Predictive factors in post-stroke epilepsy: Retrospective analysis

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Abstract

Background. Cerebrovascular disease is an important cause of epilepsy. The incidence may significantly vary (from 2.3% to 43%). Post-stroke seizures occur within 2 weeks of stroke onset (as early-onset seizures) or 2 weeks after a stroke (as late-onset seizures).

Objectives. To retrospectively evaluate and differentiate predictive factors for post-stroke seizures.

Material and methods. We retrospectively analyzed the medical histories of 164 adult patients diagnosed with post-stroke seizures but no epilepsy recognized prior to the stroke who were hospitalized at the Neurology Clinic of Wroclaw Medical University between 2012 and 2018. The seizures were classified according to the criteria of the International League Against Epilepsy (ILAE) from 2017. The relevant demographic data, type of stroke (ischemic/hemorrhagic), time of occurrence of seizures in relation to the type of stroke, score on the modified Rankin Scale, presence of cardiovascular risk factors, electroencephalography (EEG) recording, and antiepileptic treatment (AED) were collected. In the case of ischemic stroke (IS), the size of the stroke lesion was rated on the ASPECTS scale.

Results. The study involved 164 patients (average age = 68.83 years), including 86 men (average age = 66.2 years). In 20 out of 164 patients, the seizures were associated with hemorrhagic stroke (HS); in 144 out of 164 patients, the post-stroke epilepsy was associated with IS. Generalized tonic–clonic seizures occurred in 101 out of 164 patients, focal aware seizures occurred in 19 out of 164 patients and focal impaired-awareness seizures occurred in 44 out of 164 patients.

Conclusions. Our study has confirmed that generalized seizures occur mostly after an IS and are late complications of it. Early-onset seizures occur mostly after HS associated with severe disability. Seizures are more likely to happen due to the cortical location of the stroke. There is a shift from generalized to focal seizures with an increase in the extent of IS as evaluated using the ASPECTS scale.

Key words: stroke, aspect, post-stroke epilepsy

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Introduction

Complications after stroke are a growing issue in the ageing population. According to demographic data, in Canada from 2013 to 2018, the number of people suffering stroke-related disabilities will increase by up to 80%.[1]

According to the new practical definition of epilepsy by the International League Against Epilepsy (ILAE), the disorder can be diagnosed after a single seizure if other findings suggest a risk of recurrent seizure equivalent to the risk after 2 unprovoked seizures.[2] Post-stroke epilepsy is defined as recurrent convulsive seizures related to cerebral damage from a stroke, regardless of the time of onset following the stroke.[3] Early-onset epileptic seizures often occur within the first 7 days and are defined as acute symptomatic seizures. They occur in 2.5–6% of patients with stroke, more often in the course of hemorrhagic stroke (HS) than ischemic stroke (IS). In 40% of patients, this is a single epileptic seizure, while 60% of patients experience 2 or more seizures. Late-onset epileptic seizure, which affects 10–20% of patients, occurs 7 or more days after stroke symptoms.[4] The probability of a seizure occurring is estimated at 5–6.1% during the 1st year after stroke, which increases by 1–2% each subsequent year. Post-stroke epilepsy is mostly diagnosed during the first 2 years after a stroke.[4,5] In patients with acute symptomatic seizures, the risk of developing another unprovoked seizure over the next 10 years is 33%, while in patients whose 1st unprovoked seizure occurred more than 7 days after a stroke, this risk stands at 71.5%.[4,6,7]

There is high risk of epileptic seizures in HS, subarachnoid hemorrhage and cortical focus in ischemic stroke, especially in patients with high NIHSS score and modified Rankin score of over 3 points.[7–9] Another risk factor for post-stroke seizures is a patient under 65 years of age.[10,11] In a literary review on post-stroke epilepsy, patients with late-unprovoked seizure after stroke have a 71.5% risk of another unprovoked seizure.[6] No previous publications have reported that treatment with antiepileptic drugs (AED) prevents the development of post-stroke epilepsy, and the risk of seizure after stroke is relatively low, so primary prevention does not need to be indicated.[12] According to Zelano, early seizures may be a risk factor for late seizures, at least in intracerebral hemorrhagic stroke (ICH), but the risk is not described as higher than that seen after a single unprovoked seizure, making AED withdrawal reasonable in most cases.[13]

The aim of study was to retrospectively evaluate and differentiate predictive factors for post-stroke seizures.

Material and methods

We retrospectively analyzed the medical histories of 164 adult patients diagnosed with post-stroke seizures but no epilepsy recognized prior to the stroke, who were hospitalized at the Neurology Clinic of Wroclaw Medical University (Poland) between January 1, 2012 and December 31, 2018. The following data were assessed: sex, age, type of seizure, type of stroke (IS/HS), time of occurrence of seizures in relation to stroke type, score on the modified Rankin Scale, cardiovascular risk factors (hypertension, diabetes mellitus, atherosclerosis, and dyslipidemia), treatment with recombinant tissue plasminogen activator (rtPA), electroencephalography (EEG) recording, and AED.

The patients were divided into 2 groups. The 1st group consisted of patients with early seizure within 1 week after stroke, with a subgroup of patients whose seizures occurred in the first 24 h. The 2nd group consisted of patients with later-onset post-stroke seizures occurring within 1 year and over 1 year.

Seizures were classified according to the criteria of the International League Against Epilepsy (ILAE) from 2017. The following seizure types were distinguished: focal aware seizure, focal seizure with impaired awareness and generalized tonic–clonic seizure.

The stroke location was assessed based on imaging with the use of 64-slice CT scanners (GE Healthcare, Chicago, USA) with 3D isotropic resolution and a slice thickness of 0.6 mm. In the case of IS, the size of the stroke lesion was rated on the ASPECTS scale. The scale can be divided into 3 ranges: 0–4 for severe stroke; 5–7 for moderate stroke; and 8–10 for mild stroke. Hemorrhagic strokes are classified based on blood volume as mild (<30 mL), moderate (31–60 mL) and severe (>61 mL). The clinical and radiological analyses were performed by a permanent team of neurologists and radiologists with several years of experience.

All statistical analyses were performed with STATISTICA v. 12.0 (StatSoft Inc., Tulsa, USA). All tests were performed at a significance level of $\alpha = 0.05$. The interaction between the type of seizure and other characteristics was analyzed using a contingency table. The significance of the interaction was tested with the χ^2 test and Fisher's exact test (when the number of cases was less than 40).

Results

The study involved 164 patients (average age: 68.83 years), including 86 men (average age: 66.2 years) and 78 women (average age: 78.83 years). The youngest patient was 24 years old; the oldest patient was 93 years old. In 20 out of 164 patients, the seizures were associated with HS, while in the remaining 144 patients, the post-stroke epilepsy was associated with IS. Seizures occurring as the first symptom of IS appeared more often in female patients. Patients with IS were older (average age: 76 ±10.89 years) than the rest of the group. In 17 patients, a seizure occurred within the first 2 weeks of the stroke. This included 7 patients with seizures appearing as the first symptom and occurring during the first 24 h of the stroke incident. Late-onset seizures occurred in 147 patients (89.6%), including 42 patients with epilepsy in the 1st year following

Table 1. General characteristics of the group

Variable	IS, n = 44	HS, n = 20	All patients, n = 164
Gender (female/male)	69/75	9/11	78/86
Age, mean [years]	76.2 ±10.89	70.5 ±12.4	68.8 ±12.6
Generalized tonic–clonic	94	7	101
Focal aware seizures	14	5	19
Focal impaired-awareness seizures	36	8	44

IS – ischemic stroke; HS – hemorrhagic stroke.

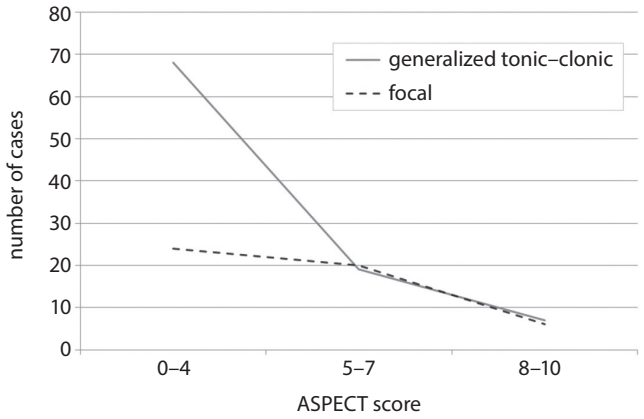

Fig. 1. Correlation between the type of epileptic seizure and the size of IS as assessed using the ASPECTS scale

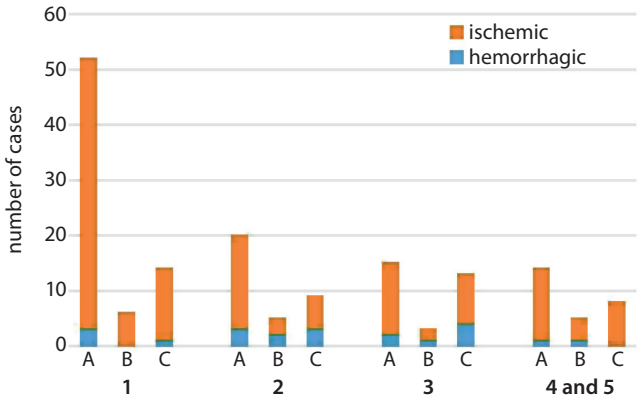

Fig. 2. Radiological range and seizures

Seizures: A – generalized seizure; B – focal aware seizure; C – focal impaired-awareness seizure. Radiological range: 1 – lacunar stroke; 2 – territories of ACA or PCA; 3 – territories of middle cerebral artery (MCA); 4 – territories of MCA and ACA or MCA and PCA; 5 – territories of MCA, ACA and PCA; ACA – anterior cerebral artery; PCA – posterior cerebral artery; IS – ischemic stroke; HS – hemorrhagic stroke.

a stroke. The average time to onset of an epileptic seizure in the study group was 19.5 months. Table 1 presents the characteristics of the study group.

Generalized tonic–clonic seizures occurred in 101 out of 164 patients, focal aware seizures occurred in 19 patients and focal impaired-awareness seizures occurred in 44 patients. The majority of patients with seizures within the first 24 h had the generalized tonic–clonic type (70% of this subgroup). No statistically significant differences were demonstrated between seizure type and the extent of the focus assessed using radiological methods.

Generalized tonic–clonic seizures occurred in 65% (93/144) of the patients with IS. The other types of seizures associated with IS were less common – focal aware seizures occurred in 10% of patients (15/144) and focal impaired-awareness seizures in 25% (36/144). Among the patients with ICH, the distribution of seizure types was different. Focal impaired-awareness seizures were the most common, occurring in 40% (8/20) of patients. Generalized tonic–clonic seizures occurred in 35% (8/20) and focal aware seizures in 25% (4/20) of patients.

There was significant correlation between the type of epileptic seizure and the ASPECTS scores for the 3 ranges. Generalized seizures were most common for severe strokes (0–4 point range) ($p = 0.01430$; Fig. 1). No significant correlation was found between the type of epileptic seizure and HS classified by blood volume.

In 105 patients, IS affected 1 cortical location (in 60%, it was the right hemisphere), and in 50 patients it involved the fronto-parieto-temporal area; in addition, the focus was in the frontal area in 17 patients, in the parietal area in 6 patients and in the temporal area in 3 patients. The right thalamus was the focus for 1 patient, while 3 patients had epileptic seizures with isolated cerebellar injury. Figure 2 shows radiological range and type of stroke.

Among hemorrhagic lesions, 14 were lobar, 2 were basal gangliar, 2 were thalamic, and 1 was cerebellar. No statistically significant differences were found regarding seizure types or a hemispheric location of the stroke focus (Table 2).

There were also no statistically significant differences in cardiovascular risk factors between the subgroups of patients. Only atrial fibrillation (AF) was statistically more common in early seizures ($p = 0.011$). Patients with diabetes and a history of AF showed a statistically significant higher score on the modified Rankin Scale ($p < 0.05$) (Table 3).

The EEGs showed generalized slowing of the basic activity of both brain hemispheres in 73 of the patients and asymmetrical seizure changes in 89 patients. No correlation was found between EEG results and the extent of radiological changes. The occurrence of seizure changes in EEG and the type of epileptic seizure did not affect the scores on the modified Rankin Scale.

Table 2. Radiological characteristics of the group

Variable	ASPECTS score		
	mild stroke	moderate stroke	severe stroke
Generalized tonic–clonic, n = 94	68	19	7
Focal aware seizures, n = 14	7	5	2
Focal impaired-awareness seizure, n = 36	17	15	4
Variable	**Intracerebral hemorrhagic stroke (ICH)**		
	mild ICH <30 mL	moderate ICH 31–60 mL	severe ICH >60 mL
Generalized tonic–clonic, n = 7	2	5	0
Focal aware seizures, n = 5	2	1	2
Focal impaired-awareness seizure, n = 8	3	4	1

Table 3. Early seizure compared to late seizures

Variable	Early-onset post-stroke seizures (within 2 weeks), n = 17		Late-onset post-stroke seizures (more than 2 weeks), n = 147		All patients, n = 164
	IS n = 12	HS n = 5	IS n = 132	HS n = 15	
Gender (female/male)	5/7	2/3	64/68	7/8	78/86
Age, mean [years]	69.4 ±15.7		68.5 ±12.0		69.8 ±12.6
	73.2 ±15.5	62.4 ±17.6	68.6 ±12.0	65.3 ±9.2	F: 73.8 ±12.0* M: 66.2 ±12.2
Generalized seizure	5	3	88	5	101
Focal aware seizure	4	0	11	4	19
Focal impaired-awareness seizure	3	2	33	6	44
Hypertension	7	3	101	15	126
Diabetes mellitus	3	2	34	3	42
Atherosclerosis	6	2	78	8	94
Atrial fibrillation	1	1	46	2	50
Smoking	4	2	17	3	26
Deaths	1	2	5	0	8
Modified Rankin Scale	4.1 ±1.5*		3.0 ±1.3		2.94 ±1.48
	3.8 ±1.4	4.8 ±1.6	3.1 ±1.3	2.6 ±0.9	

* statistical significance.

Carbamazepine was used in 72 patients, valproic acid (VPA) in 38 patients, lamotrigine (LTG) in 23 patients, and levetiracetam (LEV) in 14 patients. In 15 patients, the treatment was based on polypharmacology.

A statistically significantly higher score on the modified Rankin Scale was found in patients with early seizures compared to the group with late seizures ($p < 0.005$). There was no significant correlation between the type of epileptic seizure and the score on the modified Rankin Scale.

Thrombolytic treatment was used in 7.1% of patients (6/84) with IS. These patients had a stroke whose focus was in the areas of vascularization of the right MCA, the left MCA and the left ACA. The focal seizures in these patients manifested as behavioral disturbances. Only 1 patient had a generalized tonic–clonic seizure.

The standardized mortality rate for the study cohort was 5% (8/164).

Discussion

The most frequent cause of epileptic seizures in elderly patients is vascular brain damage. In about 50% of patients over the age of 60 years, epileptic seizure occurs in the course of stroke. According to some authors, post-stroke epilepsy occurs more often in men over the age of 70 years (56%).[14–17] In 2012, Chen et al. reported post-stroke epilepsy in 38.5% of men with subarachnoid hemorrhage, in 60.7% of men with ICH and in 58% of men with IS.[18] According to the findings of Leung et al., post-stroke epilepsy is more frequent in women (55%).[17] In our analysis, post-stroke epilepsy occurred in over 52% of cases in men. Acute asymptomatic epileptic seizures occur more often in patients with HS than in those with IS. In cases with subarachnoid hemorrhage, seizures are observed in 16.2% of patients. Our study showed that post-stroke

epilepsy was present in 88% of patients who had IS; however, in 12% of patients, epileptic seizures were related to HS. In cases of stroke covering the entire anterior circulation, i.e., the anterior and middle cerebral arteries of the brain (total anterior circulation infarct (TACI)) – most often in the course of internal carotid artery occlusion – the risk of early-onset and late-onset seizures exceeds the risk of epilepsy in the course of HS. Post-stroke epilepsy develops in 15.7% of patients with acute symptomatic seizures.[14,15]

The pathomechanism of post-stroke epilepsy is not fully understood. According to some hypotheses, the pathomechanism of early-onset seizures is different from the abnormalities that occur during late-onset seizures in the course of cerebrovascular disease.[19–25] Quoting research by Sung and Chu, Myint et al. observed that "late-onset seizure peaks within 6–12 months after the stroke and has a higher recurrence rate of up to 90% in both ischemic and hemorrhagic stroke".[3] They found significant interaction between the type of seizure and the type of stroke. As many as 93% of patients with generalized seizures had IS. Among the 44 patients with IS, 14 had focal aware seizures and 36 had focal impaired-awareness seizures. Ischemic stroke was associated with generalized seizure (65%) and there was no connection with ICH because a maximum of 40% of patients had focal impaired-awareness seizures.

The factors of early-onset epileptic seizure or post-stroke epilepsy are as follows: embolic etiology, vascular focus within the area of middle cerebral artery circulation, multifocal brain damage, and persistent paresis. In this study, AF occurred statistically more often in cases of early-onset seizures ($p = 0.024$). Kim et al. obtained similar results, i.e., AF was more common in late-onset post-stroke seizure after IS than in early-onset (≤1 week) post-stroke seizure after IS ($p < 0.05$).[14] The researchers observed that the association between seizure and cardioembolism is often mentioned in published studies.[26,27] However, this association remains controversial due to the varying study designs and diagnostic testing. Another important point to be considered is confounding factors and interaction between predictors, such as age with seizure manifestation or survival rate, or AF with cortical involvement, and so on.[14]

The occurrence of epileptic seizures also correlates with the size and location of the focus of stroke – an epileptic seizure will more often be a symptom of a stroke in patients with an extensive cortical vascular focus, originating from the anterior circulation area located superficially within the cortical component.[3,7,19,26] Epileptic seizures were observed more often in patients with stroke in the left hemisphere (2.8%) than in the right hemisphere (1.8%).[27,28] Subcortical damage and damage in the posterior circulation area increase the risk of more frequent epileptic seizures (recurring seizures). Our study showed that, in most cases, stroke was related to the right frontal and right temporoparietal regions. In our research, a statistically significant correlation was found between the ASPECTS score and the type of epileptic seizure. Perhaps the correlation between the larger area of ischemic damage and a generalized epileptic seizure is related to the spread of abnormal electrical activity throughout the brain. A similar result was obtained by Kim et al., who stated that seizure recurrence in a group of patients suffering from late post-stroke seizure after IS was more common among patients with large lesions.[14]

Also, Reddy et al. indicated 2 predictive factors for developing post-stroke epilepsy – stroke severity and hemorrhagic character – among other related factors. In addition, patients with small-vessel disease were at a significantly higher risk of developing epilepsy.[28]

According to the new seizure classification, the first step is to separate seizures by how they begin in the brain. Generalized seizures, previously defined as primary generalized seizures, engage or involve networks on both sides of the brain at the onset. By contrast, focal to bilateral seizure describes a seizure that starts in one side or part of the brain and spreads to both sides. Finally, in post-stroke epilepsy, it is sometimes difficult to determine the onset of a seizure. According to the majority of authors, this can be caused by a lack of valid medical history or witnesses of patients suffering from aphasia or disturbances of consciousness.[10,11,17,29] In the early phase of stroke, there are sporadic status epilepticus events.[12,30–32] In our group of patients, in 7 cases (41% of patients with early-onset seizure) an epileptic seizure occurred within 24 h of the stroke incident and was accompanied by hemorrhagic focus. Generalized seizures predominantly affected the group of patients who suffered an IS.

Our study has a few limitations. We reviewed the medical records of the patients retrospectively. The small sample in this study may have limited the derivation of adjusted odds ratios (ORs) with multiple predictor variables. However, we tested the distribution of all continuous variables and confirmed that they were normally distributed.

Conclusions

Our study has confirmed that generalized seizures occur mostly after IS and are late complications of it. These seizures are more likely to happen with a cortical locus of the stroke. Early-onset seizures occur mostly after HS and are associated with severe disability. Post-stroke epilepsy occurred more frequently in patients with cardioembolic stroke than in those with strokes of other etiology. There was a significant correlation between the type of epileptic seizure and the ASPECTS score. Generalized tonic–clonic seizures occurred most often after a severe stroke with 0–4 points on the ASPECTS scale.

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