Post-stroke seizures: review article

Abstract. There is a tendency towards growing number of strokes in aging population. One of the most significant complications of stroke is post-stroke seizures (PSS), which cause nearly 11% of all cases of epilepsy. The most important risk factors of seizures after stroke are severity of the stroke, involvement of the cortex and intracerebral hemorrhage. There are two main forms of PSS — early- and late-onset seizures. The pathogenesis of early-onset seizures is mainly due to cytotoxic and metabolic changes in the ischemic focus in contrast to late-onset seizures, which mostly occur as a result of persistent changes in nervous system excitability. There are following types of seizures in adult patients with post-stroke complications: simple partial, generalized tonic-clonic and generalized seizures. Evaluation of electroencephalography and computed tomography results is an important diagnostic tool of the first line. At the same time, brain magnetic resonance imaging and magnetic resonance angiography are the more preferable methods of neuroimaging due to their more informative grade in detecting cortical malformations, small lesions and cavernomas. Pharmacological management of PSS is traditionally divided into two main categories: prophylactic and symptomatic treatment. Prophylactic antiepileptic treatment in stroke patients, including those with intracerebral hemorrhage to prevent an attack, is not recommended by the American Heart Association and European Stroke Organisation guidelines. Some authors indicate that diuretics, in particular thiazides and furosemide, may be protective, reducing the risk of seizures. Carbamazepine, sodium valproate, lamotrigine, oxcarbazepine or gabapentin are the most used symptomatic drugs recommended as a first-line treatment.

Keywords: epilepsy; stroke; seizures; treatment

Introduction

There is an increase in the number of strokes around the world and therefore, various complications of stroke have a significant impact on the outcome and quality of life after stroke. The most significant complication of stroke is post-stroke seizure (PSS). It has been reported that cerebrovascular disorders account for 11% of all cases of epilepsy [1]. Furthermore, for the elderly population, stroke is the most common cause of epilepsy [2, 3]. In patients > 60 years of age, almost 50% of first seizures occur due to ischemic stroke [4]. Silverman et al. [5] have stated that seizures occur in 5 to 20% of all stroke patients but recurrent seizures occur only in a small number of patients. According to one study, the risk of late seizures is 4% one year after a stroke, while 5 years after it, this risk is 8% [6]. The main important risk factors of seizures after stroke are the severity of the stroke, involvement of the cortex and bleeding. In particular, seizures are rather a consequence of hemorrhagic than ischemic stroke [7]. Bladin et al. [8] reported that the incidence of seizures was 10.6% among 265 patients with intracerebral hemorrhage vs 8.6% among 1,632 with ischemic stroke. Another prospective series [9] reported that seizures occurred in 4.4% of 1,000 patients, including 15.4% with lobar or extensive intracerebral hemorrhage, 8.5% with subarachnoid hemorrhage, 6.5% with cortical infarction, and 3.7% with hemispheric transient ischemic attacks.

Classification

Early- and late-onset seizures are the two main forms of PSS. The classification of post-stroke seizures is based on their timing after stroke onset. The time between early- and late-onset seizures is two weeks. In turn, an early-onset seizure can occur within 24–48 hours up to 1 week after a stroke. Late-onset seizures occur 2 weeks after stroke onset [10]. Szaflarski et al. [11] found that the
incidence of early-onset seizures in the first 24 hours of a stroke was 3.1%. Late-onset seizure has a peak within 6–12 months after a stroke. The frequency of late seizures is from 3 to 4.5% [12].

There is some confusion in the literature regarding the definitions of late-onset seizures and post-stroke epilepsy. Some authors do not consider late-onset seizures as post-stroke epilepsy, whereas other studies defined the latter in case of two unprovoked seizures, with an interval > 24 hours, that occurred after a stroke [13].

Pathophysiology

The pathogenesis of early-onset seizures is mainly due to cytotoxic and metabolic changes in the ischemic focus such as glutamate excitotoxicity, depolarization, hypoxia and global hypoperfusion in the brain structures. Depolarization is caused by an increase in intracellular Ca$^{2+}$ and Na$^+$, which is observed during acute ischemic injury, leads to paroxysmal discharge of nerve cells. These ionic shifts play an important role in epileptogenesis [14]. An imbalance of neurotransmitters is also crucial in the pathogenesis of early post-stroke seizures. In particular, there is an increase in the level of the excitatory neurotransmitter glutamate and a decrease in the content of the inhibitory neurotransmitter γ-aminobutyric acid. Glutamate excitotoxicity is a well-established mechanism of cell death in experimental stroke models [15]. The degree of damage to nerve cells, edema, which may result in the breakdown of compensatory antiepileptic systems, is also important. Unlike early-onset seizures, late-onset seizures occur as a result of persistent changes in nervous system excitability. Late-onset seizures are explained by the presence of post-ischemic fibrosis or cortical atrophy in the brain, emphasizing the role of the focus as a source of seizures [10]. The processes of glial scarring, as well as the replacement of healthy cell parenchyma with neuroglia and immune cells supporting abnormal neuronal excitability, are considered the most likely cause of late seizures [1, 5].

Clinical manifestation

It should be borne in mind that most seizures are caused by focal lesions. In a study [10] about one-third of cases presented with tonic-clonic (generalized) seizures and the remaining two-thirds usually present with partial/local seizures. Early-onset seizures usually present with a focal onset while generalized tonic-clonic seizures are more common in late-onset seizures [10]. Cordonnier et al. [16] observed the following types of seizures in adult patients with post-stroke epilepsy: simple partial (in five cases), generalized tonic-clonic without signs of focal onset (in three cases), and one of 202 stroke patients had secondary generalized seizures. According to Conrad et al. [17], in almost 41% of patients, seizures were classified as partial, and 57% had generalized seizures. The frequency of status epilepticus is about 9% of all cases of post-stroke event [10]. Patients with early post-stroke seizures had the highest risk of status epilepticus. Sadie Gümüşayaya et al. [18] reported status epilepticus in nearly 77.1% of patients with early post-stroke seizures. Status epilepticus had been registered in patients with acute ischemic stroke more often than with hemorrhagic stroke (62 and 21.62%, respectively), and with stroke in the left hemisphere (54%) compared to those with stroke in the right hemisphere (27%), bilateral (10.81%), and intraventricular (8.1%) [18].

The localization and size of the ischemic lesion also affect the timing of the occurrence of post-stroke attacks. One study found that patients with cortical and larger infarction involving the middle cerebral artery had a significantly higher risk (33%) of late-onset seizures [19]. According to another study [20], 14 (13.7%) of 105 patients had post-stroke seizures. The seizures were focal and motor and began with clonic movements in the face and hands. In 11 patients, convulsions were accompanied by a violation of awareness, as well as focal convulsions with a motor onset with clonic movements of the face and limbs, with transformation into bilateral tonic-clonic convulsions. Late-onset seizures were observed in 13.5% of 615 long-term survivors with a hemorrhagic stroke [21].

Diagnosis

Modern technologies allow us to compare the clinical picture with the results of electroencephalography (EEG) and computed tomography that are extremely important diagnostic tools to determine the cause of seizures after a stroke. At the same time, brain magnetic resonance imaging and magnetic resonance angiography are the preferred imaging methods, as they are more informative in detecting cortical malformations, small lesions and cavernomas [10]. Nowadays, EEG is one of the most used diagnostic methods in case of seizures. According to several studies [13], the main types of EEG disorders in patients with stroke are: 1) non-specific abnormalities; 2) interictal epileptiform abnormalities; 3) ictal abnormalities. It was also found that EEG can be normal in about 5% of cases, which in turn does not exclude epileptogenicity [10]. In addition, it is known that about 10% of patients without epilepsy have non-specific EEG abnormalities, and about 1% can have interictal epileptiform abnormalities without seizures [22]. Another study [23] found that the absence of EEG disturbances did not exclude the occurrence of acute symptomatic seizures. At the same time, the presence of periodic discharges on the EEG was a predictor of epileptiform activity. With regard to non-specific manifestations on the EEG, focal or diffuse slowing may indicate a risk of seizures [24]. A study by Mecarelli et al. [25] analyzed the EEG of 232 stroke patients. Focal or diffuse slowing was found in 84% of them and lateralized periodic discharges, which are related to interictal epileptiform abnormalities, — in 6%. It was also found that 85.7% of patients with lateralized periodic discharges had seizures. Therefore, lateralized periodic discharges may be an indicator of post-stroke seizures. As a rule, EEG is performed in a standard regimen (20–45 min). Also, it can be conducted in the extended form (from 1 to 2 hours), or even daily monitoring of computed EEG is carried out [13]. But there is still no definite guidance regarding how to conduct an EEG and in which patients with a stroke it should be performed. Also, there are no clear instructions regarding the optimal time for EEG or registration of epileptic activity.
Treatment

Usually, pharmacological management for PSS is divided into two main categories; prophylactic treatment and symptomatic treatment. The American Heart Association and European Stroke Organisation have stated that the prophylactic antiepileptic treatment in stroke patients, including people with intracerebral haemorrhage to prevent an attack, is not recommended [13]. In addition, the interaction between antiepileptic drugs and nimodipine, which is used to prevent vasospasm in subarachnoid hemorrhage, may have deleterious effect, in particular, there is a decrease in the concentration of nimodipine in plasma [26]. Regarding prophylactic treatment, some studies are indicating that diuretics, in particular thiazides and furosemide, may have protective effects that reduce the risk of seizures [27]. Statins, which are used in patients for primary and secondary prevention of cardiovascular events, can have an anticonvulsant and anti-inflammatory effect. Guo et al. [28] found that statin use was associated with a reduced risk of epilepsy in patients with post-stroke seizures. Perhaps, the presence of an antiepileptogenic effect of these drugs may be due to the impact on the stabilization of blood-brain barrier. There are disagreements on the timing of prescribing antiepileptic drugs. Some authors recommend initiating the use of an antiepileptic drug after an early post-stroke seizure, while others recommend starting treatment only after a late seizure [29]. There is a piece of evidence that about 88% of cases of monotherapy may control seizures after stroke [10]. According to the recommendations of the National Institute for Health and Care Excellence and Scottish Intercollegiate Guidelines Network, the first-line therapy for partial seizures and secondary generalized seizures consists of carbamazepine, sodium valproate, lamotrigine, or oxcarbazepine [30, 31]. Along with this, gabapentin is also used as the first-line drug [32]. As an alternative, phenytoin, phenobarbital and clonazepam monotherapy can be used [10]. Some studies demonstrated no difference in effectiveness of levetiracetam and carbamazepine or any significant advantage of one of the drugs, but levetiracetam is better tolerated, also when it is used for one year as a primary monotherapy for focal epilepsy in the elderly [33, 34].

It was found that early-onset seizures can increase the risk of repeated attacks by no more than 33%, which is slightly higher than a single unprovoked attack in cases of a different etiology [13]. However, several studies are indicating that treatment for 1 month may help prevent late-onset seizures [13]. As for late seizures, the risk of recurrent seizures increases to 90% [10]. Taking into account the current studies, there were no significant differences in the effectiveness of the different antiepileptic drugs used, both newer and older generations [13]. Combined medications should be used carefully, especially the combination of valproate and topiramate as it can lead to valproate-induced encephalopathy [35]. Based on the fact that elderly people have reduced metabolism, in particular hepatic metabolism, carbamazepine that affects the latter should be administered in minimal doses. The same applies to levetiracetam or pregabalin, which influence renal metabolism. Therefore, in this case, creatinine clearance control is very important [36]. Moreover, the interaction between antiepileptic drugs and other agents should be considered. A study [37] has shown that drugs such as carbamazepine, phenytoin, phenobarbital and primidone can reduce the effectiveness of oral anticoagulants, calcium antagonists, steroids, antimicrobial and antitumor drugs. Valproic acid increases the concentration of phenobarbital and lamotrigine [37]. Taking into account the comorbidities in stroke patients and the need for them to use anticoagulants, according to some authors [38], the use of novel oral anticoagulants is not a clear contraindication for using levetiracetam in the treatment of post-stroke epilepsy. Recent study indicates that eslicarbazepine acetate may be the antiepileptic drug of choice for the treatment of patients with focal seizures due to its good tolerability [39].

Conclusions

The significant prevalence of cerebrovascular diseases and their role in the occurrence of post-stroke epilepsy determine a comprehensive and systematic approach to both primary prevention and the subsequent treatment of this pathology. One of the leading mechanisms of the occurrence of post-stroke epilepsy is cytotoxic and metabolic changes in the stroke area. Early-onset seizures usually present with a focal onset while generalized tonic-clonic seizures are more common in late-onset seizures. Among the diagnostic capabilities, EEG is the optimal diagnostic tool in seizures. Treatment with diuretics and statins as a prophylactic treatment of seizures should be studied. As the first-line drugs for symptomatic treatment, carbamazepine, sodium valproate, lamotrigine, oxcarbazepine or gabapentin are recommended.

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Огляд /Review/

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Постінсультні судоми: оглядова стаття

**Резюме.** Спостерігається тенденція до збільшення числа інсультів у старіючого населення. Одним з найбільш значних ускладнень інсульту є постінсультні судоми, що обумовлюють майже 11 % всіх випадків епілепсії. Найбільш важливими факторами ризику судом після інсульту є його тяжкість, ураження кори і внутрішньомозковий крововилив. Існує дві основні форми постінсультних судом — із раннім і пізнім початком. Патогенез ранніх судом в основному обумовлений цитотоксичними і метаболічними змінами в ішемічному осередку на відміну від судом із пізнім початком, що найчастіше виникають у результаті стійких змін збудливості нервової системи. У досліджених пацієнтів із постінсультними судоми виділяють наступні види судом: прості парціальні, генералізовані тоніко-клонічні і генералізовані. Оцінка результатів електроенцефалографії і комп’ютерної томографії — важливий діагностичний інструмент першої лінії. У той же час магнітно-резонансна томографія головного мозку і магнітно-резонансна ангиографія є кращими методами нейровізуалізації, оскільки вони більш інформативні при виявленні кортикальних порушень, невеликих ушкоджень і каверн. Фармакологічне лікування постінсультних судом традиційно ділиться на дві основні категорії: профілактичне і симптоматичне. Профілактичне лікування антиконвульсантами пацієнтів з інсультом, у тому числі з внутрішньомозковою крововтечкою, для запобігання нападу не рекомендується в інструкціях Американської кардіологічної асоціації та Європейської організації з боротьби з інсультами. Деякі автори вказують, що диуретики, зокрема тіазиди і фуросемід, можуть мати захисну дію, знижуючи ризик судом. Карбамазепін, валпроат натрію, ламотріджин, окскарбазепін або габапентин є найбільш популярними симптоматичними препаратами, рекомендованими як терапія першої лінії.

Ключові слова: епілепсія; інсульт; судоми; лікування

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Постинсультные судороги: обзорная статья

**Резюме.** Наблюдается тенденция к увеличению числа инсультов у стареющего населения. Одним из наиболее значительных осложнений инсульта являются постинсультные судороги, которые обусловливают почти 11 % всех случаев эпилепсии. Наиболее важными факторами риска судорог после инсульта являются его тяжесть, поражение коры и внутримозговое кровоизлияние. Существуют две основные формы постинсультных судорог — с ранним и поздним началом. Патогенез ранних судорог в основном обусловлен цитотоксическими и метаболическими изменениями в ишемическом очаге в отличие от судорог с поздним началом, которые чаще всего возникают в результате стойких изменений возбудимости нервной системы. У взрослых пациентов с постинсультными осложнениями выделяют следующие типы судорог: простые парциальные, генерализованные тонико-клонические и генерализованные. Оценка результатов электроэнцефалографии и компьютерной томографии — важный диагностический инструмент первой линии. В то же время магнитно-резонансная томография головного мозга и магнитно-резонансная ангиография являются более информативными при обнаружении кортикальных нарушений, небольших повреждений и каверн. Фармакологическое лечение постинсультных судорог традиционно делится на две основные категории: профилактическое и симптоматическое. Профилактическое лечение антиконвульсантами пациентов с инсультом, в том числе и у людей с внутримозговым кровоизлиянием, для предотвращения приступа не рекомендуется в руководствах Американской кардиологической ассоциации и Европейской организации по борьбе с инсультами. Некоторые авторы указывают, что диуретики, в частности тиазиды и фуросемид, могут иметь защитное действие, снижая риск судорог. Карбамазепин, валпроат натрия, ламотриджин, окскарбазепин или габапентин являются наиболее часто используемыми симптоматическими препаратами, рекомендованными в качестве терапии первой линии.

Ключевые слова: эпилепсия; инсульт; судороги; лечение