazepine19
- General problems such as poor compliance, cognitive decline and swallowing difficulty etc.

Elderly patients
Recently three important randomised controlled trials performed in elderly patients compared lamotrigine to carbamazepine (including one that also assessed gabapentin).21-24 These studies show that elderly patients are more likely to become seizure free on a lower dosage of AED because of reduced hepatic clearance, renal elimination, lower serum albumin levels and altered protein binding, leading to better retention of AED in comparison with younger populations. But side effects are more common in elderly patients because of these properties.19,24

Lamotrigine and gabapentin were better tolerated drugs in the elderly in these studies. Based on these findings, the International League against Epilepsy has recommended lamotrigine and gabapentin as first-line monotherapy agents for arterial seizures in older adults.25 Furthermore these two drugs do not interact with anticoagulants, antiplatelet agents and do not affect bone health. Gabapentin remains the only drug specifically evaluated in post-stroke epilepsy, demonstrating a high rate of long-term seizure freedom, but lamotrigine is among the recommended first-line drugs for generalised and partial seizures in the SIGN guidelines for epilepsy.26 NICE suggests its use as an alternative drug.18

There is also preliminary evidence to suggest that levetiracetam can be well tolerated in post-stroke epilepsy in elderly patients.27

Prognosis
It is a matter of debate whether early seizures impact on physical outcome and mortality after stroke. Overall, a majority of studies suggest that late seizure and recurrent seizures hamper long-term neurological outcome. AEDs are more likely to achieve seizure control in post-stroke epilepsy than in most other forms of symptomatic or cryptogenic seizures.28

Particular problems in elderly
Epilepsy incidence increases with age. Incidence of epilepsy in older people is higher than any other age
group except first year of life. The estimated incidence in a population over 65 years old is estimated to be about 100 per 100000 annually.

As opposed to a younger population more than 70% of the elderly population have an underlying structural cause for unprovoked seizures, the most common being cerebrovascular disease. There is >90% chances of seizure recurrence.19

Most of the seizures in elderly patients are focal seizures with rapid secondary generalisation whereas primary generalised idiopathic seizures are commonest in younger patients. There is more risk of traumatic injuries because of osteoporosis and frailty. Management is often challenging because of comorbidities and polypharmacy leading to significant drug interactions.

Conclusion

Seizures after stroke is a common problem. The diagnosis is clinical and EEG has a very limited role because of low sensitivity and specificity. Newer antiepileptic drugs are emerging as favoured drugs in post-stroke epilepsy in older patients. Further larger studies are needed to address many unresolved issues in this field.

We have no conflict of interest

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