Chapter 2
Seizures in Ischemic Stroke

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Introduction

Stroke is the most common cause of new-onset seizures in older adults. Cerebrovascular disease accounts for 11 % of adult epilepsy, and, in older adults, stroke is the underlying cause in over a third of all cases [1]. Seizures secondary to ischemic stroke are generally categorized into early seizures (occurring up to 2–4 weeks after a stroke) and late seizures (occurring after 4 weeks). Risk factors for developing poststroke seizures generally include cortical involvement, anterior hemisphere location, early seizures, and possibly cardioembolic etiology [2]. Early seizures may be associated with increased mortality, while late or recurrent seizures may hinder long-term neurologic outcome [3]. There is a paucity of evidence for the prophylactic use of antiepileptic drugs (AEDs) in ischemic stroke without seizures. The decision to start patients on a long-term AED after their first poststroke seizure is debatable; consideration of the probability of seizure recurrence and the negative influence of some AEDs on neurological recovery must be taken into account.

Epidemiology

Cerebrovascular disease is the most commonly identified antecedent for adult epilepsy, accounting for 11 % of cases [1]. Stroke becomes an increasingly common cause of seizures when examining older populations. A population-based study in Sweden found that in patients over 60 years of age, 45 % of seizures were secondary

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M. Z. Koubeissi et al. (eds.), *Seizures in Cerebrovascular Disorders,*
DOI 10.1007/978-1-4939-2559-9_2

to stroke, followed by tumors (11%), and Alzheimer's disease (7%) [4]. Stroke is associated with a 23–35-fold increase in the incidence of seizure, and a 17-fold higher risk for the development of epilepsy [2, 5]. Stroke may also be a significant source of seizures in younger adults. A prospective cohort of 697 patients 18–50 years old who suffered a cerebrovascular event was found to have a cumulative risk of poststroke epilepsy with recurrent seizures of 8% after a mean follow-up of 10 years [6].

The timing of early seizures after stroke has been examined in a number of large studies. The Oxfordshire study found in their 545 ischemic stroke patients, 2% had suffered a seizure at the onset of stroke [5]. Labovitzet et al. found that when acute stroke patients suffered early seizures, they occurred at stroke onset in 40.5% of cases [7]. The Copenhagen stroke study reported that 86% of early seizures occurred within 3 days after a stroke, with 66% occurring within the first 24 h. Seizure subtypes included focal seizures with or without secondary generalization in 68%, and generalized tonic–clonic seizures with no clear antecedent focal seizure manifestations in 22% [8]. The frequency of early seizures occurring within a 2-week window after stroke ranges from 4.8 to 6.5% [3]. This incidence may be higher due to variability in the definition and detection methods and study setting [9].

The functional impact, underlying mechanism, and epilepsy risk of late seizures may be different than early seizures. Approximately, 3–5% of stroke survivors experience a late seizure within a year of their first episode, with 54–66% of these patients going on to develop epilepsy [3]. At 5-year follow-up, the frequency of seizure after stroke was 9.7% [10]. The risk of developing epilepsy at 5 years after a first stroke is 3.8%, and increases to 9.6% when patients suffer recurrent strokes [2]. Stroke has also been demonstrated to be a risk factor for status epilepticus in 22–32% of cases [9]. The overall poststroke incidence of status epilepticus is relatively low in large series; a single-institution study reported status epilepticus in 1.1% of a cohort of 904 acute stroke patients [7].

Risk Factors

Traditionally, certain stroke subtypes, such as embolic stroke, have been thought to be associated with an increased risk of new-onset seizures. However, seizures occur with most stroke subtypes. An increased risk of seizures after embolic strokes of cardiac origin has been shown in some studies, but not others [2, 11, 12]. The Seizure After Stroke Study (SASS), a large, prospective, multicenter study found that patients with presumed cardioembolic stroke were not at an increased risk for new-onset or recurrent seizures [13]. Interestingly, seizures have been associated with lacunar strokes in up to 3.5% of cases [14]. These seizures may develop from the release of glutamate from axonal terminals arising from injured thalamocortical neurons [12]. Consistent with this theory are studies demonstrating lateralized electroencephalography (EEG) abnormalities in 22–38% of patients with lacunar infarctions [15].

In the differential diagnosis of seizures are seizure-like involuntary movements that occur with specific stroke subtypes. Convulsive movements have been described in patients with brain-stem strokes; it has been postulated that these movements are related to ischemia of the corticospinal tract rather than a true seizure [16]. Various nonseizure transient hypokinetic and hyperkinetic movements have been infrequently described in patients with acute strokes, the most common of which are hemichorea and hemiballismus in the setting of lesions involving the basal ganglia or its pathways and the frontal lobe. Some of these movements may be delayed for months or years [17]. Kim et al. described nine patients with anterior cerebral artery strokes presenting with hemi-parkinsonism or asterixis. Symptom onset ranged from simultaneous with stroke onset to 1 month, and all patients improved [18].

Transient ischemic attacks (TIAs) have been associated with seizures in 1.8–3.7%. However, the true frequency is uncertain due to the diagnostic limitations of distinguishing some TIAs with focal seizures versus limb-shaking TIA. The latter are a particular type of seizure-like movement thought to be secondary to focal cerebral hypoperfusion due to severe stenotic or occlusive contralateral carotid disease [15]. Fischer in 1962 first described these movements as brief, arrhythmic, flailing, or jerking movements of an extremity that may be confused for a focal motor seizure or a movement disorder [19]. Clues which may help distinguishing limb-shaking TIAs from other diseases are lack of a Jacksonian march, nonepileptiform EEG, ineffectiveness of AEDs, precipitation of symptoms with maneuvers that cause cerebral hypoperfusion, and cessation of symptoms when improving cerebral perfusion. Maneuvers such as rising from a chair, hyperventilation, and hyperextension of the neck may provoke shaking movements, whereas laying supine may eliminate symptoms [20, 21].

Studies examining cerebral perfusion using positron emission tomography or transcranial Doppler have demonstrated hemodynamic failure in the contralateral hemisphere on the symptomatic side [22]. Reduced cerebral blood flow to critical watershed areas in patients who suffer limb-shaking TIAs are at a high risk for stroke [23]. In 147 patients with symptomatic internal carotid artery (ICA) occlusions, 28.6% were found to have contralateral limb-shaking symptoms. Multivariate analysis found the presence of limb shaking to be a significant independent predictor of adverse short-term and long-term outcomes when compared to patients with ICA occlusions without limb-shaking symptoms, in addition to severe National Institutes of Health Stroke Scale/Score (NIHSS) and the presence of diabetes. Symptomatic patients had a nonsignificant tendency toward increased recurrent strokes and TIAs [24]. Management may entail careful optimization of blood pressure and possible revascularization procedures to improve cerebral blood flow [20, 24].

Strokes involving the cortex have been characterized as having a high incidence of early seizures [25]. Strokes involving the anterior and posterior hemisphere, as well as the temporoparietal lobe have all been associated with increased risk of seizures, with early seizures associated with stroke in the anterior hemisphere. Cortically located strokes are twice as likely to cause seizure than subcortical strokes. Large infarcts involving the supramarginal or superior temporal gyrus have a

fivefold increased risk of developing late seizures [2, 3, 12]. Denier et al. found that a watershed mechanism of stroke was associated with a fourfold increase in early seizures compared to other cortical infarcts in 328 consecutive patients with magnetic resonance imaging (MRI)-confirmed cerebral infarctions [26]. The relationship between stroke severity and seizures has been variable. The Copenhagen stroke study found that only initial stroke severity predicted the occurrence of early seizures when using multivariate analysis [8]. Stroke disability and cortical location were found to be risk factors for developing poststroke seizures in SASS and in prospective studies specifically examining affected younger adults [6, 7, 13]. So et al. found that early seizures and recurrent strokes were the only factors predictive of developing late seizures or epilepsy. Patients who suffered an early seizure were eight times more likely to develop a late seizure and 16 more times likely to develop epilepsy. Stroke recurrence tripled the risk of suffering a late seizure or developing epilepsy [2]. Other studies found that late-onset seizures were independent risk factors for developing epilepsy after stroke [6, 13]. Hemorrhagic transformation of an ischemic stroke seems to increase the risk of seizures. An Italian study of 714 stroke patients found the incidence of seizure to be 4.2% in patients with bland infarcts, 12.5% in patients with hemorrhagic transformation, and 16.2% in patients with primary intracerebral hemorrhage (ICH) [27].

Of special note is ICH occurring secondary to cerebral hyperperfusion after surgical or endovascular treatment of a critical carotid artery stenosis. Cerebral hyperperfusion syndrome is characterized by a headache ipsilateral to the treated artery, with or without nausea, vomiting, neurological deficit, post-procedural hypertension, and seizures. Chronic low blood flow from a significant carotid stenosis may cause blood vessels distally to lose their ability to autoregulate vascular resistance. Excessive blood flow directed to an impaired vascular bed may disrupt vessels and cause hemorrhage, which may be associated with seizures. Cerebral hyperperfusion syndrome peaks between 3 and 5 days postoperatively, carrying a high morbidity when ICH develops. Transcranial Doppler may be able to predict patients who are at a higher risk for this syndrome by demonstrating increased mean flow velocity and diminished pulsatility index. In a study of 450 consecutive cases of carotid artery stenting, 0.67% had cerebral hyperperfusion syndrome with ICH. Vigilant perioperative control of systemic blood pressure may prevent this syndrome [28, 29].

Pathophysiology

The mechanism of early poststroke seizure may differ from that of late seizures. Early seizures may be secondary to biochemical dysfunction, whereas late seizures may be due to epileptogenic gliotic scarring [25]. Acute ischemia is marked by glutamate-induced excitotoxicity causing an overload of intracellular calcium and sodium, which activate variety of cellular enzymes and depolarization of the transmembrane potential, ultimately leading to neuronal loss. Glutamate has also been found to induce epileptiform type of discharges in surviving neurons [30]. Seizure activity in the acute setting of cerebral ischemia may have a deleterious effect of increasing metabolic demand in tenuous hypoxic tissue. Potentially salvageable

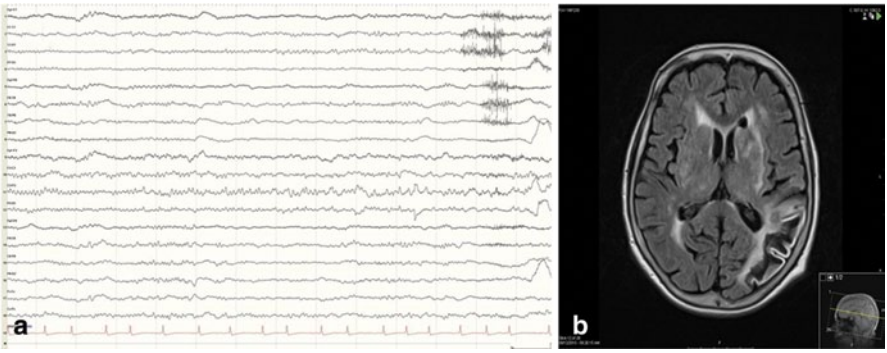


Fig. 2.1 A patient with late poststroke seizures; EEG (**a**) shows seizure pattern in left frontocentral region, onset at C3–F3 > f7–Fp1. Onset consisted of rhythmic alpha activity at F3–C3, then involved Fp1–F7, to evolve into rhythmic theta, then sharply contoured delta; seizure lasted 30–60 s. This patient suffered 18 seizures over 9 h. MRI (**b**) shows a focal encephalomalacia in the left posterior temporal and parietal lobes compatible with remote ischemic infarction

brain may be further recruited into the infarct core, leading to increased infarct size [31]. Experimental models have demonstrated transient peri-infarct depolarization in the penumbra of middle cerebral artery occlusions, and correlated the duration of depolarization with infarct volume [15]. The early phase of stroke is also accompanied by noncerebral factors such as systemic electrolyte imbalances, acid-base disturbances, and potential infections such as pneumonia which can reduce the seizure threshold [12]. Late seizures may be secondary to gliosis and development of meningocerebral scarring. Changes in membrane properties, deafferentation, selective neuronal loss, and collateral sprouting may result in hyperexcitability and neuronal synchrony sufficient to elicit seizures (Fig. 2.1a–b) [15].

Imaging

Five to thirty percent of cases identified as brain attacks may be due to stroke-mimicking conditions [23]. Winkler et al. found that of 250 consecutive patients treated with intravenous thrombolysis, 2.8 % were stroke mimics; none of whom were harmed by thrombolysis. Seizure was the most frequent diagnosis in these patients (85.7 %), with global aphasia without hemiparesis presenting ten times more frequently in the mimic than in the stroke group [33]. The clinical significance of advanced neuroimaging studies and EEG to distinguish stroke mimics from strokes before intravenous thrombolysis is unclear [33]. Furthermore, seizures may produce radiological changes that may make it difficult for a clinician to distinguish a seizure at the onset of an ischemic stroke from a seizure with postictal paresis, known as Todd's paresis. Seizure activity may lead to metabolic exhaustion of neurons within the epileptogenic focus, producing clinical paralysis. Increased regional permeability in the blood–brain barrier and edema at this site may subsequently be visualized by neuroimaging. An MRI of the brain may demonstrate focal cortical swelling, signal change in fluid-attenuated inversion recovery sequences, and

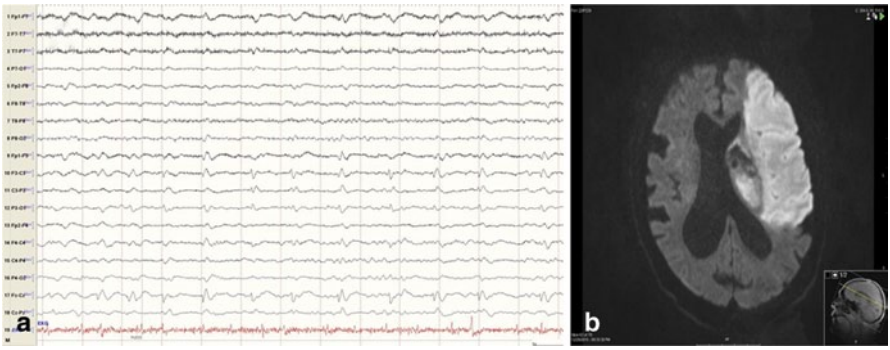


Fig. 2.2 **a–b** Periodic lateralizing epileptiform discharges (PLEDs) in a patient with acute ischemic stroke. EEG (**a**) shows intermittent PLEDs in the left parietal-central region, maximum P3 > C3, approximately 20 % of the record, lasting 3–10 s in a patient with acute ischemic stroke of the left hemisphere. MRI (**b**) shows a diffusion restriction in the left hemisphere in the distribution of the middle cerebral artery with mass effect and midline shift in an 83-year-old man who suffered acute-onset aphasia and right hemiplegia

cortical blush when contrast is administered [34]. Seizure duration may correlate with the intensity and size of these changes. Angiography after seizure may demonstrate a focal area of enhanced blood flow secondary to disruption of the blood–brain barrier [35]. Cerebral perfusion imaging may also demonstrate large areas of ictal hyperperfusion or postictal hypoperfusion. When this is observed without corresponding arterial pathology, it may be more indicative of a seizure than acute stroke (Fig. 2.2) [36, 37]. Computed tomography (CT) perfusion brain imaging has recently gained popularity as a method for evaluating penumbral tissue. Masterson et al. reported the CT perfusion changes in four patients presenting with stroke symptoms who were subsequently diagnosed with status epilepticus. Focal cortical hyperperfusion was demonstrated in all patients, with approximately 50 % increase in cerebral blood flow, 30–40 % increase in cerebral blood volume, and 40 % decrease in mean transit time. These findings were attributed to the peri-ictal phases of status epilepticus and are the opposite of perfusion changes found in acute stroke. The authors cautioned that migraines or strokes with reperfusion can produce similar results [32]. Table 2.1 demonstrates the common CT perfusion changes in ischemic infarction, penumbral tissue, and seizures.

Table 2.1 Cerebral CT perfusion changes in acute ischemic stroke and seizure

Perfusion changes	Penumbral tissue	Core infarct	Seizure
Cerebral blood flow (CBF)	↓	↓	↑
Cerebral blood volume (CBV)	Normal or ↑[a]	↓	↑
Mean transit time (MTT)	↑	↑	↓
Time to peak (TTP)	↑	↑	↓

[a] In the presence of penumbral tissue, perfusion map may show no changes in the cerebral blood volume; an important distinguishing feature for patients requiring immediate stroke intervention.
↓ indicate decrease; ↑ indicate increase

Electroclinical Manifestations of Acute Stroke

Acute ischemic stroke may have a number of EEG patterns, of which periodic lateralized epileptiform discharges (PLEDs) are of particular significance. PLEDs are electrographic phenomena characterized by widely distributed, polymorphic, and repetitive complexes of approximately 0.5–3 Hz, having one or more sharp components, present over one or more hemispheres (Fig. 2.3a) [38]. PLEDs may be an expression of dynamic brain damage in the very acute stage. While PLEDs are commonly associated with large cortical destructive processes, they may be seen in patients with subcortical, chronic lesions, or metabolic disturbances [32, 39]. Mecarelli et al. analyzed the EEGs performed within 24 h of a cohort of 232 patients admitted with acute ischemic or intraparenchymal hemorrhagic stroke. Focal

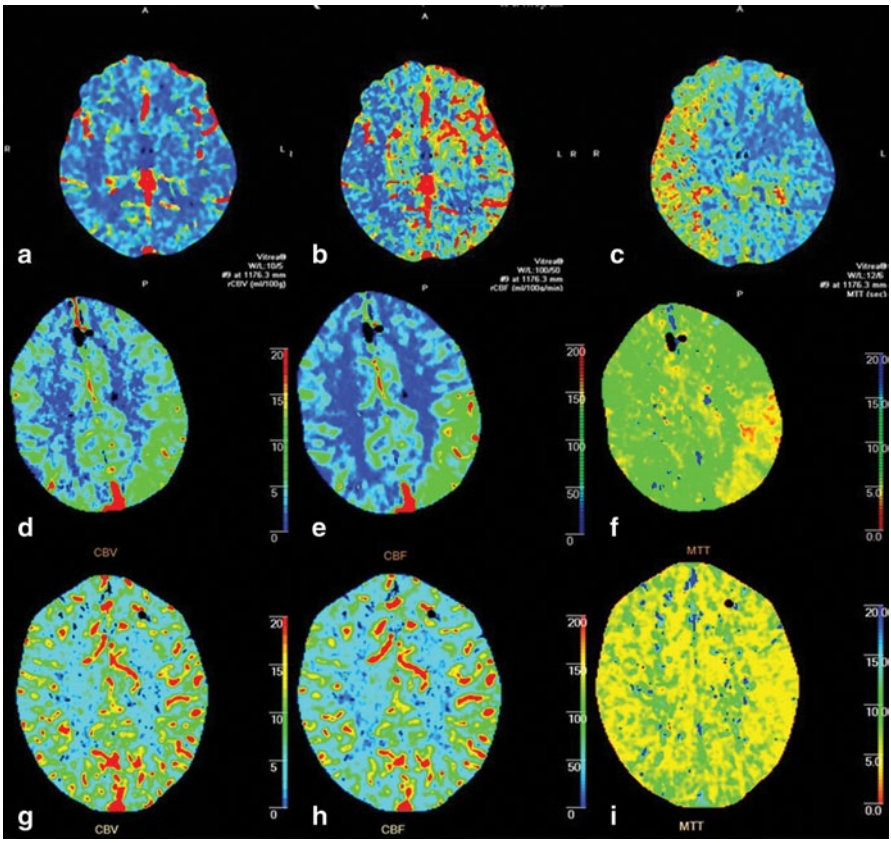


Fig. 2.3 CT perfusion analysis showing the cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT) of a patient with ischemic penumbra in the right hemisphere due to a hyperacute occlusion of the right middle cerebral artery (**a** CBV, **b** CBF, and **c** MTT), and a second patient with a seizure emanating from the left hemisphere (**d** CBV, **e** CBF, and **f** MTT) followed by a complete resolution of the hyperperfusion (**g** CBV, **h** CBF, and **i** MTT)

or diffuse slowing of background was found in 84% of patients, epileptiform focal abnormalities in 10%, and PLEDs in 6%. Three out of the 23 patients with epileptiform abnormalities developed isolated partial motor seizures without secondary generalization, while none of the patients with slowing had seizures. Of the 14 patients with PLEDs, 10 had focal status epilepticus (9 convulsive, 1 nonconvulsive), and 2 had focal motor seizures. Multivariate analysis demonstrated that only early epileptic manifestations were independently associated with PLEDs [39].Various theories regarding the neurophysiology of PLEDs have been suggested. Some authors have proposed that cortical PLEDs are produced from a large external zone of hyperexcitability, which generates synchronous discharges that communicate with subcortical structures, where they are modulated and returned via corticopetal connections. In addition, subcortical lesions disrupt the basal ganglia–thalamus–cortex network, causing oscillations to be propagated through the thalamocortical projections and eventually widespread areas of cortex [38]. An EEG maybe normal in 5% of cases, and therefore, a normal EEG does not exclude epileptogenic lesions [40]. Acute ischemia may produce EEG changes within minutes of onset, providing real-time and dynamic information of the neurophysiologic state. Progressive reductions in cerebral blood flow and degree of neuronal injury lead to changes in EEG characteristics, from loss of fast beta frequencies in reversible mild ischemia, to suppression of all frequencies, or isoelectric EEG activity in neuronal death [41].

Treatment

Treatment and recurrence of seizures of varying etiology other than stroke have been studied in depth. Berg and Shinnar used a meta-analysis to study the issue of recurrence after a first unprovoked seizure. Among 16 reports, the average risk of a first unprovoked seizure was 51%. At 2 years following the first seizure, the risk of recurrence was 36% in prospective studies and 47% in retrospective studies. Recurrence risk varied depending on a number of factors, such as seizure etiology, seizure type, and electrographic findings. The recurrence risk was as low as 24% and as high as 65% [42].

The development of poststroke epilepsy occurs in 54–66% of those who experience late seizures, and less than 43% in early-seizure patients. The risk of developing a second seizure is similar to the nonstroke patient who experiences a first unprovoked seizure. In these non-stroke patients, initiating AED treatment only after a recurrent seizure does not appear to be harmful [43]. Furthermore, indiscriminate treatment of a first unprovoked seizure without regard to patient's EEG characteristics, the presence of structural lesion, or risk–benefit profile is not recommended [27, 44]. Similarly, the use of prophylactic AEDs in acute traumatic brain injury without an initial seizure is not recommended because it has been found to be ineffective in reducing mortality, functional outcome, and eventual development of epilepsy, even if it potentially reduces the likelihood of early seizures [3].

However, strokes produce a structural lesion and some authors have favored initiating AEDs after an early poststroke seizure, while others have recommended treatment only after a late seizure [1]. Labovitz and Hauser et al. suggested that the risk of epilepsy in some patients with a single-poststroke seizure is high enough to justify the initiation of AEDs before the second seizure [40, 45]. Others have suggested treating an early seizure for 1 month, then stopping the AED if seizures have not recurred during this period [40]. One approach is to initiate one AED at standard dosage if a patient has developed immediate poststroke seizure. Therapy would be continued for 1–3 months during the time of highest risk for recurrence and discontinued if no further seizures had occurred. A more conservative approach is to attempt discontinuation of AEDs only after 1 year of seizure freedom; an approach facilitated in part by the emergence of newer-generation AEDs that have more tolerable adverse effect profiles and little to no drug–drug interactions. Recurrent seizures while on AED therapy may be milder in severity and type (focal instead of secondarily generalized). Because late seizures carry higher risk of recurrence, AED therapy is recommended.

No single AED has been shown in studies to be clearly and consistently superior to another in the treatment of early seizures or epilepsy after stroke [36]. Therefore, when choosing among the different AEDs, the clinician must take into account the potential side effects of the drug, its pharmacokinetic profile, interaction with other medications, and the potential influence on the neurologic recovery process. Phenytoin, phenobarbital, and carbamazepine are hepatic enzyme inducers, while valproic acid is an enzyme inhibitor. Phenytoin and valproic acid are highly protein bound, and the former also interferes with vitamin K metabolism. These properties of older-generation AEDs may lead to difficulties in maintaining a therapeutic drug range when a patient is concurrently on warfarin. Salicylates may displace valproate from its plasma protein binding sites, leading to reduction in total plasma level. Newer-generation AEDs do not demonstrate significant interactions with warfarin or antiplatelet agents [3]. For example, levetiracetam and lamotrigine lack hepatic metabolism and have a favorable pharmacokinetic profile in terms of drug interaction, compared to older AED [35, 46]. Animal models and clinical studies suggested that older AEDs may impair the recovery after stroke. Phenytoin, phenobarbital, and benzodiazepines have been shown to impair the motor and behavioral recovery process in brain-injured rats and functional recovery in patients [15]. In contrast, vigabatrin and carbamazepine have not demonstrated negative effects on poststroke outcome [47].

Tolerability of the drug remains an important issue to consider when initiating AEDs. Studies comparing various AEDs have suggested better tolerability and retention rates for lamotrigine, gabapentin, or levetiracetam when compared with carbamazepine, a medication known to be effective in poststroke seizure [3, 46]. The long-term tolerability and efficacy of gabapentin was studied in patients who had their first seizure at least 2 weeks after stroke: 81.7% of the cohort remained seizure-free at a mean follow-up of 30 months. Side effects were reported in 38%, but were mild to moderate with only 2.8% withdrawing from the study as a result. The authors concluded that gabapentin was safe and useful for poststroke seizures [48]. Other authors randomized 106 patients with late poststroke seizures to

levetiracetam or sustained-release carbamazepine [35]. No statistically significant difference in the number of seizure-free patients was found between the two groups. At the 52-week follow-up, 94% of levetiracetam and 85% of carbamazepine were seizure free. Attention deficit, frontal executive function, and functional scales were significantly worse in the carbamazepine group. Premature discontinuation due to serious adverse effects was not statistically significant between the groups [35]. In a smaller study, 64 patients presenting with the first (early or late) poststroke seizure received lamotrigine or carbamazepine in a randomized 1:1 ratio. After 12-month follow-up, significant differences between the two groups were found in terms of efficacy, side effects, and tolerability in favor of the lamotrigine. The number of patients remaining seizure free was found to be 72% in the lamotrigine group and 44% in the carbamazepine group. Three percent of patients in the lamotrigine group dropped out because of adverse events, compared to 31% in the carbamazepine group [46].

Prognosis

Animal stroke models suggest that early seizures may be associated with increased infarct volume; however, it is unclear if early seizures have deleterious effects on the eventual functional outcome after stroke. A significant number of studies found worse outcomes in patients with late or recurrent seizures after stroke, but others failed to demonstrate this effect. The differences in these outcomes may be due to the lack of accounting for confounding factors such as stroke severity, stroke location, or AED treatment at the time of assessment, which has been shown to independently contribute to worse functional outcome with certain drugs [3, 15]. Previous studies have demonstrated increased hospital mortality rates among patients with early seizures after stroke. These studies did not account for stroke severity or rule out seizures as an independent predictor of poor outcome. It has been proposed that seizures maybe a sign of severe brain injury rather than a predictor of poor recovery [11, 49]. It is unclear if seizures independently alter functional outcome after stroke. SASS demonstrated a worse neurological score during initial hospitalization and worse Rankin scale at 9 months of follow-up in patient who had seizures after stroke; however, SASS failed to correct for stroke severity and did not analyze the role of early versus late seizures [3, 50]. Seizures do not influence the rehabilitation outcome in poststroke patients [10, 50]. Prospective studies which did account for stroke severity found no association between early seizures and outcome or mortality [7].

Status epilepticus rarely occurs in patients with acute stroke, and constitutes less than 10% of cases of poststroke seizures [9]. The clinical relevance of poststroke status epilepticus has also been inconsistent. Patients with generalized convulsive status epilepticus after a stroke have a threefold increase in mortality rate compared to stroke patients without status epilepticus [51]. This increase in mortality is seen only if the status epilepticus occurred within the first week after the stroke [9]. A

multivariate analysis found no relationship between the occurrence of status epilepticus and stroke subtype (infarction vs. hemorrhage), stroke risk factors, stroke topography, cortical involvement, lesion size, or EEG findings [9]. In addition, no difference in mortality rate was found between poststroke patients who had status and those who had seizures. The only predictor of status epilepticus was poor functional status (modified Rankin scale > 3), and the only predictor of mortality was age [52]. Status epilepticus at presentation of stroke has not been shown to predict subsequent development of epilepsy [40].

Summary

Stroke is an important cause of seizures especially in older adults. The incidence of poststroke seizure varies based on the setting and detection method. When patients suffer these seizures, they often occur at stroke onset or very soon after; however, they continue to be at risk for seizures many years later. The mechanism of early seizures may differ from late seizures. In treating these seizures, clinicians should consider the potential negative effects of some AEDs on functional outcome and the interaction with other medications especially the antithrombotic and anticoagulants.

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Seizures in Cerebrovascular Disorders
A Clinical Guide
Koubeissi, M.; Alshekhlee, A.; Mehndiratta, P. (Eds.)
2015, XII, 134 p. 27 illus., 4 illus. in color., Hardcover
ISBN: 978-1-4939-2558-2