

Post-stroke seizures: a clinical approach to diagnosis and treatment

Francesco Brigo^{1,2}
Nicola Luigi Bragazzi^{3,4}
Raffaele Nardone^{2,5}

¹ Department of Neurosciences, Biomedicine and Movement Science, University of Verona, Italy

² Department of Neurology, Franz Tappeiner Hospital, Merano, Italy

³ School of Public Health, Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy

⁴ Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGLI), Section of Psychiatry, University of Genoa, Genoa, Italy

⁵ Department of Neurology, Christian Doppler Clinic, Paracelsus Medical University, Salzburg, Austria

Corresponding author:

Francesco Brigo
Department of Neurosciences, Biomedicine and Movement Science,
University of Verona
Piazzale L.A. Scuro 10
37134 Verona, Italy
Tel.: +39 0458124174
Fax: +39 0458124873
E-mail: dr.francescobrigo@gmail.com

Abstract

Cerebrovascular disease is the most commonly identified cause of acquired epilepsy. Differentiating between early and late post-stroke seizures is relevant from an epidemiological and clinical perspective, as they carry different risk of seizure recurrence. The occurrence of a single late post-stroke seizure is associated with high risk of seizure recurrence, and therefore enables to diagnose post-stroke epilepsy. Some clinical and stroke characteristics are associated with an increased risk of post-stroke seizures; they might prove useful in the future, when preventative measures will be available. Currently, there is no robust evidence to support the use of neuroprotective drugs for primary prevention of post-stroke seizures. There is also insufficient evidence to recommend the use of a specific antiepileptic drug for the treatment of post-stroke epilepsy. Thrombolysis with t-PA might increase the risk of early seizures

without affecting the risk of post-stroke epilepsy; further studies are however required to further investigate this association.

KEY WORDS: epilepsy, post-stroke seizures, stroke.

Introduction

The relationship between seizures and stroke is bidirectional. Recent epidemiological and clinical data suggest that otherwise unexplained late-onset seizures and epilepsy represent the very first clinical manifestation of otherwise occult cerebrovascular disease (1, 2). These epileptic seizures can therefore be regarded as a biomarker of subclinical cerebrovascular disease. Further research is however needed to further investigate the link between late-onset seizures, their underlying etiology and the risk of a subsequent clinically overt stroke (3).

Conversely, stroke is widely recognized as a major cause of seizures and epilepsy. This article provides a brief overview of the epidemiology of post-stroke seizures, and discusses the importance of differentiating between early and late post-stroke seizures. Data on clinical and stroke characteristics influencing the risk of post-stroke seizures are presented and discussed. The clinical criteria to diagnose post-stroke epilepsy are also reported. Finally, we discuss treatment issues, focusing on primary prevention of post-stroke seizures, the pharmacological management of early and late post-stroke seizures, and the relationship between thrombolysis and post-stroke seizures.

Early and late post-stroke seizures

Cerebrovascular disease is the most commonly identified cause of acquired epilepsy. It is responsible for 11% of all epilepsies, 22% of all cases of status epilepticus, and 55% of newly diagnosed seizures in the elderly (4, 5). In most cases, post-stroke epilepsy develops within 1 year from the stroke, when the epileptogenic process is considered to be more active (6). Approximately 2 to 6% of people with stroke suffer early seizures and 3 to 5% suffer late seizures (4). The occurrence of early seizures increases the risk of subsequent epilepsy, but epilepsy develops only in a minority of cases (about one third); conversely, if a late seizure occurs, the risk of recurrent seizures is much higher (5).

From an epidemiological and clinical perspective, it is important to define and differentiate early and late

post-stroke seizures. Seizures occurring at the time of or in close temporal association with stroke (i.e., within 7 days from the stroke) are termed early post-stroke seizures. If seizures occur more than 7 days after a stroke, they are defined late post-stroke seizures (6) (Fig. 1). This distinction might seem rather arbitrary, but relies on epidemiological data and is relevant for clinical practices, as it reflects a different risk of seizure recurrence.

Differentiating between early and late post-stroke seizures is justified also in terms of pathophysiology: early post-stroke seizures are the consequence of transient cellular biochemical dysfunctions or homeostatic/systemic disturbances; conversely, late post-stroke seizures are due to epileptogenic gliotic scarring or hemosiderin deposits (usually after hemorrhagic stroke or hemorrhagic transformation of the ischemic infarction) (5, 6) (Fig. 2).

Late post-stroke seizures can be preceded by early post-stroke seizures or not, with a latent period between the stroke (the acute brain injury) and the later occurrence of seizures. During this clinically silent phase progressive neuronal changes occur in the brain and alter its excitability. These changes include: selective neuronal cell death and apoptosis; changes in membrane properties; mitochondrial changes; receptor changes (e.g. loss of GABAergic receptors); deafferentation, and collateral sprouting (6). This underlying process is termed "epileptogenesis": after a stroke or a different brain injury the brain undergoes changes which increase its excitability leading to recurrent spontaneous seizure (i.e. epilepsy) (7).

Risk factors of post-stroke seizures

From an epidemiological and clinical perspective it is important to identify clinical and stroke characteristics which may influence the risk of post-stroke seizures. Efforts should be made to investigate factors predisposing to seizures-particularly if preventative measures are to be attempted - and to identify patients at high risk of post-stroke seizures. This is going to be even more relevant in the future, when preventative measures will be available.

Factors associated with an increased risk of early post-stroke seizures include: stroke with cortical involvement, intracerebral hemorrhage or hemorrhagic transformation, stroke severity and alcohol drinking (8) (Tab. 1). Conversely, cortical involvement, intracerebral hemorrhage, younger age and size or stroke severity are associated with an increased risk of late post-stroke seizures (9) (Tab. 2). Of note, development of late seizures occurs frequently in people who have experienced early seizures (5).

What is post-stroke epilepsy and how can it be diagnosed?

Epilepsy is conceptually defined as a "disorder of the brain characterized by an enduring predisposition to generate epileptic seizures" (10). From a practical perspective, epilepsy can be diagnosed in any of the

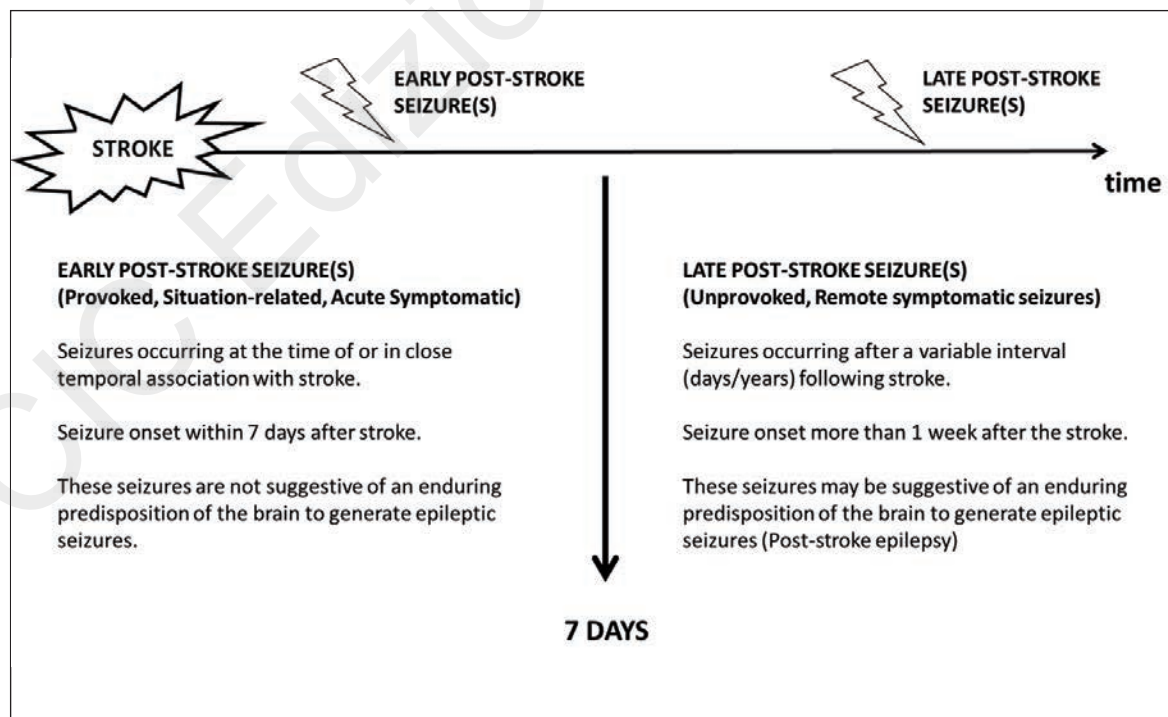


Figure 1 - Clinical characteristics of early and late post-stroke seizures.

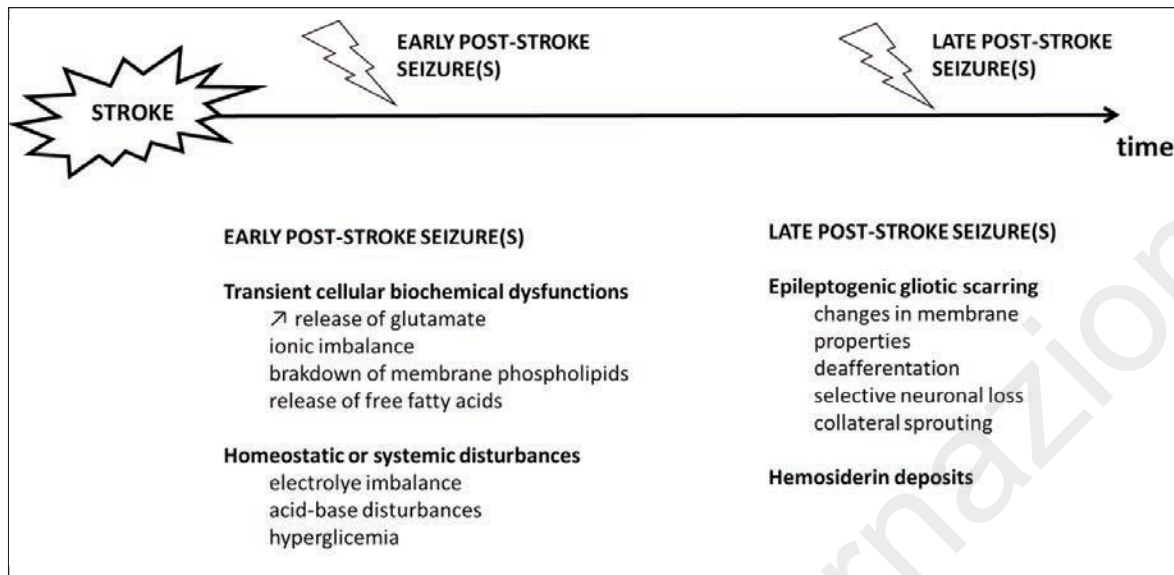


Figure 2 - Pathophysiology of early and late post-stroke seizures.

Table 1 - Clinical and stroke characteristics which influence the risk of early post-stroke seizures as reported in (8).

Stroke characteristic	N of studies	N of patients	OR (95% CI)	p-value
Gender (male)	9	6.632	1.07 (0.85-1.35)	0.54
Cortical involvement	7	NR	2.59 (1.50-4.48)	<0.001
Stroke subtype	8	5.716		
<i>Intracerebral hemorrhage</i>	6	3.472	2.23 (1.63-3.03)	<0.001
<i>Hemorrhage transformation</i>	4	3.644	3.28 (2.09-5.16)	<0.001
Stroke severity (NIHSS>15)	2	2.516	3.10 (2.00-4.81)	<0.001
Lifestyle				
Smoke	NR	NR	1.11 (0.8-1.54)	0.57
Alcohol	5	2.490	1.70 (1.23-2.34)	<0.001

NR: not reported

Table 2 - Clinical and stroke characteristics which influence the risk of late post-stroke seizures as reported in (9).

Stroke characteristic	N of studies	OR (95% CI)	p-value	Positive association
Gender (female)	13	0.94 (0.79-1.13)	0.52	
Cortical involvement	6	3.71 (2.34-5.90)	<0.001	
Stroke subtype				
<i>Intracerebral hemorrhage</i>	15	2.41 (1.57-3.69)	<0.001	
Early seizures	2	4.43 (2.36-8.32)	<0.001	
Younger age	12 ^b			3/12 studies
Size or severity of stroke	12 ^b			9/12 studies
Thrombolysis	1		0.49 ^a	
Early seizures treatment	1		0.17 ^a	

^a adjusted p at multivariate analysis

^b not included in meta-analyses

following condition (11):

1. At least two unprovoked (or reflex) seizures occurring >24 h apart.
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years. In other terms, epilepsy can be diagnosed in presence of one unprovoked seizure and a probability of further seizures of at least 60% over the next 10 years.
3. Epilepsy syndrome, such as juvenile myoclonic epilepsy.

One study showed that the risk of subsequent unprovoked seizures over the next 10 years in patients who had a first unprovoked post-stroke seizure (i.e., in patients with a first late post-stroke seizure) is higher than 70% (71.5%; 95% confidence intervals: 59.7 to 81.9%) (12). Of note, the lower confidence interval is exactly 60% (59.7%). Thus, every patient with a first late post-stroke seizure can be considered at high risk of seizure recurrence. A diagnosis of post-stroke epilepsy can therefore be made even after a single post-stroke seizure (11).

Primary prevention of post-stroke seizures

Several drugs have been claimed to have neuroprotective properties. However, to date there are no strong evidence supporting the use of antiepileptic drugs (AEDs) to prevent a first-ever occurrence of post-stroke seizures. To date only two RCTs have assessed a role of two AEDs, valproic acid (13) and levetiracetam (14), in preventing post-stroke seizures (Tab. 3). None of them yielded informative results, probably because these two studies were underpowered to detect a statistically significant and a clinically relevant difference in efficacy between the tested drugs and the placebo (14). These studies have therefore a high risk of false negative results.

Treatment of post-stroke seizures and post-stroke epilepsy

In some cases, first-ever early post-stroke seizure do not require a specific antiepileptic therapy (5).

However, it is important to consider the individuality of the patient, the presence of comorbidities, the impact of a further seizure on the clinical status and patient's quality of life, and discuss about the risks and benefits of treatment.

Post-stroke convulsive status epilepticus (SE) represents a serious medical emergency requiring urgent intravenous therapy. Stroke represents a frequent cause of SE, although post-stroke SE is a rather infrequent event, occurring in less than 1% of patients with ischemic or hemorrhagic stroke over the 8 years following the stroke (15). However, when it occurs - particularly in the context of an acute stroke - SE is associated with high mortality and morbidity (16, 17), and therefore needs to be promptly recognized and treated.

It is common practice to treat recurrent early seizures with short-term (3-6 months) antiepileptic drug treatment, although advantages and disadvantages of long-term and short-term therapy have not been formally studied (5). However, administration of antiepileptic drugs does not prevent the later development of epilepsy (18).

The MRC Multicenter trial for Early Epilepsy and Single Seizures (MESS trial) showed that immediate treatment after a first unprovoked seizure does not improve the long-term remission rate (18). Consequently, treatment should be considered after a first unprovoked seizure only in patients at high risk of recurrence. Based on results of this study, a risk score model was validated to identify patients at high risk of seizure recurrence (19): accordingly, a patient should be considered at high risk of seizure recurrence if a neurological deficit or an abnormal electroencephalogram are present. However, according to this prognostic model, the sole presence of one of these risk factors (namely neurological deficit, which is almost always identifiable after a stroke) is associated with a 60% risk of seizure recurrence at 10 years. Of note, this prognostic model was based on a study which was not exclusively conducted in post-stroke seizures, but in seizure patients with different etiologies. The generalizability of the results of this study is therefore not particularly high, and its results cannot be automatically transferred to patients with post-stroke seizures.

The assessment of seizure recurrence after a first late post-stroke seizure should therefore rely on the results of the study mentioned above (12), showing a high risk of seizure recurrence. In other terms, all

Table 3 - Antiepileptic drugs for primary prevention of post-stroke seizures.

Study	Study design	Stroke subtype	AED	N of patients	Follow-up	Post-stroke epilepsy
Gilad et al., 2011	Randomized, double-blind, placebo-controlled	Spontaneous cerebral hemorrhage	VPA	36 VPA 36 placebo	1 year	16.6% with VPA and 11.1% with placebo
van Tuijl et al., 2011	Randomized, double-blind, placebo-controlled	Lobar cerebral hemorrhage or ischemic stroke with cortical syndrome	LEV	9 LEV 7 placebo	1 year	1/7 placebo 3/9 LEV

these patients may virtually benefit from immediate treatment with antiepileptic drugs to reduce the risk of long-term seizure recurrence.

Recently, other risk score models have been proposed with the aim of identifying patients at high risk of seizure recurrence, who may benefit from immediate treatment (20, 21). One of them (21) showed a predictive value higher than the scores derived from the MESS study (19) and from another study exclusively conducted in stroke patients (22).

Although it is important to consider the individuality of the patient and discuss about the risks and benefits of treatment/no treatment, in daily practice an antiepileptic treatment is usually started after a first late post-stroke seizure has occurred.

In the literature there is no robust evidence derived from class I studies (high quality randomized controlled trials) to inform clinical practice regarding the choice of the most appropriate AED to treat patients with post-stroke epilepsy. Overall, levetiracetam, lamotrigine and carbamazepine seem to be effective whereas levetiracetam and lamotrigine are probably better tolerated than carbamazepine (22-26) (Tab. 4). When choosing a drug, it is important to consider the presence of comorbid conditions, the concomitant use of other drugs to avoid interactions, and the presence of renal or hepatic impairment requiring dose adjustment. Elderly patients are particularly prone to adverse effects of drugs, and therefore it is always advisable to start with low dose and increase the dose slowly ("start low and go slow"). Finally, it is important to consider that the use of some antiepileptic drugs (phenytoin, phenobarbital, benzodiazepines) could impair recovery after stroke (5).

Thrombolysis and risk of post-stroke seizures

Recombinant tissue plasminogen activator (rt-PA) has both neurotoxic and neuroprotective effects. An animal study has shown that the overexpression of neuronal t-PA lowers seizure threshold, but has no influ-

ence on kindling epileptogenesis (27). Accordingly, it is possible that t-PA increases the risk of acute symptomatic (early post-stroke) seizures without affecting the risk of late post-stroke seizures. This has been shown in one study revealing a positive association between thrombolysis and early post-stroke seizures (odds ratio: 4.6; 95% confidence intervals: 1.6 to 13.4; $p=0.01$) (28). Interestingly, this increased risk was not explained by hemorrhagic transformation or sign of reperfusion injury.

Regarding the association of t-PA with post-stroke epilepsy, one study found a statistically significant increase in risk of late post-stroke seizures following treatment with t-PA ($p=0.02$) (29). However, the statistical significance was lost in the multivariate analysis ($p=0.49$). The presence of confounding factors is likely to explain the positive association: treatment with t-PA appears to be associated with post-stroke epilepsy; however such association might be explained by stroke severity, which increases the risk of post-stroke epilepsy but also determines whether or not t-PA treatment is indicated (29).

Conclusions

Differentiating between early and late post-stroke seizures is clinically relevant, because they carry a different risk of seizure recurrence. More specifically, a single late post-stroke seizure is associated with high risk of seizure recurrence, and therefore enables to diagnose post-stroke epilepsy.

Currently, there is no robust clinical evidence to support the use of any neuroprotective drug for primary prevention of post-stroke seizures. There is also limited clinical evidence to recommend the use of specific AEDs for the treatment of post-stroke epilepsy.

Thrombolysis with t-PA might increase the risk of early seizures without affecting the risk of post-stroke epilepsy; further studies are however required to further investigate the association between thrombolysis and the risk of seizures.

Table 4 - Treatment of post-stroke epilepsy.

Study	Design	Evaluated AEDs	N of included patients	Main findings
Gilad et al., 2007	Randomized, open-label	LTG vs. CBZ-CR	64	No difference in efficacy LTG better tolerated
Kutlu et al., 2008	Uncontrolled, open-label	LEV	34	Good efficacy and tolerability
Belcastro et al. 2008	Uncontrolled, open-label	LEV	35	Good efficacy and tolerability
Consoli et al., 2012	Randomized, open-label	LEV vs. CBZ-CR	106	No difference in efficacy LEV better tolerated
Huang et al., 2015	Retrospective	PHT, VPA, CBZ, other new AEDs	3,622	VPA and new AEDs higher efficacy than PHT

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