

REVIEW

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Current advances on mechanisms and treatment of post-stroke seizures



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Abstract

Cerebrovascular diseases are among the most common causes of seizures in adults, especially in the elderly. With the increased incidence of stroke, the population with post-stroke seizures has grown, leading to the increased awareness of this disorder in the society. The most common seizure type after stroke is the focal seizure with or without evolution into bilateral convulsive seizures. Post-stroke seizures impair the quality of life, as well as the physical and mental health of those patients. Currently, the pathological and physical processes of post-stroke seizures are not quite clear yet. In this review, we summarize current advances in the pathogenesis, risk factors, and therapeutic targets of post-stroke seizures.

Keywords: Post-stroke seizures, Epilepsy, Pathogenesis, Treatment

Background

Post-stroke seizures are defined as seizures that occur after a stroke without a previous history of epilepsy. Epileptiform waves can be detected with electroencephalography (EEG) recording, and the location of epileptiform discharges is usually in accord with that of the stroke.

Based on the time of seizure onset, post-stroke seizures are referred to as early or late seizures. Early seizures occur ≤ 2 weeks after the stroke, while late seizures occur > 2 weeks after the insult. According to the definition by the International League Against Epilepsy, early seizures alone are not sufficient to make an epilepsy diagnosis as they are thought to be provoked, while a single late-onset seizure qualifies as symptomatic seizures due to the high risk of seizure recurrence within the next 10 years [1]. It has been reported that seizures occur in approximately 5% of subjects after ischemic stroke, of which one third occur within the first 24 h after stroke, and 50% within the first 30 days after stroke [2].

Recent prospective studies have demonstrated that 3.1–21.8% stroke patients develop post-stroke seizures

[3–5]. The wide range may be attributed to the sample size, the inclusion criteria, the definition of post-stroke seizures, and the duration of patient follow-up. Among the newly diagnosed epileptic patients over 60 years old, nearly 50% belong to the post-stroke epilepsy [3]. Meanwhile, the incidence of status epilepticus after stroke is less than 1%. The incidence of post-stroke seizure using recently updated epilepsy definitions was proved to be similar to previous studies in a recent Swedish ischemic stroke cohort study [6]. Notably, Bentes et al. found that the post-stroke seizures are clinically underestimated since most seizures (92%) were electroencephalographic without apparent clinical manifestations [4].

Seizures negatively affect stroke prognosis and the quality of life, in addition to the burdens of in-hospital costs. Thus, the diagnosis and treatment of this disorder are receiving much attention. Here, we will review the research development on post-stroke epilepsy for the purpose of advancing the understanding of both the prevention and treatment of this disorder.

Pathogenesis of post-stroke seizures

Pathogenesis of early seizures

The early epileptic seizures have been demonstrated to be caused by local metabolic disorders and increased release of excitatory neurotransmitters, leading to the

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electrophysiological instability and neurotransmitter imbalance, which facilitate the onset of seizure attack.

Electrophysiological instability

The acute cerebral hemodynamic changes disrupt the local microenvironment, which reduces the neuronal membrane stability within the lesion, and causes excessive discharges. Ischemia and hypoxic insults are demonstrated to cause a sodium pump failure, which leads to increased intracellular Na^+ and cell depolarization. When the accumulation of Na^+ reaches a certain extent inside the cell, calcium channels will be activated, leading to a sudden and quick influx of Ca^{2+} and thus a seizure attack [3]. In addition, neurons within the hippocampus, a region considered to play a crucial role in epileptogenesis, are also susceptible to abrupt ischemic insults and might become an epileptogenic focus [7]. Excessive neuronal excitation is also detected within the surrounding penumbra, which may be due to the disrupted blood supply and hypoxia. Besides, reperfusion injury, hemorrhage and vasospasm are all reported to increase the susceptibility to the seizure attack [3].

Neurotransmitter imbalance

The imbalance between excitatory and inhibitory neurotransmitters is another contributor to the early seizures. In the central nervous system, the excitatory neurotransmitter glutamate and the inhibitory gamma aminobutyric acid (GABA) can be converted into each other by certain enzymes. Upon acute disruption of the hemodynamics, excitatory transmitters such as glutamate are increased, while GABA is denatured. As a result, an increased membrane excitability is induced and finally results in a seizure attack [8]. Besides, elevated adrenaline and decreased levels of dopamine are found to impact the calcium influx and decrease the seizure threshold [9].

It has been reported that early epileptic seizures are less likely to recur compared to the late-onset post-stroke seizures, due to the fact that the epileptogenic factors including ischemia, hypoxia, and brain edema at the early stage after stroke are alleviated as disease progresses. Therefore, the early post-stroke seizures are considered to be self-limited.

Pathogenesis of late seizures

The late-onset post-stroke seizures result from a combination of complex factors including genetic factor, hemodynamic changes, inflammation, neural network reconstitution, glial proliferation, and metabolic disturbance.

Genetic factor

It has been established that about 30% of epilepsy syndromes are inherited, but only a few studies have assessed the genetic roles in epileptogenesis after stroke. Yang et al. have reported that the overexpression of aldehyde dehydrogenase 2 (ALDH2) partially blocked the increased level of malondialdehyde, which reduces the neuron apoptosis in the late stage and inhibits epileptic seizures [10]. Other factors such as CD40/-1C/T polymorphism, *REST*, *HCNI*, miRNAs, and transcription factors like mSin3A are also proven to play a role in regulating epileptogenesis in the late stage after stroke [3].

Neurovascular unit imbalance

In the late stage, the neurovascular integrity is disrupted due to the changes of regional cerebral blood flow, disruption of the blood brain barrier integrity, and inflammation. The neurovascular unit is composed of endothelial cells, neurons, and glial cells. Disruptions of the structural and functional integrity of neurovascular unit result in imbalanced micro-environment around neurons, subsequently causing abnormal discharges and the occurrence of late post-stroke seizures [11].

Disruption of the neuronal network

The epileptic seizures have been defined as a neurologic disorder with neuronal networks involved, rather than a single pathological process. This definition also applies to the post-stroke seizures. The neural network consists of neural circuits, nerve fibers and synapses. The neural repair process occurs in the late stage after stroke, including neurogenesis, integration of new neuronal loops, and synaptic connections. However, maladaptive neurogenesis and synaptic connection may overactivate the neural circuits, thereby increasing the seizure susceptibility [12].

Glial activation

The post-stroke glial proliferation and activation also play a role in epileptogenesis. In the late stage, the proliferation and activation of astrocytes in the cortex may lead to dysfunctions of ion channels, leading to cell depolarization, increased glutamate, and decreased GABA, all of which contribute to the late post-stroke seizure attack [13]. Particularly, the rise in glutamate levels in the setting of acute stroke was suggested as a potential clinically relevant biomarker for the development of post-stroke epilepsy [14]. In addition to astrocytes, oligodendrocytes and microglia may also proliferate after stroke, though their relations with epileptogenesis remain to be explored.

Risk factors for post-stroke seizures

The onset of post-stroke seizures is associated with a series of complex factors, including the type of stroke (ischemic or hemorrhagic), the location and size of the lesion, the severity of the disease, etc.

Observational studies have revealed distinct risk factors for early and late seizures. Intracerebral hemorrhage or cerebral infarction with hemorrhagic transformation, a higher stroke severity or high National institutes of health stroke scale (NIHSS) score, and alcoholism are associated with an increased risk of developing early seizures, while a significant cortical involvement and a higher stroke severity indicate a greater probability of late-onset seizures. A cohort study involving 469 stroke patients conducted from 1982 to 2003 with 20 years of follow up analyzed the incidence of seizures following stroke, and the results confirmed that moderate and severe disability was predictive of post-stroke seizure. No seizure occurred after, for example, lacunar stroke [2]. Besides, the valproic acid monotherapy and the late-onset of seizures have also been reported to be risk factors for post-stroke seizures. However, a meta-analysis which included studies published during 1990–2014, found no significant difference in the probability of late seizure episode between patients with cerebral hemorrhage and those with infarction; neither was gender proved to be the risk factor [15].

Recently, the therapeutic method for stroke has been found to be related with the incidence of post-stroke seizures. The development of reperfusion therapies, including intravenous tissue plasminogen activator (IV-tPA) and endovascular (intra-arterial therapy, IAT) thrombectomy, has caused a 68% increase in the number of ischemic stroke survivors [16]. However, since the endogenous tissue plasminogen activator (tPA) can sensitize the brain via up-regulation of the N-methyl-D-aspartate receptors, which leads to a lower threshold for a hyperexcitable state, the application of r-tPA may also increase the risk of post-stroke seizures. A retrospective cohort study, which recruited 1357 in-hospital patients between 2008 and 2015, found that compared to the medication care patients, there was a 3-fold increase of post-stroke seizures in patients treated with IV-tPA only, and a 5-fold increase in patients treated with IAT only [16]. Another study, however, reported that the incidence of post-stroke seizures was similar between the recombinant-tPA group and the naive group [17]. The discrepancy between the two studies might be explained by whether the analysis was adjusted for prognostic factors for seizure development.

Notably, Galovic et al. have developed a novel prognostic model for predicting late seizures after ischemic stroke, based on five independent risk factors. During the development and validation of a multivariable

prediction model in the study, 1200 participants who had ischemic stroke in Switzerland were recruited. Finally, five variables were selected to generate the model, named as SeLECT (corresponding to Severity of stroke, Large-artery atherosclerosis, Early seizures onset, Cortical involvement, and Territory of middle cerebral artery involvement) [18]. For the severity of stroke, 0 for those with NIHSS scores ≤ 3 , 1 for those with NIHSS scores between 4 and 10, 2 for those with NIHSS scores ≥ 11 ; for the large-artery atherosclerosis, 0 for no, and 1 for yes; for the early seizure (≤ 7 days), 0 for no, and 3 for yes; for the cortical involvement, 0 for no, and 2 for yes; for the territory of middle cerebral artery (MCA), 0 for no, and 1 for yes. Based on this model, a score of 0 was associated with a 0.7% risk of late seizures, while the highest score 9 predicted a 63% risk of late seizures within 1 year. The SeLECT score was validated in 1169 subjects from three independent international cohorts in Germany, Austria, and Italy, and showed good performance for prediction of late seizures after ischemic stroke [18, 19]. However, more studies are needed to validate the reliability of the SeLECT model.

Apart from the risk factors for post-stroke seizures, the risk factors for seizure recurrence are also under investigations. One report showed that young age and male gender are highly suggestive of seizure recurrence after the first onset of post-stroke seizures [20]. Another study reported that a relatively large volume of hematoma is associated with seizure recurrence [21]. A recent hospital-based retrospective study involving 153 patients has identified that the presence of status epilepticus is a predictor for seizure recurrence after early seizures, the young age is indicative of seizure recurrence after late seizures, and the late onset of seizures is an independent predictor for seizure occurrence since early-seizure patients are characterized by a lower likelihood of seizure recurrence and less frequent use of antiseizure medication (ASM) [22].

Treatment of post-stroke seizures

Upon the onset of post-stroke seizures, whether an ASM should be taken remains on debate. ASM are not recommended after stroke for the prevention of seizure attacks, since only one third of early seizure patients and half of late seizure patients would develop post-stroke seizures. A recent study in post-stroke epilepsy patients showed that 27.1% of patients who received ASM treatment after the first epileptic attack developed seizures 1 year later, while 53.8% of patients without ASM treatment did at the same time. Therefore, the authors concluded that ASM treatment should be recommended for post-stroke epilepsy patients [23]. However, when the ASM treatment should be given remains to be discussed. It is generally accepted that the ASM be taken after the

second early seizure attack and the first late seizure attack to prevent the recurrence [16]. However, data from a clinical research demonstrated that early seizures often suggest poor clinical outcomes and increased mortality during hospitalization [3], suggesting that ASM treatment should be given after the first early seizure attack. In an intracerebral hemorrhage model, ASM treatment was found to be poorly associated with the prevention of epileptic attack [21].

Both classic (carbamazepine, valproate, phenytoin, and phenobarbital), and new ASM (oxcarbazepine, lamotrigine, topiramate, levetiracetam, and etc.) can be used for patients with post-stroke epilepsy. The ASM exert anti-epileptic effects via their exact mechanisms including sodium and calcium channel retardation, and regulation of the neurotransmitter imbalance. However, as the mechanisms of early and late seizures are distinct and the pathophysiological change of early seizures is considered to be reversible, it is important to choose appropriate ASM for early and late epilepsies. Phenobarbital has been reported to reduce seizure attacks after stroke in mice [24]. Valproic acid has been shown to reduce post-stroke seizures by inhibiting microglial activation and down-regulating inflammatory mediator release in rat models [25]. A nationwide multi-center questionnaire survey on the management and treatment of post-stroke epilepsy in Japan found that carbamazepine is the most commonly used ASM for post-stroke seizures, followed by valproate and levetiracetam [26]. Recently, compared with the traditional ASM, new ASM are more frequently used with less side effects and fewer drug interactions. A large nationwide study showed that for late-seizure patients, valproic, carbamazepine and new ASM (including oxcarbazepine, topiramate, levetiracetam, and pregabalin) performed better in controlling seizure attacks than phenytoin [27]. Topiramate was proved to be neuroprotective for post-stroke seizures due to its function to reduce the excitatory effects of glutamate and enhance GABA-mediated inhibition [28]. Levetiracetam has been suggested as an alternative for traditional ASM against post-stroke seizures, based on safety and efficacy profiles in clinical studies [29].

Some other drugs have also been reported to have anti-epileptic effects. HMG-CoA reductase inhibitors (statins) were reported to reduce the expression of eNOS, increase the permeability of blood brain barrier, and decrease the expression of Bax, p53, Caspase-3, and inflammatory mediators, thus reducing seizures [30]. Study has shown that statins could reduce the incidence of post-stroke seizures, which might be attributed to the inhibitory effect on glial proliferation [31]. Statin was also proved to reduce the risk of post-stroke seizure, especially with intensive [32, 33]. Mild hypothermia was also reported to reduce the risk of developing post-

stroke seizures, together with down-regulations of Notch 3 and Notch 4 [34].

Conclusion and future perspective

The post-stroke seizures negatively affect the prognosis of stroke, including the length of stay, disability rate and mortality. It is generally accepted that early seizures have a greater impact on patients' prognosis than late seizures do. Various models of post-stroke seizures provide explanations for the pathogenesis and physiological process of epilepsy. However, it is more likely that a combination of factors contributes to the post-stroke seizure attacks. The mechanisms of post-stroke seizures remain to be clarified, and further preclinical and clinical research is needed to find out new targets for the treatment and prevention of post-stroke seizures.

Abbreviations

@@EEG: Electroencephalography; GABA: Gamma aminobutyric acid; tPA: Tissue plasminogen activator; NIHSS: National institutes of health stroke scale; MCA: Middle cerebral artery; ASM: Antiseizure medication ; IAT: intra-arterial therapy; IV-tPA: intravenous tissue plasminogen activator; ALDH2: aldehyde dehydrogenase 2

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Authors' contributions

FY drafted the manuscript for intellectual content, FL and XB revised the manuscript, and approved the final manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors gave consent to publication of this review.

Competing interests

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