



Incidence, Implications, and Management of Seizures Following Ischemic and Hemorrhagic Stroke

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Abstract

Purpose of Review In this review, we summarize the recent literature regarding the incidence and treatment of seizures arising after ischemic and hemorrhagic strokes. Additionally, we identify open questions in guidelines and standard clinical care to aid future studies aiming to improve management of seizures in post-stroke patients.

Recent Findings Studies demonstrate an increasing prevalence of seizures following strokes, probably a consequence of advances in post-stroke management and expanding use of continuous EEG monitoring. Post-stroke seizures are associated with longer hospitalization and increased mortality; therefore, prevention and timely treatment of seizures are important. The standard of care is to treat recurrent seizures with anti-epileptic drugs (AEDs) regardless of the etiology. However, there are no established guidelines currently for prophylactic use of AEDs following a stroke.

Summary The prevalence of post-stroke seizures is increasing. Further studies are needed to determine the risk factors for recurrent seizures and epilepsy after strokes and optimal treatment strategies.

Keywords Ischemic stroke · Hemorrhagic stroke · Cerebrovascular disease · Seizures · Epilepsy · Post-stroke seizures

Introduction

About 5% of the general population worldwide will have at least one non-febrile seizure in their lifetime [1]. In the USA, it is estimated that 150,000 adults present annually with an unprovoked first-time seizure [2]. The distribution of seizure occurrence is bimodal: the peak incidences of seizures are observed during childhood and after the age of 60 [1]. The leading cause of seizures in adults beyond the age of 60 is cerebrovascular disease and it has been shown to account for nearly 50% of newly diagnosed epilepsy in this age group [3••]. Furthermore, hemorrhagic and ischemic strokes are

currently one of the leading causes of hospitalization in this patient population.

Seizures are defined as transient, abnormally excessive synchronous neuronal activity in the brain that may be provoked or unprovoked. While unprovoked seizures can be seen in many idiopathic epilepsies, provoked seizures are typically caused by acute or chronic disturbances of the central nervous system. These frequently include cerebrovascular diseases such as ischemic stroke, intracerebral and subdural hemorrhages, posterior reversible encephalopathy syndrome, and cerebral venous sinus thrombosis. Of note, other less common processes that may provoke seizures including CNS infections, inflammation, systemic metabolic abnormalities (such as hypo/hyperglycemia, hypo/hyponatremia, hypocalcemia), alcohol toxicity and withdrawal from alcohol, benzodiazepines and barbiturates, traumatic brain injury, and intracranial surgeries may also co-exist in patients presenting with strokes.

The risk of seizures is significant in many post-stroke patients. An increasing number of patients survive after a stroke as a consequence of advances in acute and post-stroke management, and in parallel, an increase in the incidence of post-stroke seizures has been also observed over the last decades [4, 5]. Studies reporting on the incidence of post-stroke seizures can vary widely from 2 to 20% [6, 7•, 8••]; however, a

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recent meta-analysis estimated it to be about 7% [7•]. Although all forms of strokes are associated with an increased risk of seizures, the incidence is higher following hemorrhagic strokes compared with ischemic strokes [9]. Nevertheless, it is important to note that since the frequency of ischemic strokes is much greater, the actual overall seizure burden is higher in this group [9].

Post-stroke seizures are associated with longer initial hospitalization, increased mortality, and additional complications such as increased and longer need for a ventilator and delay in initiation of physical and occupational therapies [10•, 11]. Moreover, seizures and epilepsy may substantially impact the quality of life of patients and their families during recovery after strokes. This includes the unpredictable nature of seizure reoccurrence, state driving laws, challenges in school, social and employment situations, and the stigma of epilepsy in some cultural environments in addition to the associated costs related to the management of epilepsy (medications, transportation) [12]. Thus, the timely detection and optimal management of seizures are essential to improve patient care and outcomes.

The standard of care is to treat all recurrent seizures with an anti-epileptic drug (AED) regardless of the etiology. However, there is some data showing that the risk of seizure recurrence is lower in patients who are treated with an AED even after a first-time unprovoked seizure [12]. Although commonly used, there are no currently widely accepted guidelines for prophylactic use of AEDs following a stroke. Some investigators have looked at the potential benefits of prophylactic treatment of seizures in post-stroke patients and compared seizure recurrence, hospital complications, and overall recovery. These studies did not find supportive evidence that AEDs prevent or lower the risk of stroke-related seizures [13••, 14, 15].

Pathomechanism of Seizures After Ischemic and Hemorrhage Strokes

Ischemic Stroke

Many acute and chronic changes in the brain tissue can lead to the emergence of seizures following an ischemic stroke (Table 1). Neurons are highly sensitive to hypoxia compared with other cell types due to their high metabolic rate and oxygen demand. In the acute stages of neuronal ischemia, there is a lower threshold for depolarization from local excitotoxicity secondary to increased glutamate [16•, 17]. Additionally, increases in intracellular Ca^{2+} and Na^+ due to impaired function of the sodium and potassium ion pumps result in cytotoxic edema and acute metabolic dysfunction [16•, 17]. The pyramidal neurons in the cortical layers (predominantly 3, 5, and 6) that generate postsynaptic excitatory and inhibitory potentials culminating in a measurable electrical signal over the scalp [18] are especially sensitive to hypoxia. Ischemia quickly leads to pyramidal dysfunction and electroencephalographic (EEG) changes (e.g., slowing) can be usually seen within 5 min of acute ischemia [19–21]. Furthermore, the hippocampus is thought to be an epileptogenic area is particularly sensitive to ischemic insults in the setting of global hypoperfusion and a common cause of status epilepticus [6].

In the later stages of ischemic strokes, permanent changes may develop and lead to the emergence of a potential seizure focus. These include gliosis and scarring within the cortex or loss of cerebral tissue leading to disruption of neuronal networks and increased neuronal excitability. Brain dysfunction caused by strokes are often localized to the affected vascular territory; therefore, the most common seizure type following a stroke is localization-related focal onset seizures that may or

Table 1 Epileptic events based on timing, causes, and subsequent seizure risk

Proposed term	Causes	Risk epilepsy
Early seizure	<p><i>Acute changes</i></p> <ul style="list-style-type: none"> - Metabolic dysfunction of intracellular ions → lower seizure threshold - Increased glutamate → local excitotoxicity → lower seizure threshold - Disturbance of the pyramidal neurons in the cortical layers → lower seizure threshold <p><i>Hemorrhage</i></p> <ul style="list-style-type: none"> - Products of blood metabolism irritate the cortex 	Low (29–35%)
Late seizure	<p>Chronic changes: persistent changes leading to seizure focus.</p> <p><i>Ischemia</i></p> <ul style="list-style-type: none"> - Gliosis and scarring within the cortex. - Disruption of neuronal networks → neuronal excitability <p><i>Hemorrhage</i></p> <ul style="list-style-type: none"> - Hemosiderin depositions and gliotic scarring 	High (55–93%)

may not lead to secondary generalized seizures. While it is difficult to predict which patients will develop epilepsy following a stroke, there are recognized risks that are associated with a higher incidence. These risks include but are not limited to cortical involvement and multifocal areas of ischemia [22, 23]. Approximately 9.8% of patients with cortical lesions had post-stroke seizures compared with 3.8% risk in subcortical lesions in one study [22]. Strokes in anterior vascular territories are more likely to cause seizures compared with posterior ones attributed to the fact that the anterior vascular territory involves larger areas of the cortex [24]. In addition, there appears to be an association with increased risk for development of stroke-related epilepsy if the temporal lobes are affected [3•, 25]. Furthermore, it is also important to note that hemorrhagic conversion of ischemic stroke carries a higher risk of seizures than ischemic stroke alone [22].

Hemorrhagic Stroke

Seizures after intracerebral hemorrhage (ICH) may arise due to the mechanical effects of the expanding hemorrhage and/or irritation of the cortex due to products of blood metabolism acutely and from hemosiderin depositions and gliotic scarring chronically [6] (Table 1). Seizures can be dangerous in patients with ICH as a head trauma that may occur during a seizure can potentially further worsen the hemorrhage. Furthermore, in case a craniectomy is performed in the setting of large hemorrhages, seizures can cause additional damage over the unprotected and therefore more vulnerable area of the brain. A recent meta-analysis concluded that there is an increased risk of post-hemorrhagic stroke epilepsy following cortical involvement and early seizures [26]. However, identifying the location of a hemorrhage is at times difficult because blood often travels diffusely. For example, a subcortical hemorrhage may travel to involve the cortex making it difficult to differentiate the origin. Thus, patients with cortical or subcortical hemorrhages similarly more likely to have stroke-related seizures compared with patients with other types of hemorrhages [27•]. Additionally, patients with hypertension were found to be at a lower risk for post-stroke seizures likely because most commonly hemorrhages in hypertensive patients are localized to the deeper structures [27•].

Subarachnoid Hemorrhage

In subarachnoid hemorrhages (SAH), similar to ICH, the mechanical effects of the expanding hemorrhage and irritation from the blood products result in decrease of the seizure threshold [28•]. Furthermore, vasospasm secondary to SAH (i.e., delayed cerebral ischemia (DCI)) may cause hypoperfusion leading to late ischemic infarcts and thus may trigger seizures by the abovementioned mechanisms. These acute injuries can lead to cortical scarring and residual cortical

irritation. In comatose SAH patients, seizures frequently arise without obvious clinical symptoms, i.e., non-convulsive seizures (NCSz). NCSz in SAH patients are associated with higher odds of cognitive impairment and an unfavorable outcome or death after 3 months [22].

Incidence of Post-Stroke Seizures

The incidence of seizures following strokes varies greatly from 2 to 20% [6, 7•, 8•, 24, 29] and overall seems to have a higher incidence following hemorrhage stroke [30] and following SAH [31] (Table 2). One of the largest prospective multicenter studies showed the overall incidence of seizures to be about 10.6% following ICH and about 8.6% following ischemic strokes [16•]. Additional studies showed seizure activity to be present in up to 10–25% of patients following ICH [34, 38•], and about 15.2% after SAH [30]. A large recent meta-analysis that did not differentiate from ischemic versus hemorrhage reported an overall 7% risk of stroke-related seizures [7•]. Another recent large meta-analysis concluded a 5.7% reported stroke-related seizures, of which 3.3% were early onset seizures [8•]. This variability in the reported incidences is likely due to the differences between study designs, definition used to select patients, and length of follow-up. In addition, studies define variable cutoff times to classify post-stroke seizures based on the time of occurrence after stroke. The cutoff times most commonly used are 7 days or 14 days to define early versus late-onset seizures [39, 40•].

Furthermore, the definition of epilepsy was recently changed. Epilepsy is classically defined as the presence two or more (i.e., recurrent) unprovoked seizures. However, recently, this definition was revised and now one unprovoked seizure and high risk for recurrence of further seizures are sufficient to make the diagnosis of epilepsy [40•]. Typically, the risk of seizure recurrence is higher in the setting of remote brain insults such as stroke, CNS infection, or trauma (up to twofold higher, 26% and 48% at 1 and 5 years, respectively) [41]. One group found the risk of developing subsequent seizures over the next 10 years after a late unprovoked post-stroke seizure (> 1 week) is as high 71.5% and 33.0% in early post-stroke seizures (< 1 week) [32], essentially suggesting that a patient with one isolated and unprovoked post-stroke seizure now fulfills the diagnosis of epilepsy [40•]. Therefore, by definition, treatment of a single seizure after a stroke could be considered if the risk of seizure recurrence is deemed to be high.

Several studies have demonstrated that the time interval of seizure onset following a stroke seems to be the most important risk factor for developing epilepsy after a stroke [30]. The majority of early-onset seizures after a stroke (about 70–90% of them) arise within the first 24 h of the ischemic event [42] as a result of transient local irritation from underlying

Table 2 Incidence of seizures, epilepsy, status epilepticus (SE), and non-convulsive status epilepticus (NCSE) in post-stroke patients

Study	Year	No. of patients	Etiology	Cutoff for early versus late	Risk of seizure (time not specified)	Risk of epilepsy after early and late seizures respectively	Risk of SE	Risk of NCSE	Reference
Zou	2015	Meta-analysis: 102,008	Stroke (unspecified)		6.93				[7•]
Wang	2017	Meta-analysis: 34,502	Ischemic stroke		5.7				[8••]
Bladin	2000	1897	Ischemic stroke	14 days	8.65	35 and 55%			[16•]
Hesdorffer	2009	n/a	Stroke (unspecified)	7 days		33.0 and 71.5%			[32]
Beghi	2011	714	609 ischemic and 105 hemorrhagic		6.3		3% (of 45 patients with seizures)		[22]
Bladin	2000	1897	Hemorrhagic stroke	14 days	10.6	100% in late			[16•]
Sung	1989	1402	ICH	14 days	4.6	29 and 93%	17% (of 64 patients with seizures)		[33]
Neshige	2015	1920	ICH	7 days		4.3 and 2.3% and collective risk of 15.7%			[34]
Rumbach	2000	3205	Ischemic		4.9		19.4% (of 159 patients with seizures)		[35]
Choi	2009	547	SAH		15.2	3.1% collectively			[31]
De Marchis	2016	402	SAH					12%	[36•]
Belcastro	2014	889	Ischemic					3.6%	[37]

excitotoxicity and local and systemic metabolic derangements. Many clinicians feel early seizures are provoked and generally do not relate them to increased risk of recurrent seizures and epilepsy [16•, 43]. Seizures occurring within 7 days of stroke have a 33.0% chance of recurrent seizures over the next 10 years which is significantly less than late seizures [32]. Another study, classifying early seizures as less than 14 days following ischemic strokes, found the risk of recurrent seizures to be 35% [16•]. However, while early seizures have a lower prevalence of recurrent seizures compared with late seizures, they were associated with 16 times more likelihood of developing epilepsy compared with stroke patients without any seizures [44]. Moreover, seizures within 7 days of a brain injury (strokes, TBI, or CNS infection) have been associated with higher 30-day mortality than an unprovoked seizure occurring after 7 days (21.4% and 3.4% of patients, respectively) [32]. Additionally, 10-year mortality has been found as high as 73.8% (early seizures) and 71.6% (late seizures) risk compared with those without seizures [32]. Late seizures are likely to arise due to a permanent focal lesion following either a hemorrhage or ischemic stroke and they are associated with a significantly higher risk of developing epilepsy compared with early seizures [33, 45]. However, one study found that 35% of post-stroke patients with early unprovoked seizures developed epilepsy during a 9-month follow-

up period [16•]. Other studies have also demonstrated an associated risk of epilepsy with early seizures in intracerebral hemorrhage patients [27•]. The peak incidence for late seizures appears to be the highest in the 6–12-month period after a stroke [16•], and another study found the risk of having subsequent seizures over the next 10 years after an unprovoked seizure that occurred at least 7 days after a stroke to be 71.5% [32].

Status epilepticus is common following a stroke. Studies have shown that 14 to 19% of patients admitted for a first-time seizure after a stroke develops status epilepticus [33, 35]. Other studies demonstrated the presence of non-convulsive status epilepticus (NCSE) in 4% of patients after an acute stroke, of which 62.5% were early onset seizures (within 7 days) and 37.5% were late onset [37]. Status epilepticus poses additional risks to the patient by potentially leading to further neuronal damage and neurological deterioration and increased mortality from complications such as ventilator dependence, increased risk of infections, and hypotension. NCSz are also common in stroke patients and the incidence is particularly high in the SAH group; studies have found as high as 12% of the SAH patient monitored with EEG had NCSz [36•]. Furthermore, NCSz have been found in 8% of comatose patients from any etiologies, 20% of which had an ischemic stroke [46]. In addition, following

global hypoxia (e.g., after a cardiac arrest), a common complication is status epilepticus including myoclonic status epilepticus. Poor outcomes are especially associated with the presence of electroencephalographic suppression-burst pattern with high amplitude polyspikes with corresponding myoclonic jerks [47•].

Relationship of EEG Findings and Risk of Post-Stroke Seizures

EEG is the current gold standard to identify seizures and to assess the risk of seizures in post-stroke patients. The most common early EEG pattern in acute ischemic stroke patients is focal slowing and attenuation of faster frequencies. However, widespread areas or multifocal ischemia affecting both hemispheres may cause generalized slowing and smaller lacunar infarctions are generally not detectable on EEG. A recent study assessed routine EEGs in acute ischemic stroke patients without prior history of or ongoing seizures and 43.5% showed focal slowing that correlated to the territory of ischemia [48•]. In patients with EEG background asymmetry, there was a 3.2 times higher risk of post-stroke unprovoked seizures [13••]. Epileptiform discharges on EEG indicate an increased risk of epileptic risk and often can be seen in the area of ischemia or hemorrhage. Patients with focal epileptiform EEG findings (i.e., discharges) and partial onset seizures have a greater seizure recurrence rate [48•]. A recent prospective study concluded that patients with anterior circulation ischemic strokes and an early (within the first 72 h) EEG background asymmetry had a 3.2 times higher risk of an unprovoked seizure; if the early EEG showed epileptiform discharges, there was a 3.8 times greater risk of seizures compared with patients with a normal early post-stroke EEG [49]. Lastly, to perform EEG monitoring for at least 24–48 h in patients admitted to ICUs after a stroke (especially SAH) is critical if there are suspected NCSz or unexplained altered mental status. Many studies demonstrated that at least 11% to 18% of critically ill patients have NCSz detected only on scalp EEG [50•, 51].

Management of Post-Stroke Seizures

Primary Prevention

Although commonly used, there are no accepted guidelines currently to support the prophylactic use of AEDs after ischemic or hemorrhage strokes (i.e., without any seizure occurrence). In early studies, the use of prophylactic medications was supported in hemorrhagic strokes [52]. However, in 2009, a study showed that phenytoin was

associated with more complications including increased frequency of fevers (longer duration of medication use was associated with more febrile days) and worse functional outcomes at 3 months post-ICH compared with the group without prophylaxis [53]. Furthermore, a possible drug-drug interaction between enzyme-inducing agents (phenytoin, carbamazepine) and nimodipine (commonly used to prevent vasospasm in SAH) may exist; studies have shown a marked reduction in plasma nimodipine concentrations, suggesting the concurrent use of these medications in SAH patients is potentially dangerous. Conversely, nimodipine concentrations have been found to increase by 50% with the concurrent use of valproic acid due to its enzyme inhibition [54] that needs to be taken into consideration when these medications are used together. Valproic acid has also been shown to be associated with increased mortality in TBI patients when used for seizure prophylaxis [55]. Consequently, given its side effect profile and potential drug-drug interactions, valproic acid is not widely used in post-stroke patients. Furthermore, some AEDs such as phenytoin and phenobarbital could also inhibit neural plasticity and hinder recovery [56]. More recently, newer AEDs with fewer side effects and less drug-drug interactions than older seizure medications, including levetiracetam and lacosamide, are more frequently used. These AEDs have not been systematically studied in trials and therefore further studies are needed to assess their risks and benefits for prophylactic use after strokes. Accordingly, the most recent guidelines updated in 2010 by the American Heart Association recommend that prophylactic AEDs should not be used after strokes [57••]. The European stroke organization last updated its guidelines in 2017 and also does not recommend prophylactic AEDs in post-stroke patients [58••].

Furthermore, there is increasing evidence that some AEDs may have a neuroprotective effect in addition to their anti-seizure properties. Felbamate, which potentiates GABA-mediated events and acts on NMDA glutamate receptor, has been shown to be neuroprotective in experimental models of ischemia in animals [59]. Studies have also shown that topiramate may have a promising neuroprotective profile due to its ability to reduce excitatory effects of glutamate and enhance GABA-mediated inhibition. Vigabatrin, levetiracetam, and zonisamide have been also shown to have some neuroprotective potential [59, 60]. Given these additional potential beneficial properties of some AEDs, further studies are required to see if these agents may be effective both for seizure control and to bolster neuronal repair. In summary, given the increased risks of complications secondary to seizures, it is reasonable to consider their prophylactic use on a case by case basis in the setting of certain types of strokes (such as ICH or SAH) and EEG findings that predispose patients to higher risk of seizures.

Secondary Prevention

The standard of care of recurrent seizures regardless of their etiology is pharmacologic treatment with AEDs. Clinical trials have suggested that stroke-related epilepsy tends to respond better to AED treatment and has a better prognosis compared with other forms of focal epilepsies (e.g., hippocampal sclerosis or cortical malformations) [61, 62]. These trials suggested drug resistance in 5% to 46% of stroke-related epilepsies without known predictive factors. Many times, monotherapy alone can be successful in controlling post-stroke seizures. Newer AEDs are better tolerated, have less drug-drug interactions, and better side effect profiles. The risk of AED adverse events in post-stroke patients has been shown to range from 7 to 31% [12]; therefore, concurrent medication use and comorbid conditions need to be considered when choosing an AED. There are no evidence-based guidelines for AED choice in these patients; however, studies have suggested that levetiracetam has the potential for breaking SE and stroke-related epilepsy [60]. A randomized trial in late-onset post-stroke seizures demonstrated no difference in seizure control between levetiracetam and carbamazepine at 1 year after the stroke. Nevertheless, fewer patients in the levetiracetam group reported side effects compared with the carbamazepine group [8••]. Intravenous lacosamide is another reasonable option which was shown to have good efficacy and safety profile in a group of post-stroke NCSE patients greater than 70 years of age [63]. Many of the commonly used AEDs are appropriate for treatment of stroke-related seizures and epilepsy as long as they are selected after consideration of drug-drug interactions and side effects.

Influence of Stroke Treatment Modalities on Seizure Risks

Thrombolysis with recombinant tissue plasminogen activator (tPA) is the standard of care for all acute ischemic stroke meeting inclusion criteria; therefore, it is important to note that there has been some evidence suggesting an increased risk of post-stroke seizures with the use of tPA [64, 65]. However, other studies did not find a statistically significant difference with regard to increased post-tPA seizure incidence [66, 67]. Statins, which are widely used in stroke and cardiac patients for lipid control, on the other hand, have been shown to be beneficial against post-stroke seizures [68, 69]. Although the mechanisms of this are not well understood, it could be secondary to their well-known anti-inflammatory properties.

A recent study examined the association between the incidence of new-onset seizures after aneurysmal subarachnoid hemorrhage (aSAH) based on the severity of hemorrhage and treatment choice (surgical clipping versus endovascular coiling). Overall, new-onset seizures were found in 5.5% of patients treated with coiling compared with 10.6% of patients treated with surgical clipping. When patients were divided into subgroups based on SAH severity, there was no significant difference found

in seizure incidence with regard to treatment modality in low-grade SAH patients; however, a higher incidence of new-onset seizures was observed in high-grade SAH patients who were treated with clipping compared with coiling [29].

Conclusions

In summary, the leading cause of seizures in adults beyond the age of 60 is cerebrovascular disease. Due to recent progress in treatments of post-stroke patients, the prevalence of stroke-related seizures is increasing. While both ischemic and hemorrhagic strokes may increase the risk for seizures, it is greater following hemorrhagic strokes compared with ischemic strokes. The location of the stroke can predict greater risk, e.g., anterior circulation or temporal ischemic strokes have been associated with greater risk for seizures; subcortical and cortical hemorrhages are considered to carry higher risk of developing seizures compared with hemorrhages in deeper structures. The timing of seizures in relation to the onset of the stroke is also an important factor in determining the risks for developing epilepsy. Early seizures following a stroke are thought to be the result of transient derangements and may not be related to the development of a seizure focus often seen in late seizures; therefore, early seizures are associated with a lower risk in the development of subsequent epilepsy compared with late-onset seizures. Strokes are also associated with the development of non-convulsive status epilepticus; therefore, overnight EEG monitoring is strongly recommended in post-stroke patients with altered mental status. While there are no currently accepted guidelines for seizure prophylaxis in post-stroke patients, the standard of care is to treat all patients with unprovoked seizures who are at risk for further seizures regardless of the etiology. When choosing an AED, it is important to take into consideration concurrent medication use and comorbid conditions to attempt to decrease adverse reactions.

Stroke-related seizures have detrimental effects on the patient and their families. Seizures increase mortality and risk of complications after a stroke resulting in lower neurological functional outcomes and delay in rehabilitation with longer hospital stays. Further studies are paramount to determine the optimal course of AED use in the treatment or prevention of seizures in post-stroke patients.

Compliance with Ethical Standards

Conflict of Interest Joseph W. Doria and Peter B. Forgacs each declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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