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Long-term epilepsy after early post-stroke status epilepticus

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ABSTRACT

Purpose: The risk of developing epilepsy at long term after post-stroke status epilepticus (PSSE) is unknown. We aimed to evaluate post-stroke epilepsy (PSE) after early-onset PSSE and its associated factors.

Method: All consecutive patients with early-onset PSSE and no history of epilepsy admitted to our hospital between February 2011 and April 2017 were included. We analysed status epilepticus (SE) and stroke-related factors in relation to the development of PSE.

Results: Fifty patients with early-onset PSSE were analysed. Mean age was 74.8 ± 14.3 years and 22 (44%) were women. Median NIHSS at the onset of PSSE was 11 (IQR 4–16) and median PSSE duration was 12 h (IQR 4.69–57). Median follow-up was 214 days (IQR 7.5–747). Ten patients (20%) developed PSE at a median delay of 153 days (IQR 20–334). On multivariate analysis, NIHSS > 4 (p = 0.019; hazard ratio: 15.757; 95% CI, 1.564–158.799) and PSSE > 16 h (p = 0.023; hazard ratio: 7.483; 95% CI, 1.325–42.276) were independently associated with a greater risk of PSE. The mean time from PSSE to onset of recurrent seizures was 142 days (IQR 19–153) in patients with PSSE > 16 h and 310 days (IQR 147–480) in PSSE < 16 h (p = 0.094).

Conclusions: NIHSS score > 4 at the stroke presentation and PSSE duration > 16 h may predict of PSE in patients with early-onset PSSE. Recurrence may develop earlier in PSSE patients with longer duration of the episode.

1. Introduction

Cerebrovascular disease is involved in 11% of epilepsy cases, and the rate increases with age, reaching up to 45% of incident cases in the older population (> 65 years) [1,2]. In addition, stroke is one of the most frequent aetiologies of status epilepticus (SE), although this condition occurs in only 1.5% of strokes [3,4].

The main predictive factors for post-stroke epilepsy (PSE) are stroke severity, cortical involvement, lesion size, haemorrhage, total anterior circulation infarcts, young age at stroke, and early-onset seizures [5]. As to post-stroke status epilepticus (PSSE), this condition usually occurs within the first few days after the stroke, and the main risk factor is extensive cortical involvement (cortical infarction or lobar haemorrhage) [3,6–9].

Recently, Galovic et al proposed a prognostic model for predicting late seizures after ischaemic stroke (SeLECT score). It is composed of five predictors (including early-onset seizure) as risk factors for PSE: stroke severity, large-artery atherosclerosis, early seizure (≤7 days), cortical involvement, and involvement of the middle cerebral artery (MCA) territory [10].

Early-onset post-stroke seizures occur within the first week after stroke [11]. Patients with a first acute post-stroke seizure have a risk of a subsequent recurrent seizure over the following 10 years of around 30%, whereas patients with a first unprovoked seizure have a risk of 70% [12].

Overall, the available evidence does not suffice to identify which patients are more likely to develop PSE or to determine whether treatment can prevent it. Although some guidelines have been proposed for the management of post-stroke seizures, the recommendations are weak due to the lack of related randomized trials [13].

Evidence is even more limited about the prognosis and recurrence of seizures after PSSE [14]. Although SE has been described as a risk factor for the development of further seizures, this relationship more likely depends on the underlying cause of the episode [15].

Because of the paucity of information on the development of epilepsy in patients with SE following a stroke [14], the aim of this study

Abbreviations: PSSE, post-stroke status epilepticus; SE, status epilepticus; PSE, post-stroke epilepsy

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was to evaluate PSE in a cohort of stroke patients with PSSE and attempt to identify those with a greater probability of having remote recurrent seizures.

2. Materials and methods

All SE patients older than 16 years seen at our hospital are prospectively included in a database that has received the approval of our hospital ethics committee. For our objective, we included all the patients with acute PSSE attended from February 2011 to April 2017. Patients with a previous history of epilepsy, arteriovenous malformation, subarachnoid haemorrhage, or subdural haematoma were excluded. All patients underwent neuroimaging examination of the brain with computed tomography (CT) or magnetic resonance imaging (MRI). For the detection of SE, all patients were clinically monitored during the acute/subacute phase of the stroke in the acute stroke unit. If a clinical fluctuation was noted, a long electroencephalography (EEG) was recorded.

Demographic characteristics, smoking and alcohol use, psychiatric history (including mood disorders or any other psychiatric disorder requiring drug treatment), previous cognitive impairment, and functional disability at discharge after stroke (modified Rankin scale) were recorded. The stroke-related variables included the affected cerebral artery territory according to the Oxford Community Stroke Project (OCSP) classification [16], type and severity of stroke according to the National Institutes of Health Stroke Scale (NIHSS), and lesion size and aetiology (Trial of ORG 101,172 in Acute Stroke Treatment [TOAST] classification) [17]. The PSSE features included the timing from stroke to PSSE onset, NIHSS at the time of SE, and SE type, duration, and treatment. SE patients included after 2015 were directly classified according to the last ILAE classification of SE, whereas those recruited before that time were retrospectively classified. the modified Status Epilepticus Severity Score (mSTESS) [18] was used to evaluate SE severity and outcome. This instrument assesses SE severity using the modified Rankin scale (mRS) together with the STESS [18,19].

SE cases with prominent motor symptoms, including generalized SE, were defined as showing unremitting seizure activity for > 5 min or 2 or more seizures between which there is incomplete recovery of consciousness. For non-convulsive SE we used the Salzburg criteria [20]. Early-onset PSSE was established when SE occurred within the first week (≤ 7 days) following the event [11]. Epilepsy was diagnosed when a single unprovoked seizure occurred > 7 days after the stroke, according to the latest definition of the International League Against Epilepsy [21].

2.1. Statistical analysis

Descriptive and frequency statistics were obtained, and comparisons were made using IBM SPSS Statistics 22.O (SPSS Inc., Chicago, IL, USA) and R software (version 3.4.4). Recurrent epilepsy rates over follow-up were analysed with the Kaplan-Meier product limit survival method using the log-rank test to determine statistical significance between patients with recurrent seizures and those without. Continuous variables were assessed by performing simple Cox proportional hazard models. Patients who died were censured at the time of death if they had not experienced a seizure before. The survival ROC R package was used to perform time-dependent ROC curve analyses to calculate cut-off points for SE duration and NIHSS with the best sensitivity and specificity to predict the development of epilepsy. Variables with a p-value < 0.1 on univariate analysis were entered into a multiple Cox regression model with the forward stepwise method to identify factors independently associated with the development of epilepsy over follow-up. Results are shown as hazard ratios (HR) with the 95% confidence interval (CI). P-values < 0.05 were considered statistically significant.

3. Results

3.1. Demographics and clinical characteristics

From a total of 117 patients with PSSE attended during the study period, 50 patients (42.7%) with early-onset PSSE and no history of epilepsy were included. Mean age was 74.8 ± 14.26 years and 44% were women. The median baseline mRS was 2 (IQR 1–3). Median follow-up was 214 days (IQR 7.5–747). Thirty-four patients (68%) died during the follow-up period, 50% of them due to a cause other than PSSE; 12 patients (35.3%) died within the first week after the stroke.

3.2. Stroke and PSSE baseline characteristics

Thirty-two patients had experienced an ischemic stroke (64%). In 26 patients, the MCA territory was affected (52%). Median NIHSS score at stroke onset was 11 (IQR 4–16).

Almost three-quarters of the SE episodes occurred within the first 24 h after the stroke (IQR 0–2). SE was convulsive in 64% (n = 32) and refractory in 58% (n = 29). Eighteen patients (36%) required tracheal intubation. Median duration of PSSE was 12 h (IQR 4.69–57). The episode resolved within 24 h in 48% of patients (n = 24), within 24–72 h in 16% (n = 8), and after 72 h in 12% (n = 6).

The remaining clinical characteristics are shown in Tables 1 and 2.

3.3. Post-stroke epilepsy

With regard to seizures at long term, 10 patients (20%) developed a first remote recurrent seizure at a median delay of 153 days (IQR 20–334). Two of these patients were not under antiepileptic drug treatment at the time of seizure recurrence. The estimated epilepsy rate was 35.3% (95% CI: 14.3%–46.3%) in the first year and 53.8% (95% CI: 27.5%–80.1%) in the second year (Fig. 1). Only 1 patient (3.3%) recurred after 17 months of follow-up.

On the univariate analysis, a higher NIHSS at the onset of stroke was associated with a greater risk of experiencing an epileptic episode at long term (p = 0.046). The best cut-off-point observed was an NIHSS score > 4, as the estimated seizure relapse rate within the first year of follow-up was higher in these patients (62.1% [95% CI: 35%–88.8%] vs 0%; p = 0.007) (Fig. 2).

Regarding the SE-related factors, the risk of having seizures at long-term was slightly higher in patients who had a lengthier PSSE episode. Patients with PSSE lasting > 16 h had a greater risk of developing epilepsy at long term, and the estimated seizure relapse rate within the first year of follow-up was higher in these patients (79.5% [95% CI: 41.5%–99.1%] vs 21.8% [95% CI: 7.4%–54.8%] ; p = 0.014) (Fig. 3).

No other clinical, stroke-related, or SE-related factors were associated with a higher risk of seizure recurrence.

Considering early-onset PSSE as an early-onset seizure, we attempted to replicate the SELECT score prognostic model, but no statistically significant differences were found (p = 0.635).

Finally, on multivariate analysis, the only independent predictors associated with a higher risk of developing epilepsy during follow-up were NIHSS > 4 (p = 0.019; hazard ratio: 15.757; 95% CI: 1.564–158.799) and PSSE > 16 h (p = 0.023; hazard ratio: 7.483; 95% CI: 1.325–42.276). The mean time from PSSE to the onset of recurrent seizures was 142 days (IQR 19–153) in patients with PSSE > 16 h and 310 days (IQR 147–480) in those with PSSE < 16 h (p = 0.094).

4. Discussion

The results of this study indicate a higher likelihood of PSE in patients in a more severe clinical condition during the acute stroke event, in agreement with previous findings [6]. In addition, there was a notable association between longer duration of PSSE and the development

Table 1
Demographics and stroke-related characteristics.

			Total n = 50	Remote recurrent seizures		p
				No (n = 40)	Yes (n = 10)	
Age, years, mean ± SD			74 ± 14.26	75.53 ± 15.16	71.80 ± 10.04	0.518
Sex (female)			22 (44%)	19 (47.5%)	3 (30%)	0.218
Alcohol use			3 (6%)	3 (7.5%)	0 (0%)	0.406
Vascular risk factors	**Hypertension**		39 (78%)	31 (77.5%)	8 (80%)	0.760
	Diabetes mellitus		18 (36%)	14 (35%)	4 (40%)	0.682
	Dyslipidaemia		16 (32%)	13 (32.5%)	3 (30%)	0.682
Ischaemic heart disease			27 (54%)	23 (57.5%)	4 (40%)	0.525
Previous stroke			13 (26%)	11 (27.5%)	2 (20%)	0.961
Psychiatric history			13 (26%)	13 (32.5%)	0 (0%)	0.154
Previous cognitive impairment			13 (26%)	13 (30%)	1 (19%)	0.746
Previous mRS (median, IQR)			2 (1-3)	2 (1-3)	1 (0-3)	0.679
NIHSS at stroke onset, median (IQR)			11 (4-16)	12 (3-18)	9 (6-13)	0.046
NIHSS > 4 at stroke onset			33 (66%)	24 (60%)	9 (90%)	0.007
Stroke type (ischaemic vs. haemorrhagic)			32 (64%)	22 (55%)	6 (60%)	0.482
Oxford Stroke Classification (n = 32)		**TACI**	20 (62.5%)	18 (69.2%)	2 (33.3%)	0.738
		PACI	11 (34.4%)	7 (26.9%)	4 (66.7%)	
		POCI	1 (3.1%)	1 (3.8%)	0 (0%)	
Ischaemic aetiology (TOAST) (n = 32)		**Atherothrombotic**	3 (9.4%)	3 (11.5%)	0 (0%)	0.589
		Cardioembolic	20 (62.5%)	17 (65.4%)	3 (50%)	
		Undetermined-dissection	9 (28.1%)	6 (23.1%)	3 (50%)	
Cortical involvement (n = 32)			31 (96.9%)	26 (100%)	5 (83.3%)	0.188
Stroke territory (n = 32)		**MCA**	26 (81.3%)	20 (76.9%)	6 (100%)	0.660
		PCA	2 (6.3%)	2 (7.7%)	0 (0%)	
		> 1 territory	4 (12.5%)	4 (15.4%)	0 (0%)	
SELECT score, median (IQR) (n = 32)			7.5 (6.5-8)	8 (6.5-8)	7 (7-8)	
Lobar haemorrhagic aetiology (n = 18)		**Arterial hypertension**	6 (33.3%)	4 (28.6%)	2 (50%)	0.826
		Amyloid angiopathy	7 (38.9%)	6 (42.9%)	1 (25%)	
		Other aetiologies	5 (27.8%)	4 (28.6%)	1 (25%)	
Lesion size (median, IQR)			38.75 (15-92.5)	40 (11.7-102.5)	26 (16.5-62.5)	0.496

mRS: modified Rankin scale, TACI: total anterior circulation infarct; PACI: partial arterial circulation infarct; POCI: posterior circulation infarct; TOAST: Trial of ORG 101,172 in Acute Stroke Treatment; MCA: middle cerebral artery, PCA: posterior cerebral artery; IQR: interquartile range.

of PSE at long-term follow-up.

Among the 50 patients with a first-time early-onset PSSE in our study, nearly a quarter developed PSE, which is in line with previous studies reporting similar or even higher seizure recurrence rates [14,15,22]. According to the literature, the risk of experiencing remote recurrent seizures at 10 years of follow-up for those with an acute symptomatic SE is 41% compared 13% for those without SE (13%) increasing the risk 3.3-fold. Moreover, SE increased the risk for recurrent unprovoked seizure 7.1-fold for patients with a structural cause [23]. However, few studies have discussed the prognosis or the factors associated with seizure recurrence specifically in patients with PSSE. Tomari et al reported that patients with early post-stroke SE were more likely to experience a remote recurrent seizure than those with a single early post-stroke seizure [24]. Rumbach et al reported a seizure recurrence rate of 61.3% in PSSE, including early and late-onset events [14], whereas Velioglu et al only examined recurrent SE (29.4%) [25]. Nonetheless, the factors that make patients with early post-stroke SE more likely to have remote recurrent seizures relative to those who do not recur have not been reported.

Severe stroke has been associated with a greater risk of early- and late-onset seizures [6]. The NIHSS score has been commonly used to determine stroke severity, although some authors have used other measures, such as the Glasgow Outcome Scale, Barthel Index, presence of incontinence, Canadian Neurological Scale, and Scandinavian Stroke Scale [7–9, 26,27]. We chose the NIHSS scale because it is an accurate tool to specifically evaluate the clinical neurological severity. Our results showed an association between stroke severity according to the NIHSS score and the risk of developing remote recurrent seizures after SE. These results are consistent with findings in the literature: higher NIHSS scores predispose to a greater likelihood of recurrent seizures at long-term [28]. However, to our knowledge, there is no specific NIHSS cut-off point to differentiate between patients with a higher or lower risk of post-stroke epilepsy. According to the literature, the definition of a minor stroke includes those categorized as NIHSS ≤ 3 [29,30]. Hence,

Table 2
Status epilepticus-related characteristics.

	Total n = 50	Remote recurrent seizures		p
		No (n = 40)	Yes (n = 10)	
PSSE onset, < 24h	36 (72%)	30 (75%)	6 (60%)	0.250
mSTESS, median, (IQR)	4 (3-6)	5 (4-6)	4 (3-5)	0.952
PSSE with motor symptoms	32 (64%)	27 (67.5%)	5 (50%)	0.480
Level of consciousness, stupor/coma	26 (52%)	22 (55%)	4 (40%)	0.797
Sedation	16 (32%)	12 (30%)	4 (40%)	0.905
PSSE duration (hours) (median, IQR)	12 (4.69-57)	12 (4.4-51.2)	17.5 (5-69)	0.312
PSSE duration > 16h	18 (36%)	13 (32.5%)	5 (50%)	0.014
Refractory PSSE	29 (58%)	25 (62.5%)	4 (40%)	0.574
Death at the time of discharge	18 (36%)	18 (45%)	0 (0%)	0.845

PSSE: post-stroke status epilepticus; mSTESS modified Status Epilepticus Severity Score; IQR: interquartile range.

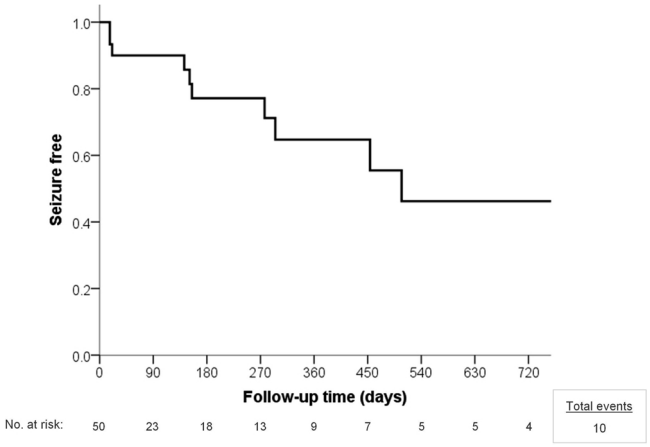

Fig. 1. Epilepsy rate during follow-up. Kaplan Meier curve showing that the estimated epilepsy rate was 35.3% (95% CI: 14.3–46.3%) for the first year and 53.8% (95% CI: 27.5%–80.1%) for the second year.

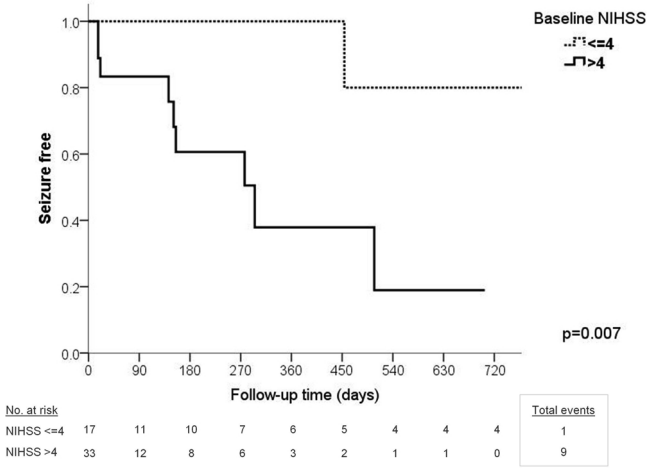

Fig. 2. Epilepsy on follow-up according to NIHSS score. Kaplan-Meier curves showing higher epilepsy rates on follow-up in patients with NIHSS > 4 at onset of PSSE. Estimated seizure relapse rates within the first year of follow-up were higher in patients with an NIHSS score > 4 (62.1% [95% CI: 35%–88.8%] vs 0%; p = 0.007).

based on our results, patients with minor stroke would have a lower risk of developing epilepsy at long-term.

The stroke-related factors have been more extensively studied than epilepsy-related ones in post-stroke epilepsy, and none of the characteristics of epilepsy have been associated with long-term recurrent seizures in stroke patients. The likelihood of recurrent seizures is thought to be higher after early-onset PSSE than after a single early-onset post-stroke seizure, although conclusive scientific evidence to support this notion is lacking [15,24]. In an earlier study we found that patients with PSSE lasting > 12 h have a poorer prognosis at short- and long-term [31]. To our knowledge, no previous studies have analysed the association between epilepsy at long-term and PSSE duration. Our results showed that patients with PSSE lasting > 16 h are more likely to develop seizures at long term. Interestingly, recurrence was earlier in these patients than in those with PSSE < 16 h, although the difference did not reach statistical significance. It may be that with prompt detection of PSSE and early treatment to reduce SE duration, long-term recurrent seizures could be prevented. As SE aetiology was similar in all our patients, we used the mSTESS score instead of the EMSE (Epidemiology-based Mortality Score in Status Epilepticus), which considers the aetiology of SE, to evaluate the prognosis.

In all the assessments performed for the study, we did not separate

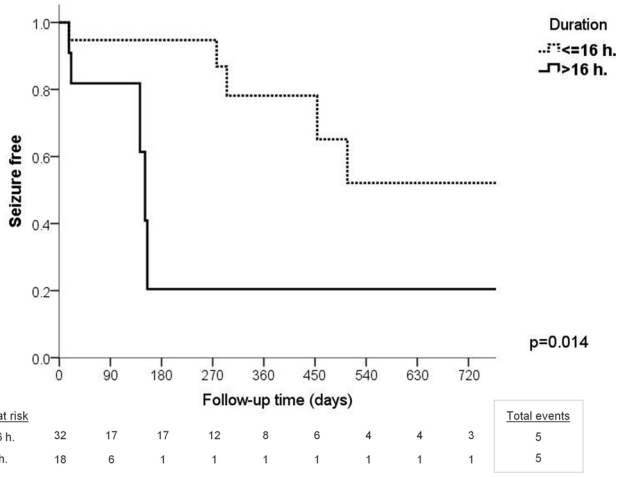

Fig. 3. Epilepsy follow-up according to PSSE duration. Kaplan-Meier curves showing higher epilepsy rates on follow-up in patients with PSSE longer than 16 h. The estimated seizure relapse rates within the first year of follow-up were higher in these patients (79.5% [95% CI: 41.5%–99.1%] vs 21.8%]95% CI: 7.4%–54.8%]; p = 0.014). Patients with PSSE longer than 16 h had recurrent seizures with a mean time from PSSE to seizure onset of 142 days (IQR 19–153) vs 310 days (IQR 147–480) (p = 0.094).

ischemic and haemorrhagic strokes. Although the presence of haemorrhagic content has been related to a higher risk of seizures, we exclusively evaluated SE in our sample, the most serious situation of vascular epilepsy for both ischemic and haemorrhagic causes. There were no differences in the NIHSS at stroke onset, PSSE duration, or seizure recurrence rates between these patient groups.

The overall epilepsy rate at 2 years of follow-up was 53.8%. Patients with NIHSS > 4 and SE duration > 16 h had a risk of recurrence within the first year of follow-up greater than 60%. In the light of this high recurrence risk, these patients might be considered to have epilepsy rather than an acute symptomatic seizure, and therefore be candidates for antiepileptic treatment at long-term [12]. However, given that these results might be secondary to the effect occurring in small remaining groups, these findings would require further study.

The main limitations of our study are its observational nature and the high mortality rate. However, even though only patients with an ischemic or haemorrhagic lobar stroke were included, and sample size is small to draw strong conclusions, this study provides insight into the development of post-stroke epilepsy in a large cohort of PSSE patients.

In conclusion, an NIHSS score > 4 at the stroke presentation and a duration of PSSE > 16 h may predict of long-term recurrent seizures in patients with early-onset PSSE. Recurrence may develop earlier in PSSE patients with longer duration of the episode.

5. Disclosures

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

The author(s) declared no potential conflicts of interest.

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