RISK FACTORS FOR THE DEVELOPMENT OF SYMPTOMATIC EPILEPSY IN PATIENTS DIAGNOSED WITH STROKE

Biljana Živadinović1,2, Aleksandra Lučić Prokin3,4, Jelena Živadinović5, Aleksandar Stojanov2

Stroke is one of the leading causes of mortality in older population. Little less than 50% of patients with stroke, remain with different degrees of disabilities and consequences. Symptomatic epilepsy (PSE) is one of them. The aims of the study were to determine: the frequency of PSE in the group of examinees, the difference in the frequency of PSE in the ischemic stroke and intracerebral hemorrhage (ICH) group, the influence of the size and location of the lesion, as well as the influence of comorbidity on the occurrence of PSE.

This prospective study analyzed patients with the first stroke of ischemic and hemorrhagic genesis, with the follow up period of two years. Out of the total of 536 patients, 267 patients (aged 47-92) who had the first stroke, were analyzed. In the control group (n = 246) after the stroke, PSE did not develop and the other group (n = 21) included patients who had PSE. Cortical and subcortical lesions had a statistically significant (p < 0.05) influence on the development of epileptic seizures after the stroke. A statistical significance between the size of the lesion as well as type of stroke and PSE was not determined. Combination of cardiovascular and pulmonary disease was statistically significantly more often associated with the development of PSE after the stroke (p < 0.05).

The frequency of PSE in the examined group was 7.86%. Younger age, as well as cortical and subcortical lesion were shown to be statistically significant for the occurrence of PSE. The presence of cardiac and pulmonary disease significantly increases the risk of PSE. Although the significance of ICH and big lesion for the onset of PSE has been described in literature, we have not found statistical significance regarding their impact on PSE occurrence in our experimental group of patients.


Key words: risk factors, epilepsy, stroke

Introduction

Stroke is defined as a sudden loss of brain functions of various degrees, from focal to global, caused by insufficient or complete disruption of blood flow in a specific region of the brain or by bursting of a blood vessel, which causes bleeding (1). It is caused by brain blood vessel occlusion, which is induced thrombosis or embolism, material from the heart or large blood vessels, small blood vessel diseases, systemic hypoperfusion or venous thrombosis. Hemorrhagic stroke is a consequence of bursting of a blood vessel of vascular malformation with intraparenchymal hemorrhage into the chamber system or subarachnoid space. Besides the already present incapacitation related to motoric and non-motoric consequences of the stroke, the development of post stroke symptomatic epilepsy (PSE) significantly contributes and additionally incapacitates the patient (2).

The seizure in symptomatic epilepsy (SE) are a consequence of structural damage of the brain or of certain brain function of various types. Symptomatic epilepsy represents the appearance of epileptic seizures some time after the primary brain disorder without a provoking event. Majority of experts agree that many symptomatic lesions generate permanent predisposition for repeated spontaneous seizure with probability equal to or higher than the probability for new seizure after two spontaneous seizures (≥ 75%) (3). The risk for developing epilepsy after the stroke is considered seven times higher than in normal population (4).
The etiopathogenesis of SE epileptogenesis is explained by pathological changes that develop in the damaged brain tissue after the stroke. This process is composed of a cascade of morphological and biological changes in the neurons and glial cells, which lead to hyperexcitability of the nervous tissue (5). The pathogenesis of early seizures depends on local ionic imbalance and the release of high level of excitotoxic neurotransmitters (glutamate) which leads to extended depolarization of the neurons, which is described in the penumbra zone (6). The inflammation and remodeling of synaptic networks of neurons reduce the convulsion threshold of neurons. Gliosis, the death of potentiating neurons, and repeated seizures cause meningoencephalic cicatrix, remodeling of neural networks, hyperexcitability of neurons and are the basis of epileptogenesis and subsequent seizures (7). The very risk of repeated seizures as well as the pathophysiology of the development of early into late seizures are not clearly determined (5, 8, 9).

The recommendations concerning treatment and application of antiepileptic therapy (AET) in PSE are controversial and with the first unprovoked seizures mostly direct to individual approach, without clear evidence that the application on AET after the first unprovoked seizure significantly impacts long-term remission of the diseases (5). Before deciding to include AET, it is important to estimate its ictogenic effect, the range of the safety profile and counterindicators as well as the smaller number of interactions with other drug groups that stroke patients use in everyday treatment (primarily with antiaggregant drugs and anticoagulant therapy).

This paper aims at determining the risk factors for selecting patients with stroke in whom PSE will develop and who would benefit from AET so that their timely application could prevent severe forms of PSE and enable its successful control and treatment.

**Materials and methods**

This prospective study included 267 patients with the first stroke treated between January 1 and December 31, 2016. The follow up of all patients lasted for the following two years. Out of the total number, 246 patients had no symptomatic epilepsy and they composed the control group whereas 21 patients who developed epileptic seizures after the stroke during the two-year follow-up period composed the experimental group. All patients and their families are informed about investigation and they gave signed agreement for including in this study. Besides that, local Ethics Committee approved this study.

A detailed medical history was taken from all patients. Significant information included the beginning of epileptic seizures, whether the seizure was an initial symptom, whether the seizure appeared within the first seven days from the stroke or later. The severity of neurological findings was graded according to the NIHSS Scale of the American National Institute of Health (10). The following steps included standard laboratory testing, computerized tomography (CT) or magnetic resonance imaging (MRI) of the endocranium (in patient with small or undefined lesion as well as a lesion in the area of the brainstem) and the patients were monitored for internal medicine comorbidities.

Both groups were analyzed with regard to gender and age. The study did not include patients with arteriovenous malformations of the brain blood vessels, patients with history of previous epilepsy of any genesis, patients with recurrent stroke, patients with transitory ischemic attacks and with previous alcoholism as well as patients who were taking antiepileptic therapy for other indications or who were taking large doses of benzodiazepine.

The analysis of data obtained after the research was done using IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 18.0. Armonk, NY: IBM Corp.

Cluster analysis (k-means clustering method) was used for additional classification of groups based on NIHSS values, i.e. age and NIHSS values. Statistical analysis of data included the use of Chi-squared ($\chi^2$) independence test, Mann-Whitney test and Kruskal-Wallis test. Statistically significant connection was determined if $p < 0.05$.

Binary logistic regression analysis was used to examine the model for the prediction of binary outcome, in our case the appearance of epileptic seizure. The model included independent variables, which had low p values in the previous part of the statistical analysis ($p < 0.4$), which meant that they could significantly impact the appearance of epileptic seizures after stroke.

**Results**

Figure 1 shows the age of patients from the control and experimental group. Average age of patients in the experimental group was 67.19 and 75.5 in the control group. Mann-Whitney test showed that the group of patients who developed epileptic seizures after the stroke was significantly younger ($p = 0.009; Z = -2.618$).

The distribution of patients based on the type of stroke and defined group is shown in Figure 2. Although the presence of PSE in the ICH group is more than twice as big, no statistically significant difference in the number of patients with regard to the type of stroke and the defined group was determined ($\chi^2 = 1.55; p = 0.213$, phi = 0.097).

With regard to the size, the lesions after the stroke were classified into small and big. Small lesions included changes $\leq 3$ cm in diameter while big lesions included changes with individual or collective size $> 3$ cm. No statistical significance was determined between the size of lesions and the appearance of epileptic seizures ($\chi^2 = 1.536; p = 0.215$; phi = 0.09). Figure 3 shows the distribution of patients with regard to the size of lesion after the stroke and the defined group. Twice as big number of patients with a big lesion (bigger than 3 cm) was observed in the PSE group.
**Figure 1.** Patient age in the control and experimental groups

**Figure 2.** Distribution of patients with regard to the type of stroke and the defined group ($\chi^2 = 0.817; p = 0.366$)

**Figure 3.** Distribution of patients with regard to lesion size after the stroke and the defined group ($\chi^2 = 1.536; p = 0.215$)
A detailed analysis of 146 patients with a lesion in the middle cerebral artery flow, the lesions were first classified into deep lesions and those with cortical and subcortical location. The distribution of lesions classified in this way, according to the defined groups of patients is shown in Figure 4. The depth of the lesion has a statistically significant impact on the development of epileptic seizures after the stroke ($\chi^2 = 3.96; p = 0.047; \phi = 0.156$) in the sense that the lesions with cortical and subcortical location statistically significantly impacted the development of epileptic seizures after the stroke. With the same statistical significance, the deep lesions were more often joined with strokes after which the epileptic seizures did not develop.

Figure 5 shows the distribution of patients with regard to comorbidities and the development of epileptic seizures. Comorbidity had no statistical significance in the development of epileptic seizures after the stroke ($\chi^2 = 9.831; p = 0.132, \text{Cramer's } V = 0.192$). The experimental group had comorbidities of oncological, cardiological, nephrological and pulmonological origin, as well as co-occurring cardiological and pulmonological morbidity and cardiological and nephrological morbidity. The co-occurring cardiological and pulmonological morbidity was statistically significantly correlated with epileptic seizures after the stroke in the sense that a combination of cardiological and pulmonological disease was statistically significantly more often joined with the development of epileptic seizures after the stroke ($p < 0.05$).

![Figure 4. Distribution of patients with lesion in the ACM circulation with regard to the depth of lesion and defined group](image1)

![Figure 5. Distribution of PSE findings in patients from the control and experimental group with regard to the presence of comorbidities](image2)
Logistic regression analysis was used to determine the impact of several factors on the probability that a patient will develop epileptic seizures after the stroke (Table 1). The model contained nine independent variables which had lower p values obtained by the previous analysis (age, type of stroke, the circulation where lesion is located, lesion size, lesion level with regard to cerebral cortex, type of comorbidity, NIHSS values, group according to cluster analysis) and defined by previous analysis. The whole model with all the predictors was statistically significant, $\chi^2 (6, n = 267) = 25.523, p = 0.03$ which shows that the model differentiates between the examinees who did and those who did not develop epileptic seizures after the stroke. The model completely explains between 9.1% (Cox & Snell R square) and 21.5% (Nagelkerke R square) variables and it correctly classifies 92.1% of cases.

Table 1. Probability predictions that a person will develop epileptic seizures after the stroke

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Standard error</th>
<th>Wald</th>
<th>No. of deg. of freedom</th>
<th>p</th>
<th>OR</th>
<th>95% confidence interval for cotient probability</th>
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<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Upper limit</td>
</tr>
<tr>
<td>Age &gt; 65 y.o.</td>
<td>-1.076</td>
<td>0.572</td>
<td>4.042</td>
<td>1</td>
<td>0.039</td>
<td>0.335</td>
<td>0.125</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1.393</td>
<td>0.755</td>
<td>3.405</td>
<td>1</td>
<td>0.065</td>
<td>4.027</td>
<td>0.917</td>
</tr>
<tr>
<td>ACM circulation</td>
<td>-0.514</td>
<td>0.942</td>
<td>0.298</td>
<td>1</td>
<td>0.585</td>
<td>0.598</td>
<td>0.094</td>
</tr>
<tr>
<td>Lesion size &gt; 3 cm</td>
<td>0.503</td>
<td>0.56</td>
<td>0.81</td>
<td>1</td>
<td>0.368</td>
<td>1.654</td>
<td>0.553</td>
</tr>
<tr>
<td>Cortical and subcortical lesions</td>
<td>1.236</td>
<td>0.938</td>
<td>3.736</td>
<td>1</td>
<td>0.048</td>
<td>3.441</td>
<td>0.548</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.731</td>
<td>0.561</td>
<td>1.696</td>
<td>1</td>
<td>0.193</td>
<td>2.282</td>
<td>0.78</td>
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<tr>
<td>Without comorbidities</td>
<td>6.866</td>
<td></td>
<td>7</td>
<td>0.482</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiological and cerebral comorbidities</td>
<td>0.403</td>
<td>0.563</td>
<td>0.511</td>
<td>1</td>
<td>0.474</td>
<td>1.496</td>
<td>0.496</td>
</tr>
<tr>
<td>Pulmonary comorbidities</td>
<td>-18.08</td>
<td>10297.5</td>
<td>0</td>
<td>1</td>
<td>0.999</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nephrological comorbidities</td>
<td>-18.942</td>
<td>10467.69</td>
<td>0</td>
<td>1</td>
<td>0.999</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiological and pulmonological comorbidities</td>
<td>2.321</td>
<td>1</td>
<td>5.384</td>
<td>1</td>
<td>0.02</td>
<td>10.191</td>
<td>1.434</td>
</tr>
<tr>
<td>Cardiological and nephrological comorbidities</td>
<td>-18.415</td>
<td>12262.91</td>
<td>0</td>
<td>1</td>
<td>0.999</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Oncological</td>
<td>0.436</td>
<td>1.248</td>
<td>0.122</td>
<td>1</td>
<td>0.727</td>
<td>1.546</td>
<td>0.134</td>
</tr>
<tr>
<td>NIHSS 7-12</td>
<td>-0.724</td>
<td>0.519</td>
<td>1.946</td>
<td>1</td>
<td>0.163</td>
<td>0.485</td>
<td>0.175</td>
</tr>
<tr>
<td>Cluster 2 (younger and lower NIHSS)</td>
<td>0.615</td>
<td>0.602</td>
<td>2.045</td>
<td>1</td>
<td>0.05</td>
<td>1.85</td>
<td>0.569</td>
</tr>
</tbody>
</table>

B - unstandardized coefficient of independent variable; Std - standard error; Wald - contribution of independent variable; No. of deg. of freedom - number of degrees of freedom; OR - odds ratio.
As shown in Table 1, only one independent variable provided a statistically significant contribution to the model. The strongest predictor of epileptic seizures after stroke was cardiological and pulmonological comorbidity whose odds ratio (OR) is 10.191. This shows that the examinees who have cardiological and pulmonological comorbidity 10 times more often develop epileptic seizures than those who do not have these two comorbidities along with other factors from the model being equal.

According to their influence the following factor were: age (as binomial variable: > 65 years and ≤ 65 years), location of changes on the level of cerebral cortex and subcortically and group 2 according to cluster analysis which described younger patients with lower NIHSS values.

Age had 0.341 OR, which shows that patients over 65 years of age develop epileptic seizures after stroke 3 times less often than patients under 65 whereas other factors are equal and controlled.

The next independent variable that statistically significantly impacts the development of epileptic seizures is the location of changes on the level of cerebral cortex and subcortically with OR 3.411. Epileptic seizures after the stroke are 3.411 times more frequent in patients with cortical and subcortical changes than in patients with changes in the deep structures of the central nervous system, when the other factors from the model being equal.

The last independent variable according to significance is group 2 in cluster analysis which described younger patients with lower NIHSS values. These patients developed epileptic seizures after stroke 1.85 times more often than the older patients with higher NIHSS with other factors from the model being equal. These three factors have a 95% confidence interval which includes number 1 (age: 95% CI 0.125-6.953; location of changes in the cortical and subcortical level: 95% CI 0.5-21.6; group 2 in the cluster analysis that described younger patients with lower NIHSS: 95% CI 0.695 - 6.021).

Discussion

PSE incidence after the stroke, which is available in literature, is within the 3-30% range (11, 12). In our research, this percentage is 7.86% because out of 267 patients with stroke, 21 had the clinical picture of PSE and composed the experimental group. The remaining 246 patients who did not develop PSE after the two-year follow up period, composed the control group.

Patients age in the control group was between 47 and 92, whereas in the experimental group the youngest patients was 50 and the oldest was 85 years old. Younger patients were statistically significantly in the PSI group (Figure 1).

Younger age is described as a separate risk factor for PSE (13-16). Cumulative risk for developing PSE in the group of young adults with intracerebral hemorrhage, ischemic stroke and transitory ischemic attack was 31%, 16% and 5% respectively (16). Contrary to increased frequency of PSE in the group of patients under 65 (17, 18), some authors also had other findings where higher frequency of PSE was recorded in patients over 84 years of age (19).

Sarecka et al. (20) showed a higher frequency of PSE in men. Graham et al. (21) found that gender had no impact on PSE development.

Numerous research has been conducted to investigate the type of stroke as risk factor and its relation to PSE. Along these lines, intracerebral hemorrhage is listed as the second most significant risk factor for the development of PSE. It is believed that PSE is more frequent in the group with hemorrhagic compared to ischemic stroke (13, 14, 22). In our research, there is a significantly higher number of patients with PSE in the group with ischemic stroke (15%) compared to patients with ICH (7%) which is in accordance with the literature data (23) (Figure 2).

The size of the lesion is also a significant risk factor for PSE (5, 24). Our patients with stroke were classified into two groups - with lesion bigger than 3 cm and patients with lesion smaller than 3 cm. There is a significantly higher number of patients with PSE with a lesion bigger than 3 cm (67%) compared to 33% of patients with a lesion smaller than 3% but this finding had no statistical significance (Figure 3). The impact of the lesion size on the development of PSE is described by other authors (25, 26), concluding that a bigger lesion represents a higher risk for PSE.

Out of 146 patients with stroke in ACM circulation, the lesions were classified into those with cortical and subcortical presentation while the other group included the patients with lesions in the deep brain structures. Our results show a statistically significant correlation between PSE and cortical and cortical lesions in the first group while deep lesion had lower risk for PSE (Figure 4). Other authors also had similar results pointing out the significance of cortical presentation of stroke for the development of PSE (17, 18). Contrary to that, some research showed no significance of cortical lesion for the development of PSE (27, 28).

The presence of other comorbidities (cardiovascular disease, lung disease, malignancy, renal insufficiency, hematological diseases) was significant only in cases with a co-occurring pulmonological (HOBP) and cardiovascular (condition after cardiac arrest, absolute arrhythmia, pacemaker insertion, coronary artery bypass) disease. Independently, all other comorbidities and co-occurring diseases had no statistical significance for the development of PSE after stroke (Figure 5).

Available literature mentions severity of stroke as a significant factor for the occurrence of PSE (13, 18, 29). The design of our study which required a two-year follow up of patients with stroke probably impacted the NIHSS score values where the most severely diseased patient had a score of 14. Patients with higher score died and were not part of the research. A comparison of age and severity of stroke showed that in the PSE group, the younger patients with lower NIHSS score were statistically significantly more dominant (Table 1). These results are in accordance with previous research (17, 25).

The precise mechanism for the occurrence of PSE is not completely clarified. It is believed that
Hyperexcitability is at the basis of the process (24, 30). The mentioned ischemic cascade which causes cell death is composed of numerous components (energetic metabolism breakdown, excitatory neurotransmitters release, primarily glutamate, disturbance of Ca, Na, Cl, K ion homeostasis, activation of cell enzymes, release of free radicals, damage to cell organelles, cell death). The probable mechanisms are considered to be inflammatory reaction, perforation of synaptic networks, hereditary predisposition which determines the degree sensitivity of neurons to ischemia and inflammation (9, 18).

Glial cells have an important role in epileptogenesis. They have a direct impact on neural excitability, release of energy, recovery of cells after injuries and infections. The pathology of glial cells is associated with numerous neurologic diseases, first of all mesial temporal epilepsy, hippocampal sclerosis, cortical dysplasia, tuberous sclerosis. The experimental models of epilepsy show a significant abnormality in glial cell activity which is considered a determining factor for the development of epileptogenesis (30).

The understanding the occurrence of early and late seizures is based on the existence of a latent period from the beginning of the disease as well as the understanding of various risks of recurrent seizures in both patient groups. Some authors consider this to be a ‘grace’ period or, in terms of stroke treatment - a therapeutic window when antiepileptic therapy should be introduced (30, 31).

It is believed that a clear answer concerning the risks of recurrent seizures will be provided by research of biochemical parameters that are yet to come. The already mentioned increased risk of PSE in younger patients, those with ICH, cortical lesions, bigger lesions, the fact that a significant number of patients with early seizures develop PSE justifiably poses the question whether the preventive use of current antiepileptic drugs makes sense and whether it reduced the total risk of recurrent seizures. There is a clear recommendation in literature concerning the use with ICH (32-35).

In clearly defined situation, such as the occurrence of PSE after the first stroke according to ILAE classification (epileptiform activity on EEG, existence of clear focus in CT or MRI of the brain), as well as in late seizures after stroke, a practitioner has no dilemma about the need to introduce specific treatment (34, 35).

The treatment of PSE represents a great challenge and establishing the correct diagnosis and its adequate treatment are an important task for a neurologist. There are still a number of questions related to epileptogenesis and development of PSE. Numerous ongoing studies will probably in the future provide additional answers to what is currently still unknown about symptomatic epilepsy after stroke.

**Conclusion**

In summary, total PSE frequency in patients treated for stroke is 7.86%. With respect to age, PSE more often occurs in younger patients. Regarding the type of stroke and occurrence of PSE, although the percentage of patients with PSE is higher in the group of patients with ICH compared to ischemic stroke (15.7%), no statistical significance was observed. Patients with stroke in whom CT showed a lesion bigger than 3 cm were more often in the PSE group. Cortical and subcortical lesion in stroke (in the group of patients with stroke and MCA territory) is statistically significantly more often associated with the occurrence of PSE. The presence of associated cardiac and pulmonary comorbidities has been shown to statistically significantly increase the risk of PSE occurrence.


FAKTORI RIZIKA ZA NASTANAK SIMPTOMATSKE EPILEPSIJE KOD BOLESNIKA NAKON MOŽDANOG UDARA

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Moždani udar (MU) je jedan od vodećih uzroka smrtnosti u starjoj populaciji. Oko 50% obolelih od moždanog udara ima neki vid slabosti i posledica. Simptomatska epilepsija (post stroke epilepsy - PSE) je jedna od njih.

Cilj rada je bio da utvrdi učestalost PSE u ispitivanoj grupi bolesnika nakon MU, razliku u učestalosti PSE u grupi sa hemoragijskim i ishemijskim MU, uticaj veličine i lokalizacije lezije, kao i uticaj postojanja komorbiditeta za nastanak PSE.

U pitanju je bila prospektivna studija koja je analizirala bolesnike sa prvim MU (ihemijijske i hemoragijske geneze) sa periodom praćenja od dve godine.

Od ukupno 536 lečnih bolesnika, njih 267 (starosti 47-92) koji su imali prvi MU bilo je analizirano. U kontrolnoj grupi (n = 246) nije došlo do pojave PSE, dok je njih 21 razvilo PSE u periodu od dve godine nakon MU. Kortikalne i subkortikalne lezije kao i mlada životna dob su pokazale statističku značajnost za pojavu PSE (p < 0,05). Nismo dokazali statističku značajnost za nastanak PSE kada je u pitanju veličina lezija i vrsta MU. Udruženo postojanje kardiološkog i plućnog oboljenja statistički je češće bilo povezano sa nastankom PSE nakon MU (p < 0,05).

Učestalost PSE u našoj grupi ispitanika bila je 7,86%. Mlade životno doba kao lokalizacija lezije pokazali su statističku značajnost za nastanak PSE, dok veličina lezije i vrsta MU te nisu pokazali u našoj grupi ispitanika. Od značaja za nastanak PSE pokazalo se i postojanje udruženog pulmonalnog i kardiološkog oboljenja.


Ključne reči: faktori rizika, epilepsija , moždani udar