



Diagnosis and Treatment of Poststroke Epilepsy: Where Do We Stand?

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Abstract

Purpose of Review Stroke is the most common cause of seizures and epilepsy in older adults. This educational paper aims to give an update on current clinical aspects of diagnosis and treatment of poststroke epilepsy.

Recent Findings Regarding epileptic seizures related to stroke, it is important to distinguish between acute symptomatic seizures and unprovoked seizures as they differ in their risk for seizure recurrence. In fact, after a single unprovoked poststroke seizure, a diagnosis of epilepsy can be made because there is a greater than 60% risk for further seizures. Clinical models that can predict the development of epilepsy after a stroke have been successfully established. However, treatment with anti-seizure medications is advised only after a first unprovoked poststroke seizure, as current treatments are not known to be effective for primary prevention. The management of poststroke epilepsy requires consideration of

aspects such as age, drug-drug interactions and secondary vascular prophylaxis, yet evidence for the use of anti-seizure medications specifically in poststroke epilepsy is limited. *Summary* This text reviews the epidemiology and risk factors for poststroke epilepsy, explains the role of EEG and neuroimaging in patients with stroke and seizures and provides an overview on the clinical management of stroke-related acute symptomatic seizures and poststroke epilepsy.

Introduction

One in four adults aged over 25 will develop a stroke during their lifetime, which comes with significant individual and public health consequences [1]. Among these are acute symptomatic seizures (ASS) and poststroke epilepsy (PSE). Stroke represents by far the most common cause of epilepsy in older adults [2]. An increased recognition of PSE as an important clinical entity over the past decades has led to growing research interest in the field, including into pathophysiology and (anti-)epileptogenesis [3]. This development holds promise for effective future treatments or, even more desirable, prevention of PSE, with antiepileptogenic and disease-modifying therapies that aim to reduce

the risk of poststroke seizures and drug-resistant PSE. This review will focus on current clinical aspects of diagnosis and treatment of PSE. Substantial progress in clinical research has better characterized PSE and by now allows clinicians to address the clinical management more specifically. Nevertheless, comparatively little guidance on how to manage PSE has been available until more recently, and clinicians might therefore frequently be faced with questions in the everyday management of patients with stroke and seizures. This review aims to give answers and to provide the clinician with an evidence-based update on the diagnosis and treatment of PSE.

Definitions

With seizures related to stroke, ASS or early seizures need to be distinguished from unprovoked remote symptomatic or late seizures. By definition, stroke-related ASS are seizures that occur on presentation or within 7 days of a stroke, whereas seizures that occur later than 7 days after a stroke are unprovoked remote symptomatic seizures (Fig. 1) [4••]. Accurate classification of a stroke-related seizure as either acute symptomatic or unprovoked remote symptomatic is necessary as this carries different implications for treatment and prognosis. Different pathophysiological mechanisms lead to stroke-related ASS and unprovoked remote symptomatic poststroke seizures. Stroke-related ASS arise from transient changes in neuronal excitability due to acute biochemical dysfunction and excitatory neurotransmitter release following the acute ischemic brain injury [5]. Remote symptomatic seizures are the result of the brain acquiring a predisposition for the generation of unprovoked seizures after structural poststroke changes to neuronal networks in the process of epileptogenesis [6]. These two distinct pathophysiological concepts reflect a different risk of seizure recurrence after ASS and unprovoked poststroke seizures. A landmark study by Hesdorffer et al. found a 71% seizure recurrence rate over 10 years for patients with a first unprovoked seizure after

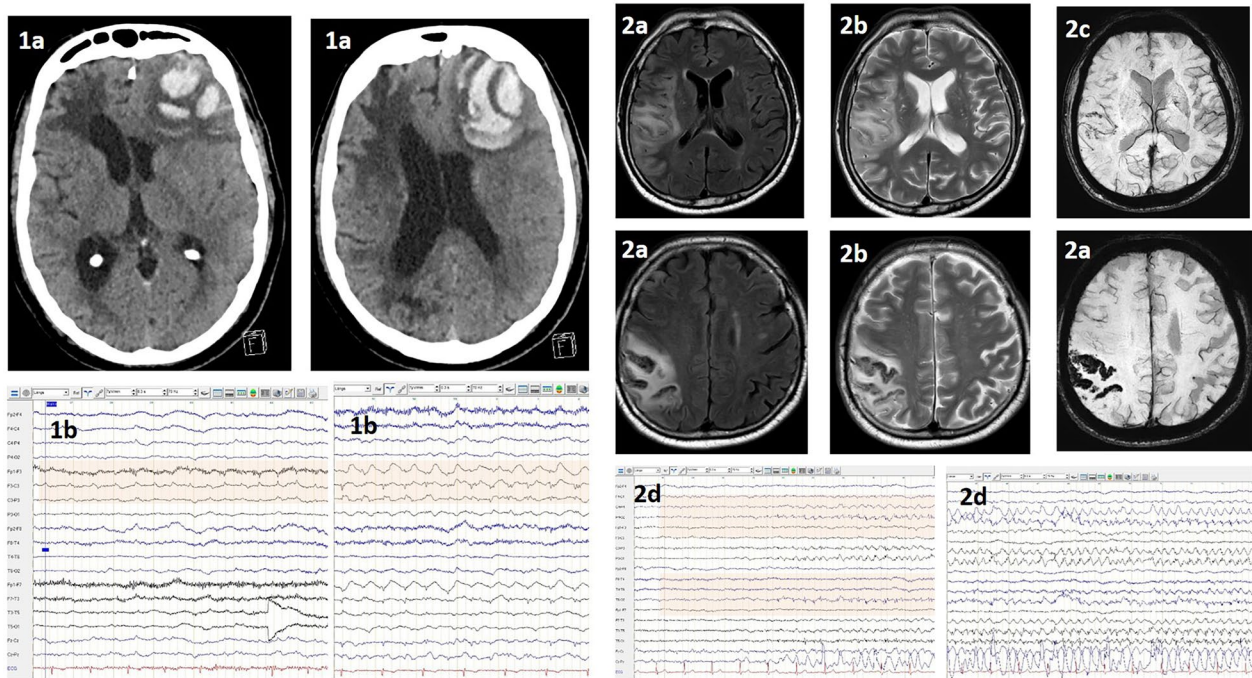


Fig. 1 Cases of stroke-related ASS and PSE. **(1a)** A 79-year-old patient with a spontaneous intracerebral hemorrhage, probably due to cerebral amyloid angiopathy. **(1b)** On day 3, the patient develops a clinically overt focal to bilateral tonic-clonic ASS. Subsequent EEG monitoring reveals the occurrence of non-convulsive seizures starting over the left frontal region. **2.** A 76-year-old patient with ischemic stroke in the territory of the right MCA **(2a)** with secondary hemorrhagic transformation **(2b, c)**. **(2d)** Occurrence of an acute symptomatic focal motor SE with seizure onset over the right posterior region on day 5. The patient later developed drug resistant PSE with recurrent episodes of SE.

a stroke (defined as a seizure occurring at least 7 days after a stroke) [7••]. This compared to a rate of 33% for an unprovoked seizure over 10 years for patients who had had a stroke-related ASS (the latter defined as a seizure that occurred within 7 days of a stroke) (Fig. 2). Based on the results of this study, 7 days are the cut-off by which ASS should be distinguished from remote symptomatic poststroke seizures. The new practical definition of epilepsy by the International League Against Epilepsy (ILAE) states that epilepsy exists in a person who has had one unprovoked seizure and has a probability for the recurrence of further seizures of at least 60% over the next 10 years [8••]. Accordingly, PSE can be diagnosed after a single unprovoked poststroke seizure. The reason is a risk for the recurrence of seizures of greater than 60% according to the Hesdorffer study. The data from Hesdorffer et al. also confirm that stroke-related ASS are not epilepsy because of their significantly lower risk for further unprovoked seizures. However, a seizure recurrence risk of 33% after a stroke-related ASS is substantial and ASS by themselves are an important risk factor for the development of PSE [9•]. When specifying stroke for severity, etiology and localization, as done by the SeLECT Score (see below), the risk for an unprovoked seizure after a stroke that manifested with an ASS can approach or even surpass the threshold of 60% [10••]. The general

Seizure recurrence risk in percent

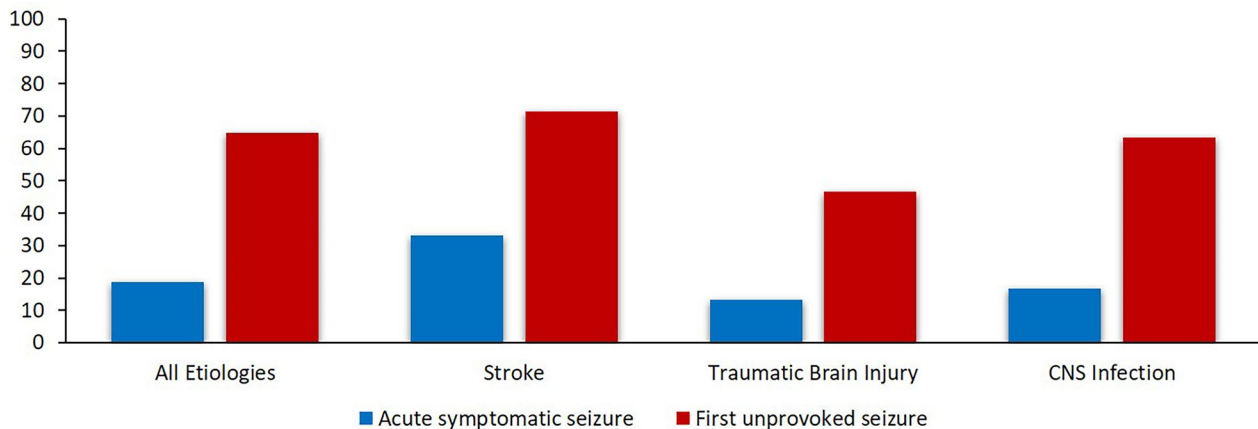


Fig. 2 The seizure recurrence risk after an ASS is significantly lower than after a first unprovoked seizure, independent of etiology. For stroke, the seizure recurrence risk is 33% after an ASS and 71% after a remote symptomatic seizure. Based on data from Hesdorffer et al. [7••]. Is a first acute symptomatic seizure epilepsy? Mortality and risk for recurrent seizure. *Epilepsia*, 50, 1102–8.

concept of ASS suggests that seizure recurrence risk should be low. However, the risk for unprovoked seizures after stroke-related ASS is not negligible and, in some situations, might come close to the recurrence risk after a first unprovoked remote symptomatic seizure.

Epidemiology of stroke-related acute symptomatic seizures and poststroke epilepsy

ASS occur in at least 3–6% of patients with stroke. The risk for ASS is significantly greater in hemorrhagic (10–18%) compared to ischemic stroke (2–4%) [4••, 11]. Lobar intracerebral hemorrhage, subarachnoid hemorrhage and ischemic stroke with secondary hemorrhagic transformation all provide a greater risk for ASS than ischemic stroke [5]. The majority of stroke-related ASS occurs within the first 24h after stroke [12]. The frequency of ASS in ischemic stroke might be underestimated when seizures are ascertained only clinically: a video-EEG study in acute ischemic stroke patients found ASS in 14.6% of patients of which 22.7% had electroencephalographic seizures only [13•]. Similar to ASS, the rates for PSE vary between the stroke populations that are studied and depend on the methodology used in the respective studies. A long-term cumulative incidence for PSE that varies between 2 and 15% has been reported in the literature [14]. As with ASS, the risk for PSE is generally higher after a hemorrhagic than an ischemic stroke. An exception seems to be total anterior circulation stroke, which might convey an even higher risk for epilepsy than intracerebral hemorrhage. In a prospective

UK population-based study that included 3310 newly diagnosed ischemic and hemorrhagic stroke patients of all ages, 6.4% developed epilepsy after a mean follow-up period of 3.8 years [15]. PSE was defined as at least two unprovoked seizures in this study. The overall cumulative risk for PSE was determined as 3.5% at 1 year, 9.0% at 5 years, and 12.4% at 10 years. The 10-year cumulative risk was found to be highest for total anterior circulation infarction (28.7%), followed by subarachnoid hemorrhage (21.7%), primary intracerebral hemorrhage (18.2%) and partial anterior circulation infarct (13.4%), while the risk for epilepsy was low with lacunar infarct and posterior circulation infarct. A cumulative incidence of 6.4% for PSE after ischemic stroke and a cumulative incidence of 12.4% for PSE after intracerebral hemorrhage were reported from a retrospective Swedish cohort study that included 106,455 stroke patients [16]. This study already used the new definition for PSE of a single unprovoked remote symptomatic seizure. The greatest risk for the development of PSE is within the first year of stroke [6]. Of all patients who ultimately develop PSE, more than 50% have their seizure onset in the first poststroke year. The risk for the development of epilepsy declines steadily thereafter but has been reported to remain elevated for at least 10 years [17, 18].

Risk factors for stroke-related acute symptomatic seizures and poststroke epilepsy

Several independent predictors for both stroke-related ASS and PSE have been identified by various studies. The higher risk for ASS and for PSE with hemorrhagic stroke compared to ischemic stroke has already been mentioned

Table 1 Risk factors for PSE

Risk factors for poststroke epilepsy
Acute symptomatic seizures
Cortical stroke location
Hemorrhagic stroke
Clinical stroke severity
Etiology (Large-artery atherosclerosis)
Younger age
Territory of MCA
Greater lesion size on imaging

above. Secondary hemorrhagic transformation of ischemic stroke lesions also predisposes to an increased risk for ASS [19] and PSE [20] compared with ischemic stroke alone, pointing to the epileptogenicity that is associated with the extravasation of blood products. Cortical stroke location is a well-characterized risk factor for ASS in both ischemic and hemorrhagic stroke [20, 21]. Other risk factors for ASS are clinical stroke severity, lesion size and younger age (<65 years) [5]. Stroke location in the territory of the posterior cerebral artery and stroke caused by large artery atherosclerosis were risk factors for ASS in another recent large retrospective multicenter registry study [9•]. For PSE, ASS, cortical stroke location, clinical stroke severity, stroke etiology (large-artery atherosclerosis), hemorrhagic stroke and younger age have been consistently identified as independent risk factors (Table 1) [22]. In the aforementioned retrospective multicenter study of more than 4000 stroke patients, ASS were the strongest predictor of PSE [9•]. Stroke location in the territory of the middle cerebral artery and greater lesion size as assessed on brain imaging have also been reported to be associated with an increased risk for poststroke seizures [20, 23]. Younger age has been determined as an independent risk factor for PSE [24, 25] and relatively high rates of epilepsy have been found in studies that specifically investigated the poststroke seizure risk of younger stroke patients [26]. However, longer and higher rates of survival rather than a higher susceptibility for epileptogenesis might influence the poststroke seizure incidence of younger patients [6]. Acute symptomatic status epilepticus (SE) occurs in around 0.5–1.5% of all stroke cases and probably is a greater risk factor for PSE than ASS alone [27, 28]. Compared to ASS of normal duration, acute symptomatic SE overall increases the risk of subsequent epilepsy 3.3-fold and acute symptomatic SE due to a structural pathology 7.1-fold [29•]. In a study of 50 patients with stroke-related acute symptomatic SE, 20% developed epilepsy and a longer duration of SE was associated with a higher risk [28].

Prediction of poststroke epilepsy

Information about the risk factors for poststroke seizures is usually routinely available in clinical practice and can be used to predict a patient's risk for the development of PSE. The SeLECT Score uses five of the risk factors discussed above as predictors for the risk of unprovoked seizures after ischemic stroke: Severity of stroke, Large-artery atherosclerotic etiology, Early seizures, Cortical involvement, and Territory of middle cerebral artery involvement [10••]. It has been shown to predict the risk for PSE accurately in different cohorts of stroke patients. In the most unfavorable scenario of the highest SeLECT score (9 points) the predicted seizure risk is 63% after 12 months and 83% after five years (Table 2). The SeLECT score is available as a smartphone app and can easily be used as a clinical tool. The CAVE score is another prognostic model that has been developed to predict the risk of seizures after intracerebral hemorrhage [30]. Predictors in this model are Cortical location, younger

Table 2 The SeLECT score predicts the risk of PSE. **A.** Calculation of the SeLECT score. **B.** Risk for an remote symptomatic seizure at one and five years after stroke. Based on Galovic M, Döhler N, Erdélyi-Canavese B, Felbecker A, Siebel P, Conrad J, et al. Prediction of late seizures after ischaemic stroke with a novel prognostic model (the SeLECT score): a multivariable prediction model development and validation study. *The Lancet Neurology.* 2018;17(2):143-52

A		B		
Risk factors	SeLECT Score Points	SeLECT Score Value	Risk for epilepsy after stroke	
Severity of Stroke			at 1 year	at 5 years
NIHSS ≤ 3	0	0	0.7%	1.3%
NIHSS 4-10	1	1	1%	2%
NIHSS ≥ 11	2	2	2%	4%
Large-artery atherosclerosis		3	4%	6%
No	0	4	6%	11%
Yes	1	5	11%	18%
Early (acute symptomatic) seizures		6	18%	29%
No	0	7	28%	45%
Yes	3	8	44%	65%
Cortical Involvement		9	63%	83%
No	0			
Yes	2			
Territory of MCA				
No	0			
Yes	1			

Age (<65 years), hematoma Volume (> 10 ml) and acute symptomatic seizures. In the case of the highest CAVE score (4 points) the estimated seizure risk is 46%.

Acute stroke therapies and seizures

There has been uncertainty about the effects of acute stroke reperfusion therapies on the poststroke seizure risk. Thrombolysis and endovascular thrombectomy have been suggested to increase the risk for ASS and PSE in some studies [31–33]. Other studies however did not find such an association [34, 35]. Comparisons between groups of reperfusion therapy and no reperfusion therapy might be confounded by treatment selection bias: more severe strokes, which more often result in ASS and PSE, might just be more likely to receive reperfusion treatment. A large retrospective multicenter study that analyzed the effects of reperfusion therapies on poststroke seizure risk used propensity score matching to correct for treatment selection bias [9•]. This study found that reperfusion therapies (IV thrombolysis and mechanical thrombectomy) were not associated with an increased risk for either ASS or PSE. Whether successful stroke reperfusion therapies that decrease the extent

of ischemic brain damage actually have a preventive effect on the development of PSE is unclear [36].

Prestroke seizures

Epileptic seizures not only occur at stroke onset or after a stroke but can also precede a stroke [37 38•]. Since stroke is the most common cause of epilepsy in higher age groups, it has been assumed that cerebrovascular disease is the cause of late-onset epilepsy (variably defined as epilepsy onset after the age of 60 or 65 years) even in many patients without any previous clinical stroke event [39, 40]. Thus, seizures in middle-aged and elderly patients could be a potential biomarker for subsurface cerebrovascular disease and herald an impending stroke (Fig. 3). An UK database study compared 4709

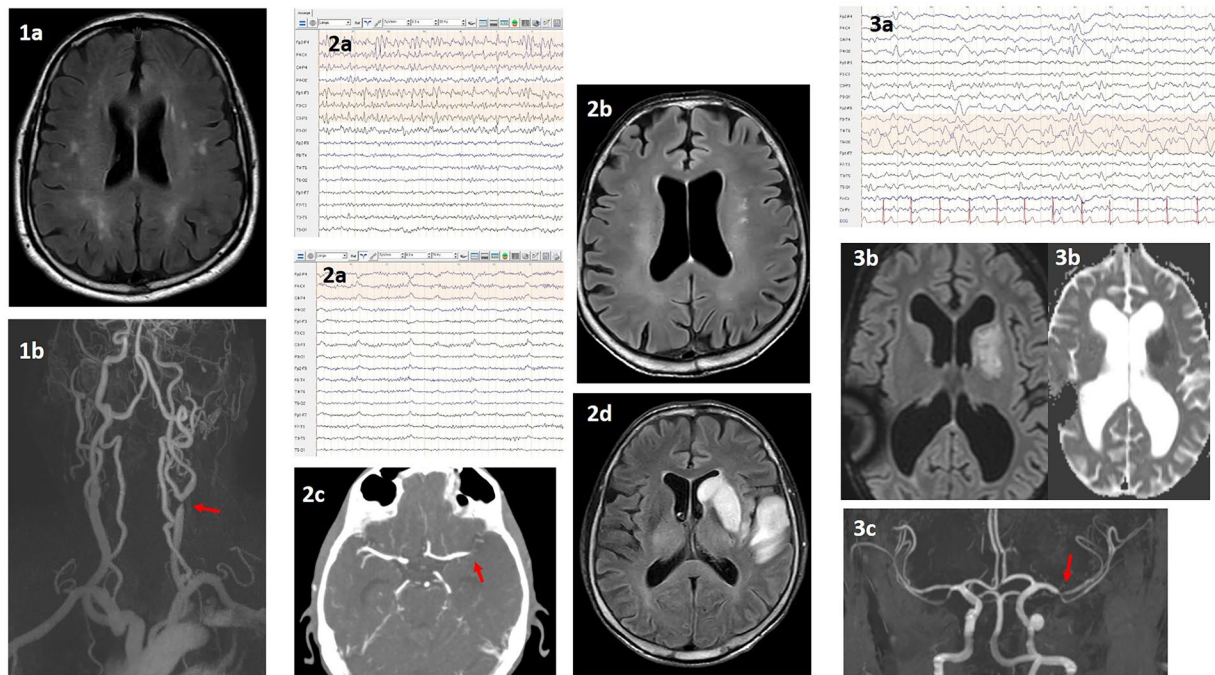


Fig. 3 Cases of prestroke seizures. 1. A 75-year-old patient with two unprovoked bilateral tonic clonic seizures. **(1a)** MRI (FLAIR) shows evidence of cerebral small vessel disease, Fazekas 2–3. **(1b)** MR-angiography reveals asymptomatic high-grade stenosis of the left internal carotid artery (ICA). Apart from ASM, the patient received medical treatment of vascular risk factors and stent implantation of the left ICA. 2. A 77-year-old patient presented with recurrent episodes of impaired awareness and aphasia. **(2a)** EEG shows epileptiform discharges over the right central region and a non-convulsive seizure starting from right central. **(2b)** MRI shows moderate atrophy and mild to moderate vascular changes. Diagnostic work-up identified no definitive etiology of epilepsy. **(2c, d)** Occurrence of an ischemic stroke in left MCA territory due to occlusion of the left MCA nine months after diagnosis of epilepsy. 3. A 31-year-old patient with drug resistant focal epilepsy after resection of a right temporoparietal meningioma in childhood. **(3a)** EEG shows a right posterior epileptogenic focus. **(3b)** At age 31, the patient develops a lenticulostriate infarction. **(3c)** MR-angiography reveals a stenosis of the left MCA. Long-term ASM treatment, including with CBZ, possibly has contributed to enhanced atherosclerosis.

individuals with onset of seizures after the age of 60 years with an equal number of matched controls and found that the risk to develop a stroke was 2.89 times higher for persons who had already experienced seizures [38•]. Similar results of an increased risk for stroke in epilepsy patients were reported by studies from Taiwan [41] and Sweden [42]. The pathophysiology behind the increased risk for stroke in epilepsy patients probably varies with age: in younger people with epilepsy, an increased risk for stroke might be mediated by genetic background, acceleration of atherosclerosis by long-term ASM intake or due to possible effects of seizures on the cardiovascular system [14, 41]. In elderly people with seizures, the increased risk of stroke might reflect the presence of subclinical cerebrovascular disease. Imaging studies have shown a greater burden of vascular lesions in patients with late-onset epilepsy than in age-matched controls without seizures [43, 44]. Late-onset epilepsy patients not only exhibit more cortical vascular lesions respectively large artery disease lesions, but especially show a higher and more extensive burden of leukoaraiosis on imaging [45]. These and other findings suggest a role of small vessel disease in the epileptogenesis of late-onset epilepsy [6]. It has been recommended that patients with late-onset seizures without an obvious cause should be considered at risk for a stroke and should be screened and — if present — treated for vascular risk factors [39, 46].

Clinical diagnosis of poststroke epilepsy

The diagnosis of ASS and PSE is based on the definitions discussed above. Using the 7-day cut-off as a rule will probably allow seizures to be attributed correctly as either acute symptomatic or epilepsy in most cases. However, the clinical situation might sometimes be complex, rendering it more difficult to distinguish between acute symptomatic and unprovoked remote symptomatic seizures. For example, there might be a prolonged and unstable acute clinical situation in which seizures might still be classified as acute symptomatic even after 7 days. In another situation, it might be difficult to judge whether a seizure is acute symptomatic or unprovoked because the exact date of the last stroke is not known. If it is in doubt whether a seizure is truly unprovoked, a diagnosis of epilepsy should not be made [3]. This also applies if both a potential remote symptomatic (e.g. a chronic stroke lesion) and an acute symptomatic cause (e.g. an acute new stroke or a non-stroke cause such as severe hyponatremia) are concomitantly present. In such a case, the seizure should be rated as acute symptomatic [4••]. Moreover, a poststroke seizure might not necessarily be stroke-related. A clinical correlation between semiological features and the location of a stroke lesion will support a causal relationship between a stroke and a seizure. Clinical findings of a cortical stroke lesion (e.g. aphasia, neglect, etc. ...) and of high stroke severity also increase the likelihood that a seizure is actually stroke-related. Additionally, if there is doubt whether an unknown paroxysmal event in a stroke patient really is a seizure, one should refrain from diagnosing PSE.

The role of the EEG in acute stroke and for the prediction of poststroke epilepsy

The main role of the electroencephalogram (EEG) in acute stroke is to detect subclinical, exclusively electroencephalographic, seizure activity. Most seizures (around 75%) in critically ill patients that are recorded with the use of continuous EEG (cEEG) monitoring do not have any detectable clinical signs at the bedside and would be missed without recording EEG [47]. Early recognition and treatment of non-convulsive seizures and non-convulsive status epilepticus (NCSE) is important to potentially prevent a negative outcome. In an intensive care unit study of 570 critically ill patients with various diagnoses who underwent cEEG monitoring, patients with ischemic stroke were reported to have had non-convulsive seizures in 9% and NCSE in 7% [48]. Non-convulsive seizures are also not uncommon in acute stroke patients in a stroke unit environment. A Video-EEG study found NCSE in 3.6% of 889 acute stroke patients on a stroke unit [49]. In 40.6% of cases, there had been no clinical suspicion for NCSE. Another stroke unit Video-EEG study found epileptiform EEG activity in 17.9% of 151 acute stroke patients [13•]. NCSE occurred in 2.6% of patients. The study reported 22 ASS of which 22.7% were detected by cEEG only. Thus, seizure frequency in acute stroke patients might be underestimated when cEEG is not deployed. cEEG should be performed in all critically ill acute stroke patients who do show persistent impairment of consciousness or sudden changes in mental status or in whom non-convulsive seizures are otherwise suspected clinically [50]. A study of 81 stroke patients who were monitored with cEEG because of neurological deterioration found non-convulsive seizures and NCSE in 12% of cases [51]. Apart from electroencephalographic seizures, EEG can detect patterns such as lateralized periodic discharges (LPDs), which are associated with the occurrence of ASS [52]. The presence of epileptiform abnormalities such as LPDs on routine EEG might therefore also be an indication for cEEG monitoring. Whether EEG findings can predict the development of PSE is a relevant clinical question but has so far been addressed only in a few studies. In a retrospective study of 110 stroke patients who developed poststroke seizures, LPDs were found in 5.8% [53]. Contrary, LPDs were not found in a control group of 270 stroke patients without seizures in this study. More recent studies did also show that epileptiform abnormalities on cEEG in the acute phase after stroke are an independent predictor of PSE development [54, 55•]. However, other studies have failed to show an independent value of the EEG in the prediction of PSE [9••, 56]. The role of the EEG for the prediction of PSE, whether alone or potentially in combination with existing prediction tools such as the SeLECT Score, therefore needs further investigation [3].

Neuroimaging in the differential diagnosis of seizures and stroke

Epileptic seizures can clinically imitate a stroke (“stroke mimic”), particularly if there is a transient focal neurological deficit (e.g. Todd’s paralysis) after the seizure. On the other hand, an acute ischemic stroke can present in the disguise of an ASS at onset and the underlying ischemia might thus not be immediately recognized (“stroke chameleon”). The latter might have severe consequences if there is a delay or failure in administering reperfusion therapy [57]. Clinical predictors for differentiating between mimics and a true stroke exist, but are limited [58–60] and the EEG is not specific as it can show focal slowing and epileptiform abnormalities in both the postictal state and acute ischemia [61]. Advanced neuroimaging is the most accurate method to distinguish between a seizure and an acute ischemic stroke. CT-angiography can be useful to distinguish between Todd’s paralysis and acute ischemic stroke by detection of an intracranial artery occlusion in the presence of the latter [62]. Hyperperfusion, often in a nonvascular distribution, demonstrated by perfusion-CT, is seen with ongoing seizure activity or recently resolved SE, whereas in acute ischemic stroke there is hypoperfusion within the boundaries of a vascular territory [63, 64]. Standard MRI sequences will often suffice to accurately differentiate between an acute stroke and a seizure that presents as a stroke mimic [3]. Negative diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) sequences in a patient with postictal focal neurological symptoms will confidently rule out the differential diagnosis of acute ischemia. However, DWI lesions are not specific for ischemic stroke and have also been reported in association with epileptic activity [65]. In addition, various etiologies associated with seizures and epilepsy can present with DWI restriction themselves, e.g., abscesses, tumors, encephalitis or mitochondrial disease [66]. DWI alterations associated with epileptic activity occur mainly after SE and seizure clusters, but have also been observed after single epileptic seizures [67]. Clues that can help to discriminate SE or seizure-related DWI changes from ischemic DWI lesions can be the following: In opposition to ischemic stroke, seizure-related DWI changes often do not respect vascular territories [68]. SE or seizure-related DWI restrictions often occur simultaneously with hyperintensity on T2-weighted sequences, whereas in ischemia T2-weighted lesions appear only with some delay to the diffusion restriction [69]. The DWI and T2-image alterations seen with SE and seizures are most often found to be completely reversible, but T2-sequence lesions persist in ischemic stroke. There is a predilection for SE and seizure-related DWI changes to occur in certain brain regions: the neocortex, hippocampus, pulvinar of the thalamus, splenium of the corpus callosum, and the contralateral cerebellum are most often affected [70•]. Quantitative analysis of DWI lesions may also be helpful to distinguish between SE- and stroke-related DWI

changes as DWI lesions associated with ischemic stroke were recently reported to be significantly more intense than SE-related DWI alterations [70•] (Fig. 4). In addition, MR perfusion sequences can demonstrate hyperperfusion in SE, again often in a non-vascular territory distribution [69]. Hyperperfusion may be already seen in an early ictal phase and precede the appearance of seizure-related DWI lesions.

Management of stroke-related acute symptomatic seizures

Anti-seizure medication (ASM) therapy directly after a stroke for primary prophylaxis of ASS would prove unjustified due to the relatively low incidence of ASS after stroke. Even in “high risk” clinical scenarios of a large cortical intracerebral or subarachnoid hemorrhage the risk for ASS is only around 35% [71]. ASM treatment for the primary prophylaxis of ASS is therefore not recommended. A randomized, placebo-controlled trial of valproic acid (VPA) in patients with acute intracerebral hemorrhage did not find a primary prophylactic effect on the incidence of ASS [72]. However, the results of this study are not conclusive as the trial was underpowered and did not investigate ASS as the primary endpoint. After a first stroke-related ASS, further ASS can occur, but this happens only in around 10–20% of patients [21, 73]. Based on this relatively low risk, temporary ASM treatment to prevent a second ASS has not been recommended by guidelines [71]. Nevertheless, in clinical practice, patients are often started on ASM after an ASS with the aim of preventing a seizure-related clinical worsening in the setting of an acute stroke. This

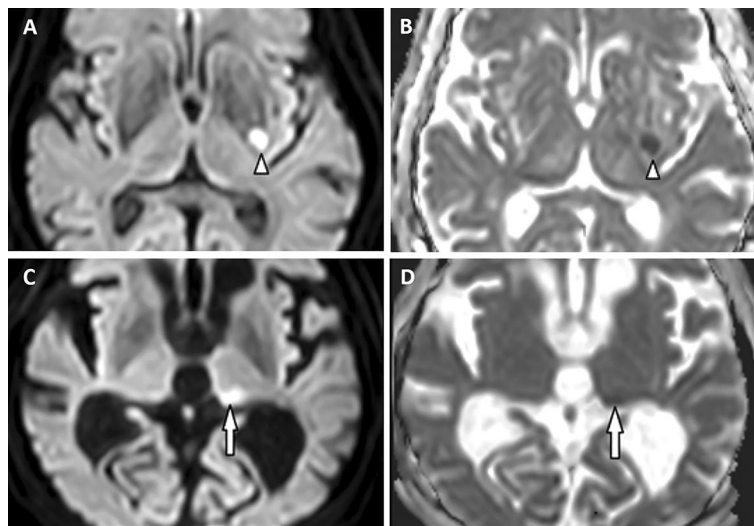


Fig. 4 Differentiating stroke- and seizure-related diffusion-restricted MRI lesions. (A, B) Stroke-related diffusion restriction in the left Globus pallidus on DWI (A) and ADC (B). (C, D) SE-related diffusion restriction in the left pulvinar on DWI (C) and ADC (D). The DWI/ADC lesion due to ischemic stroke is significantly more intense than the SE-related DWI/ADC alteration.

approach is pragmatic, but is not evidence-based as there are no randomized controlled trials available. However, ASMs might be effective to reduce the risk of further ASS as was shown in studies of patients with traumatic brain injury [74]. As the acute effects of the cerebrovascular injury subside after the first few days, the risk for ASS correspondingly decreases. The risk for unprovoked seizures after a stroke-related ASS is then relatively low and there is no evidence that long-term ASM treatment will reduce the risk to develop epilepsy. Thus, if treatment with ASM is chosen after a stroke-related ASS, the ASM should be withdrawn after the acute stroke phase, probably ideally at the time of hospital discharge [71].

Management of poststroke epilepsy

Treatment with ASM is advised after the diagnosis of PSE, i.e. the first unprovoked poststroke seizure [71]. The reason is the high seizure recurrence risk (71%) that has been reported from observational studies [7••]. A diagnosis of PSE must not necessarily result in the start of ASM. After a first unprovoked poststroke seizure, the patient should be informed about the high recurrence risk and offered ASM treatment. However, reasons not to start immediate ASM treatment might be individual factors such as mild (e.g. pure sensory) seizures only or a low risk for seizure-related injuries (e.g. due to lack of ambulation). The usual principles of pharmacotherapy in epilepsy such as “start slow, aim low” and “monotherapy before polytherapy” also apply in PSE. In the stroke population, general aspects of pharmacotherapy in the elderly need to be taken into account. First, altered pharmacokinetics that occur with aging including decreased renal function, lower protein binding because of reduced albumin levels and diminished hepatic metabolic capacity. These often require slower titration and lower target doses of ASMs [75]. Second, there is a higher risk for drug-drug interactions, dose-dependent adverse events and drug toxicity due to the polypharmacy that is common in elderly patients [46]. Only limited evidence is available to guide the selection of specific ASMs in PSE. Two randomized, open-label trials compared controlled-release carbamazepine (CR-CBZ) versus either lamotrigine (LTG) [76] or levetiracetam (LEV) [77] in patients with PSE. The studies did not report a significant difference in the 12-month seizure freedom rate between both LTG and CR-CBZ (72% vs. 44%) and LEV and CR-CBZ (94% vs. 85%). However, both trials included only small numbers of patients and were therefore underpowered to detect a significant difference in efficacy [78••]. LTG as well as LEV were found to be significantly better tolerated than CR-CBZ. A meta-analysis of the two studies did not reveal any difference in the rate of seizure freedom between LTG and LEV (OR 0.86; 95% CI: 0.15–4.89), but showed a higher risk for adverse events with LEV compared to LTG (OR 6.87; 95% CI: 1.15–41.1) [78••]. Information can also be obtained from randomized comparison studies of ASMs that have been conducted in focal epilepsy in general [79, 80] or in patients with late-onset epilepsy [81–85]. Overall, most studies do not show significant

differences in efficacy but newer ASMs such as LTG and LEV tend to be better tolerated than standard ASMs such as CBZ. A network meta-analysis on ASM monotherapy in elderly patients did not reveal any significantly more efficacious treatment but found lacosamide (LCM), LTG and LEV to have the highest probability for achieving seizure freedom [86]. LTG had been previously shown to be non-inferior to CBZ for time to 12-month seizure remission and superior to CBZ, topiramate (TPM), gabapentin (GBP) and oxcarbazepine (OXC) for time to treatment failure in an unblinded randomized controlled trial (SANAD I) of focal epilepsy [79]. LTG was more recently found to be superior (per-protocol analysis) over both LEV and zonisamide (ZNS) for 12-month seizure remission in patients with focal epilepsy in another unblinded randomized controlled trial (SANAD II) [80]. An interpretation of the results regarding PSE is somewhat limited by the fact that the proportion of patients with cerebrovascular etiology varies between the studies. However, there is no evidence that in focal epilepsy, any specific ASM works better for any specific cause of epilepsy [80]. Hence, the selection of ASMs is usually not determined by etiology. The choice of the appropriate ASM for a patient with PSE is rather an individual treatment decision that needs to consider patient factors such as age, sex, comorbidities and comedications [3]. From the perspective of drug interactions and adverse events, enzyme-inducing ASMs such as CBZ, phenytoin or phenobarbital are probably less ideally suited choices in PSE patients. Enzyme-inducing ASMs can have a problematic influence on the metabolism of comedications which are administered for secondary stroke prophylaxis. An example is their interaction with oral Vitamin K anticoagulants such as warfarin which can lead to a subtherapeutic anticoagulatory effect [87]. Another reason to avoid enzyme-inducing ASMs in PSE patients is their potentially negative effect on the risk for vascular events. Long-term treatment with enzyme-inducing ASMs has been shown to increase biomarkers for vascular disease such as carotid artery intima-media thickness, cholesterol, homocysteine and C-reactive protein [88, 89]. An increased risk for cardiovascular disease after long-term exposure to enzyme-inducing ASMs has been recently reported by a large retrospective cohort study [90]. Avoiding cognitive adverse effects of ASMs is desirable in stroke patients as up to one-third are affected by some form of poststroke cognitive impairment [91]. In general, newer ASMs have a more favorable cognitive side effect profile than the older standard ASMs [92]. LEV, LTG and GBP are all associated with fewer cognitive side effects than CBZ, whereas TPM stands out from the newer generation of ASMs for being particularly associated with a negative effect on cognition [93]. The high prevalence of depression after stroke (30–50%) [94] demands caution when using LEV, which has a relatively high risk for psychiatric and behavioral side effects [95]. Withdrawal of ASM is a difficult but relevant issue, as a majority of PSE patients will become seizure-free. A meta-analysis of ten studies that included 1769 seizure-free patients who had an ASM subsequently withdrawn established predictors of seizure recurrence and developed a risk model that was converted into an online prediction tool [96]. The usefulness of this prediction model for PSE is unclear, as most patients in this study were children and brain lesions on imaging were not included. However, PSE

patients usually do have a brain lesion after their infarction which will probably decrease their chances of seizure freedom after ASM withdrawal [22]. Thus, ASM withdrawal should be approached cautiously in PSE patients. Any decision on ASM withdrawal will need to be individualized for each patient.

Prognosis and outcome of poststroke epilepsy

The perception that PSE is easy to manage and responds well to ASM monotherapy does exist [97•]. Indeed, a review of the available literature found quite high rates of seizure freedom reported from prospective clinical trials, but lower rates were reported from retrospective studies that more specifically investigated outcome [97•]. Selection bias towards inclusion of easier-to-treat patients into the clinical trials was mentioned as a possible explanation for this discrepancy. Overall, the seizure freedom rate for PSE might be just similar to the seizure freedom rate of the general epilepsy population (around two-third), as reported by a small retrospective study that investigated long-term outcome [98, 99]. A more recent study reported 20% of patients from a PSE cohort as having drug resistant epilepsy [100•]. Predictors for developing drug resistant epilepsy were younger age at onset, hemorrhagic stroke, stroke severity and the occurrence of focal to bilateral tonic-clonic seizures and SE. Earlier occurrence of poststroke seizures was also associated with drug resistance [101]. The development of seizures and epilepsy might have a detrimental effect on multiple outcomes after stroke, including neurological function and rehabilitation, quality of life and mortality. Mortality after a stroke is high in general, because of both the stroke and its consequences and the usually advanced age of stroke patients. Nevertheless, a retrospective Swedish register study that compared PSE patients to stroke patients without epilepsy identified a slightly increased risk for death in PSE patients even after adjusting for age and stroke severity in a multivariate analysis (HR: 1.36, 95% CI: 1.20–1.55) [16]. Another study in young stroke survivors (18–50 years) replicated the finding of an increased mortality associated with epilepsy independent of stroke severity [102]. Reasons for the excess mortality seen with PSE might be the effects of seizures itself but also an increased risk for recurrent vascular disease [97•]. Neurological function and outcome of neurorehabilitation in PSE patients is, as in all stroke patients, probably largely determined by stroke severity and stroke severity is an important risk factor to develop epilepsy. However, epilepsy was found to be an independent predictor of poor functional outcome in a prospective cohort study of young stroke survivors [26]. In addition, there are several studies that describe seizure-induced worsening of functional status in stroke patients after their first seizure [103, 104]. Evidence regarding quality of life in PSE is scarce, but seizure frequency, depression, and functional impairment were identified as independent predictors of poor quality of life in a more recent study [105].

Conclusion and future directions

While our understanding of PSE has improved, there remain several issues that require further investigation. In particular, further research that better characterizes the mechanisms of epileptogenesis after a stroke and identifies biomarkers for the development of PSE is necessary, as these are important preconditions to find a successful antiepileptogenic treatment [106]. Currently, a first antiepileptogenesis trial in PSE patients investigating eslicarbazepine acetate has recently stopped recruiting and awaits the follow-up investigations [107, 108], while a second trial that studies perampanel is ongoing [109]. More information on the value of EEG in the prediction of PSE and on vascular prophylaxis in patients treated with ASMs is needed. Finally, the efficacy and safety of ASMs specifically for PSE have been studied only insufficiently. Large, prospective studies addressing the management of PSE are needed to provide information that will allow the development of evidence-based treatment guidelines.

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Compliance with Ethical Standards

Conflict of interest

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