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Post-stroke epilepsy

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ABSTRACT

Post-stroke epilepsy (PSE) is a common complication after stroke, yet treatment options remain limited. While many physicians prescribe antiepileptic drugs (AED) for secondary prevention of PSE, it is unclear which treatments are most effective in the prevention of recurrence of symptoms, or whether such therapy is needed for primary prevention. This review discusses the current understanding of epidemiology, diagnoses, mechanisms, risk factors, and treatments of PSE.

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1. Introduction

Advances in stroke treatment, including tissue plasminogen activator and endovascular treatment in the acute phase, have resulted in a dramatic reduction in the mortality rate of stroke. Whilst encouraging, the number of stroke survivors living with disability worldwide has consequently increased. In Canada, the

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number of stroke survivors living with disability is expected to climb by 80% by 2038 (Krueger et al., 2015). Stroke survivors exhibit a wide range of neurological, physical and psychological issues, including: paralysis, muscle stiffness, dysphasia, dysarthria, language difficulties, unilateral neglect, numbness and pain, fatigue, cognitive impairment, depression, and difficulty controlling emotions.

Post-stroke epilepsy (PSE) has been identified as a significant clinical issue in stroke survivors. In a total of 34 longitudinal cohort studies involving over 100,000 patients, the incidence rate of PSE was approximately 7% (95%CI 0.05–0.09) (Zou et al., 2015). Likewise, in individuals aged ≥65, PSE has been shown to account for 30–49% of all new-onset seizures (Assis et al., 2015; Brodie and Kwan, 2005; Stefan et al., 2014). The occurrence of PSE has also been shown to lead to poor prognosis and increased mortality in post-stroke survivors (Arboix et al., 1996; Bladin et al., 2000; Labovitz et al., 2001).

PSE has a high recurrence rate. We recently found that PSE recurred in 30% patients within 360 days (Tanaka et al., 2015) and a further observational study reported approximately 50% of patients experienced a recurrence of symptoms during a follow-up period of 47 months (Olsen, 2001). The recurrence of PSE may lead to heightened anxiety and thus worsen recovery and quality of life in stroke survivors, making effective treatment vital. While the aetiopathology of PSE remains unclear, this review introduces concepts concerning the definition, diagnosis, mechanisms, risk factors, and treatment for this significant, and growing, public health issue.

2. Prevalence of early and late seizure

Post-stroke seizure is divided into two categories: early and late, according to the cutoff time-point, the first week after stroke onset (ILAE, 1981). Early seizures typically occur within the first few days after stroke and are also termed 'acute symptomatic seizures', whereas late seizures have a peak within 6–12 months and result in a higher frequency of stroke (Bladin et al., 2000; Burn et al., 1997; Hsu et al., 2014; Lamy et al., 2003). The cumulative seizure rate after stroke has been found to be 6.1% after 1 year, 9.5% after 5 years, and 11.5% after 10 years (Roivainen et al., 2013). In addition, Belcastro et al. showed non-convulsive status epilepticus (NCSE) was more frequent (1.67 times) in the early rather than late seizure group (Belcastro et al., 2014). The lack of obvious clinical manifestations of seizure means NCSE is difficult to detect in the acute phase of stroke and continuous electroencephalography (cEEG) is required for detection. It may therefore be necessary to perform cEEG to implement appropriate treatment of NCSE after stroke.

The importance in differentiating between early and late seizure is salient as the occurrence of late seizure results in a higher recurrence rate. Thus, distinguishing categories of post stroke seizure can help determine the need for AED treatment. A previous study found recurrent seizure developed in about 50% of patients who had experienced late seizures but only in approximately 30% of patients with early seizures (Olsen, 2001). Furthermore, in our retrospective study of 104 patients with late seizure after stroke, 29.8% of the patients developed recurrent seizures after a median follow-up of 362 days (Tanaka et al., 2015).

3. New definition and diagnosis of PSE

A commonly-used definition of epilepsy has been the occurrence of two unprovoked seizures, spaced more than 24 h apart (Fisher et al., 2005). Many clinicians have thus hesitated to use AED treatment after the first unprovoked seizure after stroke. Furthermore, it has been noted that some individuals who have had experienced one seizure in combination with other risk factors of epilepsy have the same high recurrence rate as those who have experienced more than two seizures.

In 2014, epilepsy was newly defined (Fisher et al., 2014) by the presence any of the three conditions: *(1) at least two unprovoked (or reflex) seizures occurring greater than 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; (3) diagnosis of an epilepsy syndrome.*

Criterion (1) mirrors the old definition of epilepsy. However, (2) allows the consideration of epilepsy after one seizure, if there is a high risk of having another seizure. Factors increasing the likelihood of seizure include remote structural lesions, such as other stroke damage, central nervous system infection, certain types of traumatic brain injury, diagnosis of a specific epilepsy syndrome, or the presence of other risk factors.

In PSE the risk of subsequent unprovoked seizure after 10 years of follow up was 33.0% (95% CI = 20.7–49.9%) for those who experience first acute symptomatic seizure within 7 days of the stroke onset and 71.5% (95% CI = 59.7–81.9%) for first unprovoked seizure in at least more than one week after stroke (Hesdorffer et al., 2009). A further observational study reported approximately 50% of patients who had received AED after a first seizure episode had at least one recurrence during the follow-up period of 47 months (Hauser et al., 1993). Based on the above findings, only a single unprovoked seizure in stroke patients occurring at least in one week after stroke may result in PSE diagnosis. By using this new definition and diagnosing PSE correctly, an appropriate treatment for PSE patients could be promptly applied, reducing recurrence rate, and improving management in individuals who have experienced post stroke seizure.

However, the new definition has generated some controversy as it has been viewed as applicable for clinical use without sufficient medical evidence. While a clear differentiation exists between the new and previous definitions of seizure, increasing knowledge of PSE will make its application more precise.

4. Risk factors of PSE

Numerous studies have examined risk factors of PSE (Pitkanen et al., 2015). However, because of high heterogeneity and difficultly in diagnosis, relatively few predictors of PSE have been identified (summarized in Table 1).

Most studies have shown the location of cortical infarct region, especially from middle cerebral artery lesions, influenced PSE occurrence (Awada et al., 1999). A meta-analysis reported significantly increased probability of PSE involving cortical lesions from the combined analysis of 12 studies (OR = 2.35, 95%CI = 1.87–2.94, $p < 0.01$) (Zhang et al., 2014b); stroke severity was also identified as a significant risk factor.

Many studies have indicated hemorrhagic, rather than ischemic, stroke is a more likely predictor of PSE (Arntz et al., 2013; Burn et al., 1997). The mechanisms behind PSE following hemorrhage are unclear. However, hemosiderin deposits are thought to cause cerebral irritation leading to seizure (Silverman et al., 2002). Subarachnoid hemorrhage also leads to widespread damage extending into parenchymal component of cortex, which may increase the likelihood of PSE.

PSE is associated with higher severity of initial neurologic deficits and disability after stroke. Conrad, et al. used the National Institute of Health Stroke Scale (NIHSS) to measure stroke severity and found that a higher NIHSS score was significantly associated with PSE (Conrad et al., 2013), suggesting that severe, critical strokes tend to involve wider cortical lesions.