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Research Article

Brain Areas Predisposing to the Stroke-Related Epilepsy Development

Viktor Weiss,[1,2] **Pavel Říha**,[1,3] **Irena Doležalová**,[1] **Martin Kojan**,[1] **Vladimír Červeňák**,[4] **Julius Šimko**,[2,3] **Roman Herzig**,[2,5] **and Ivan Rektor**[1,3]

[1]*The First Department of Neurology, St. Anne's University Hospital and Faculty of Medicine, Masaryk University, Brno, Czech Republic*
[2]*Department of Neurology, Charles University Faculty of Medicine, Hradec Králové, Czech Republic*
[3]*Central European Institute of Technology (CEITEC), Multimodal and Functional Neuroimaging Research Group, Masaryk University, Brno, Czech Republic*
[4]*Department of Medical Imaging, St. Anne's University Hospital and Faculty of Medicine, Masaryk University, Brno, Czech Republic*
[5]*Department of Neurology, Comprehensive Stroke Center, University Hospital Hradec Králové, Czech Republic*

Correspondence should be addressed to Ivan Rektor; ivan.rektor@fnusa.cz

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Background. Stroke-related epilepsy (STRE) represents a significant health problem. We focused on identifying brain areas, which involvement in ischemia predisposes a patient to STRE development. *Methods*. We retrospectively identified a group of patients with STRE consisting of 33 subjects. Subsequently, age-, sex-, and territory-matched controls who underwent stroke but did not develop STRE (control group (CG)) were identified. The CG was composed of 37 patients. The total ischemia volume and distribution of ischemic changes were compared between STRE and CG. We also analyzed multivariate statistics to identify independent variables predisposing to STRE development. *Results*. The patients with STRE exhibited a bigger volume of ischemia than CG (average volume of ischemia in STRE 60.8 cm^3, in CG 42.4 cm^3, $p = 0.029$). When comparing STRE and CG, there were differences in the distribution of ischemic changes in the temporal lobe (transverse (Heschl's) temporal gyri, superior temporal gyrus, and middle temporal gyrus) and parietooccipital region (postcentral gyrus, supramarginal gyrus, angular gyrus, parietal operculum, lingual gyrus, and superior occipital gyrus). The involvement of transverse temporal (Heschl's) gyri ($p = 0.0222$, odds ratio 30.0767), age ($p = 0.0110$, odds ratio 1.0745), and SeLECT score ($p = 0.0480$, odds ratio 1.8682) were identified as independent predictors for STRE development. *Conclusion*. The higher volume of ischemia correlates with a higher risk of STRE development. Some areas, particularly in the temporal and parietal neocortex, predispose the brain to generate epilepsy after the stroke.

1. Introduction

Stroke has been identified as a leading risk factor for epilepsy development at a higher age. The incidence of stroke-related seizures varies between 2% and 20%, depending on the study cohorts, length of follow-up, and applied definitions [1–3]. Vascular diseases were responsible for 15% of newly diagnosed epilepsies, but this number attacks the 50% boundary in the elderly [4]. Moreover, the number of patients with stroke and epileptic seizures will increase in the future, conditioned by population aging and improved care for stroke patients with rising survival rates. However, the ongoing epileptic activity can interfere with poststroke recovery and condition poor functional outcomes in these patients [4]. To estimate STRE risk, a prediction model, the so-called SeLECT score, was calculated. This model is based on the severity of stroke (Se), large artery atherosclerosis (L), early seizures (≤7 days), cortical involvement (C), and territory of the middle cerebral artery (MCA, T) [5].

When speaking about the association of stroke and seizures, we have to distinguish between acute symptomatogenic seizures and late seizures, synonymously stroke-related

epilepsy (STRE). Acute symptomatogenic seizures are closely related to stroke, i.e., occurring several days up to one week after stroke onset. Long-term treatment with antiseizure medication (ASM) is not standardly recommended, but ASM could be indicated for a time-limited period [1]. On the contrary, STRE or late seizure appears in a more extended period after stroke. The patients are classified as having structural epilepsy, and long-term ASM is indicated. The pathophysiological mechanism of STRE is an acquired brain ability to generate seizures conditioned by cerebral ischemia leading to gliosis, deafferentation, neuronal inflammation, neurodegeneration, and changed synaptic plasticity [6, 7].

In the presented study, we focused on identifying brain areas that may play a crucial role in STRE development in stroke patients.

2. Material and Methods

Firstly, we retrospectively identified a group of patients who developed STRE (STRE group). Secondly, we defined a control group (CG) consisting of age- and sex-matched controls who underwent stroke but did not develop STRE. Thirdly, in STRE and CG, we analyzed poststroke CT scans with clearly developed ischemic changes. The ischemic borders were marked manually. Subsequently, the localization of ischemic changes was compared to reveal differences in the total volume and the distribution of ischemic changes.

The ethical committee approved the study. The patients gave their informed consent before involvement in the project.

2.1. Subjects. We retrospectively reviewed the database of patients hospitalized in the 1st Department of Neurology, St. Anne's University Hospital in Brno, and Department of Neurology, University Hospital Hradec Králové, for acute stroke between 2010 and 2016. We reviewed all patients with stroke and identified patients with STRE (STRE group), who developed epilepsy during the first five years after stroke.

For our study, STRE was defined as epileptic seizures or convulsive status epilepticus at least one month after stroke. The exclusion criteria were as follows: (1) the preexistence of epilepsy before stroke, (2) the presence of another lesion than ischemia which can potentially be responsible for the epilepsy development, (3) unavailability of CT with clearly expressed ischemic changes, (4) patients with dementia, (5) intracerebral bleeding, (6) strokes in the brainstem, and (7) venous infarcts, including the sinus thrombosis.

In every patient, we identified CT with expressed ischemic changes. Based on their localization, we divided the patients into conventional large-vessel territories (MCA, posterior cerebral artery (PCA), and anterior cerebral artery (ACA)). The patients' demographic data were obtained by review of the hospital information system. Subsequently, we defined age-, sex-, and territory-matched controls with stroke (CG). In the CG, we involved only patients who did not report any epileptic seizures or attacks suspected of epilepsy at least five years after the stroke. The other exclusion criteria for the CG were the same as for the STRE group.

The subjects from the STRE group and CG were contacted via phone. They and their caregivers were actively asked about developing epilepsy and seizures. Documentation from the local hospital or outpatient clinics was obtained and reviewed if necessary. We included only subjects in whom the diagnosis of STRE was established for the STRE group or excluded for CG. The present study did not include subjects with unclear mental status alterations, loss of consciousness, or falls of undetermined origin.

2.2. Imaging. CT examinations were performed on 64 GE Lightspeed VCT and 254 Philips Brilliance CT scanners. For acute ischemic stroke detection at unenhanced CT, standard window settings (width 80 HU, center 20 HU) with voxel size $0.5 \times 0.5 \times 3$ mm were used. The CT was performed at least two days after the stroke onset.

Specialized radiologists manually marked hypodense postischemic borders in CT scans in native space. Subsequently, ischemic change masks were normalized into common space using the SPM 12 segmentation tool. Because the involvement of the side (right vs. left) was not found to be associated with a higher or lower risk of STRE development, we did not assume hemisphere dependency. We flipped the left-side masks to the right side for more precise anatomical localization.

2.3. Statistical Analysis. Differences between the STRE and CG study groups in sex and territory subgroups were explored using Fisher's exact test; the age difference was explored using the two-sample t-test.

2.4. STRE Compared to CG: Voxel-Wise Comparison. The study objective was to explore associations between epilepsy development and postischemic changes. A four-field contingency table for each in-brain voxel was built; the first categorical variable was epilepsy development (STRE or CG group), and the second variable was the occurrence of postischemic changes (pathological or normal tissue). Association between these variables was assessed using Fisher's exact test. As significant, we consider voxels with a p value ≤ 0.05.

2.5. Prediction of STRE Development: Multivariate Analysis with SeLECT. This analysis is aimed at assessing the effect of region defined based on automated anatomical labeling (AAL) atlas, age, sex, and SeLECT score on the development of poststroke epilepsy. The SeLECT score is calculated based on the following variables: (1) severity of stroke, (2) large artery atherosclerosis, (3) early seizures, (4) cortical involvement, and (5) territory of MCA [5].

Firstly, the stroke masks were parcellated using the AAL atlas. For each area, the percentage that was affected by the stroke was determined. Then, for each AAL area, the binary logistic regression model was estimated to evaluate the effect of the independent variables: stroke~SeLECT+sex+age+coverage, where stroke is the dependent variable with two levels for the STRE and CG groups and coverage is the percentage coverage of the given AAL area (R notation is used for the model description).

Table 1: Demographic characteristics of included patients.

	Sex							
	Males				Females			
	n	Age (years)			n	Age (years)		
		Median	Min	Max		Median	Min	Max
STRE*								
All	21	70	38	80	12	75	64	88
MCA	11	67	38	80	9	77	64	88
PCA	6	70	66	76	1	68	68	68
ACA	1	72	72	72	0	0	0	0
Controls*								
All	24	66	48	81	13	61	34	86
MCA	10	65	55	80	9	63	34	92
PCA	6	68	57	81	1	34	34	34
ACA	0	0	0	0	1	58	58	58

MCA: middle cerebral artery; PCA: posterior cerebral artery; ACA: anterior cerebral artery; n: number; STRE: stroke-related epilepsy. *Some patients exhibit the involvement of more than one territory. These patients were not subdivided into MCA, PCA, or ACA subgroups.

Based on the results, we calculated the odds ratio (OR) for each independent variable to explain the effect of each variable on the development of stroke: OR = 1, the variable has no effect on the occurrence of stroke; OR > 1, the variable increases the probability of stroke; and OR < 1, the variable decreases the likelihood of stroke [8].

3. Results

3.1. Subjects. In the STRE group, there were 33 patients (median age 70 years, minimum 38 years, and maximum 88 years; 12 females). In the CG, there were 37 patients (median age 64 years, minimum 34 years, and maximum 92 years, 15 females, Table 1).

The STRE and CG groups were not significantly different in sex and territory subgroups, and p values are 1 and 1, respectively, but they differed in age with p value = 0.02.

3.2. Differences in the Total Volume of Ischemia—Comparison between STRE and CG. The average volume of ischemia in STRE was 60.8 cm^3 (SD 37.7 cm^3, min 2.8 cm^3, and max 134.3 cm^3). The average volume in CG was 42.4cm^3 (SD 32.3 cm^3, min 2.7 cm^3, and max 98.4 cm^3). These differences reached statistical significance ($p = 0.029$).

3.3. Differences in Stroke Localization—Comparison between STRE and CG. The differences between the STRE and the CG in localization of ischemic changes were present in the following cerebral regions: (1) temporal lobe and (2) parietooccipital region. The most pronounced differences were present in the temporal lobe, where they were found in the transverse temporal (Heschl's) gyri, superior temporal gyrus, and middle temporal gyrus. In the parietal, the lingual gyrus, postcentral gyrus, supramarginal gyrus, angular gyrus, parietal operculum, and superior occipital gyrus were significantly more often affected in the STRE group (Figure 1).

3.4. Prediction of STRE Development—Multivariate Analysis. When analyzing individual variables (the involved brain area based on ALL atlas, age, sex, and SeLECT score; Table 2), we found that the involvement of transverse temporal (Heschl's) gyri is essential for STRE development ($p = 0.0222$, odds ratio 30.0767). The other variables predicting the STRE development were age ($p = 0.0110$, odds ratio 1.0745) and SeLECT score ($p = 0.0480$, odds ratio 1.8682).

4. Discussion

Stroke is the leading factor for epilepsy development in the elderly [9]. The occurrence of acute symptomatogenic seizures significantly increases the risk of STRE [10].

Several factors have been identified to be associated with the risk of STRE development, namely, stroke severity, large artery atherosclerosis, acute symptomatogenic seizure, cortical involvement, the territory of a MCA, cortical intracerebral bleeding, and the volume of ischemic lesion > 10 mm [11]. The other factors include hyponatremia and alcohol abuse. Younger patients (<65 years) tend to develop STRE more often than older ones (>85 years) [12]. The other variable predicting STRE is the so-called SeLECT score. If a patient reaches the lowest score (0 points), the probability of STRE development is 1% in the first year. It contrasts with the highest score (9 points), where the likelihood of SRE is 63% in the first year [5]. Surprisingly, no association between STRE and stroke etiology (atherothrombotic vs. cardioembolic), sex, comorbidities, or infection was proved [13]. When speaking about subclinical cerebrovascular disease, i.e., patients without stroke, it was found that arterial hypertension increases the risk of epilepsy development approximately two times [14].

In our study, we could confirm that the higher volume of cerebral ischemia predisposes to STRE development. The average volume of ischemia in STRE was 60.8 cm^3, while in the control group, it was 42.4 cm^3. The difference was significant.

Several authors highlighted that cortical involvement is essential for STRE development [6, 15]. The vital role of cerebral cortex ischemia was demonstrated by Zhang et al. based on a large meta-analysis of 19 studies (15 prospectives

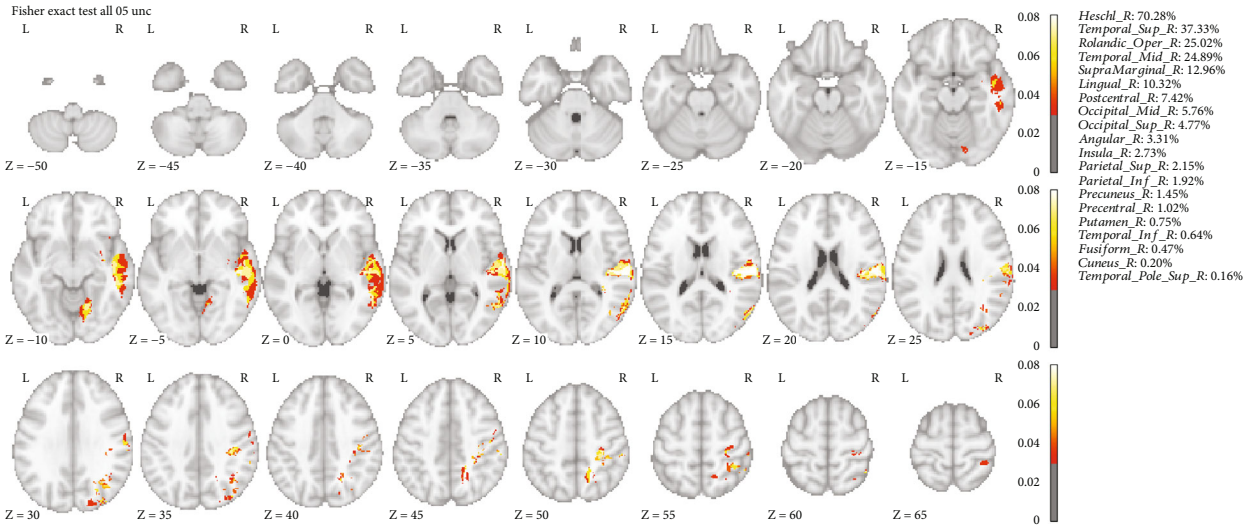

Figure 1: The differences in the distribution of ischemic changes between the stroke-related epilepsy patients' group (STRE group) and the control group (CG group). In the STRE group, the ischemic changes were more expressed in marked areas localized in (1) the temporal lobe and (2) the parietooccipital region. Left-side results were flipped to the right side, so the results are only in the right hemisphere. The differences between STRE group and CG group are marked by color.

Table 2: The predictors for stroke-related epilepsy (STRE) development based on logistic regression.

Variable	Coefficient	p value	Odds ratio	95% confidence interval
Transverse temporal (Heschl's) gyri	3.4038	0.0222*	30.0767	(1.6254, 556.5308)
Age	0.0719	0.0110*	1.0745	(1.0166, 1.1358)
SeLECT score	0.6250	0.0480*	1.8682	(1.0055, 3.4711)
Sex	-0.0870	0.8828	0.9167	(0.2886, 2.9120)
Constant	-7.1527	0.0016		

The asterisk signs the statistically significant differences.

and four retrospectives) dealing with STRE. However, the authors found insufficient data to analyze the association between lesion localization in cerebral lobes and STRE [16]. In our study, we could see significant differences between STRE and CG in the transverse temporal (Heschl's) gyri, superior temporal gyrus, middle temporal gyrus, lingual gyrus, postcentral gyrus, supramarginal gyrus, angular gyrus, parietal operculum, and superior occipital gyrus. The importance of transverse temporal (Heschl's) gyri was proved in the multivariate analysis.

It is questionable why these areas are involved in STRE development. In our opinion, the crucial role of these brain structures can be attributed to their function and complex network density. Transverse temporal (Heschl's) gyrus, known as the primary auditory cortex, is a critical brain region involved in auditory processing. Heschl's gyri play a pivotal role in the early stages of sound perception, including analyzing basic acoustic features such as frequency and temporal characteristics of auditory stimuli [17]. The other areas are parts of brain circuits that provide fundamental human activities (language, auditory, visual, and semantic memory processing and social cognition) [18–20]. These brain regions can be characterized by widespread connectivity, which could correspond to the results of Marchi et al. In their study focusing on STRE, most patients showed a complex organization of the epileptogenic zone with the involvement of both perilesional and more remote structures [21]. It is possible that affections of areas with more dense connections could potentially predispose to epilepsy development.

Our study is limited by the relatively low numbers of patients involved, which did not allow us to evaluate the differences in the level of individual large-vessel territories (MCA, PCA, and ACA).

The selection of patients can also influence our results. When involved within an epileptogenic network, some brain areas are associated with clearly visible seizure semiology (e.g., clonic jerks related to the involvement of central regions or hypermotor seizure in frontal lobe epilepsy). Conversely, some areas can be relatively silent, and the seizures can be easily overlooked or attributed to "normal" behavior (e.g., tiredness) [22].

The other limitation of our study is that we did not analyze seizure semiology in individual enrolled subjects. We can presume that seizure semiology corresponds to the involved brain areas, as demonstrated in the work of Gasparini et al. [23]. Based on the localization of middle cerebral artery territory, we can expect temporal and frontal seizure semiology or pseudotemporal semiology conditioned

by extratemporal seizures' origin with propagation to temporal structures.

5. Conclusion

The cortical involvement predisposes a patient to the development of long-term epilepsy after a stroke. A bigger volume of ischemia means higher risks of STRE development. However, which areas are essential for epilepsy development are not clear so far. It is still questionable. Our study found that involvement of the temporal lobe and the parietooccipital regions is critical on the level of all patients with brain ischemia. Our results especially highlight the pivotal role of transverse temporal (Heschl's) gyri.

Abbreviations

ACA: Anterior cerebral artery
ASM: Antiseizure medication
MCA: Middle cerebral artery
PCA: Posterior cerebral artery
STRE: Stroke-related epilepsy.

Data Availability

Data will be made available on reasonable request.

Additional Points

Highlights. The cortical involvement predisposes to stroke-related epilepsy (STRE) development. The bigger volume of ischemia predisposes to STRE development. The temporal lobe and parietooccipital regions play an important role in STRE development. The involvement of transverse temporal (Heschl's) gyri, age, and SeLECT score are independent predictors for STRE development.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgments

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