Original Article

Early Post-Stroke Seizures in Acute Ischemic Stroke: A Prospective Cohort Study

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Abstract

Introduction: Stroke is the most common cause of epilepsy in the adult population. Post-stroke seizures (PSSs) are classified into early-onset seizures (ES) and late-onset (LS). ES can significantly affect the clinical outcome and occurrence of LS. **Methods:** We analyzed data from a prospective cohort of acute ischemic stroke patients between June 2018 and May 2020 in a neurology unit at a tertiary hospital. We screened all acute stroke patients and included consecutive patients older than 18 years of age, presenting with acute, first-ever neuroimaging-confirmed ischemic stroke. We excluded patients with a previous stroke, transient ischemic attacks, hemorrhagic stroke, cerebral venous thrombosis, prior history of seizures, or any other epileptogenic comorbidity. ES were classified as spontaneous seizures occurring within 1 week of the stroke. The main outcome assessed was the occurrence of ES. The secondary outcome was to determine predictors of ES and create an ES prediction score. **Results:** We screened 432 patients; of them, 291 were enrolled. ES occurred in 37 patients (12.7%). Cortical location (OR: 4.2), large artery disease subtype (OR: 2.9), mRS at presentation (OR: 1.4), use of anticoagulants (OR: 2.6), and hypertension (OR: 0.3) were significantly associated with the occurrence of ES. Patients with ES had a statistically significant worse clinical outcome at 3 months follow-up ($P = 0.0072$). **Conclusion:** We could formulate an ES prediction tool using the following components: (a) cortical location, (b) large vessel stroke, (c) mRS at admission, (d) anticoagulant use, and (e) presence of hypertension. This tool might help in treating patients at high risk for ES with prophylactic ASD, thereby preventing seizures and their complications.

Keywords: Cortical, early seizure, ES, seizure, stroke

INTRODUCTION

Stroke is the most common cause of epilepsy in the adult population above 35 years of age and accounts for approximately 45% of the newly diagnosed epilepsy cases over 60 years of age.[1] Improvements in stroke management have reduced the mortality following a stroke while increasing the number of survivors with significant morbidity, of which patients with post-stroke seizures (PSSs) are an integral and important fraction.[2] Studies have reported that approximately 5–20% of stroke patients develop PSS.[3,4] These can be classified into early-onset (ES) and late-onset (LS) types. The cut-off between the two is arbitrary, and generally, seizures occurring one week after stroke are called LS.[5-7] This distinction is important since their underlying seizure-inducing mechanisms and future risk of transformation to epilepsy are different. ES occurs due to acute neuronal injury and concomitant glutamate-mediated excitotoxicity, disruption of the blood-brain barrier, and ion channel dysfunction.[8-10] LS occurs due to gliotic scarring and associated changes in the properties of the neuronal membrane, neurodegeneration, persistent inflammation, and altered synaptic plasticity, with eventual hyperexcitability and hyper-synchronization of neuronal activities.[11,12] Definitions of ES and LS have varied between studies leading to a reported incidence of 2.2–33% and 3–67%, respectively.[5,13-15] Despite this, the incidence of PSS is relatively consistent with two peaks: the first day and 6–12 months post-stroke.[13-15]

PSS adversely affects the functional outcome and mortality of stroke survivors.[16] Data from animal studies have suggested that frequent ES can lead to an increase in the infarct size and impaired recovery. This might be triggered by the seizure-induced increased metabolic demands of the penumbral tissue surrounding the ischemic zone.[16-18]

We analyzed the frequency and clinical characteristics of early PSSs and compared them to those without seizures in a prospective cohort of acute ischemic stroke.

METHODS

Setting

We analyzed data from a prospective cohort of acute ischemic stroke patients between June 2018 and May 2020 in a neurology

unit at the All India Institute of Medical Sciences (AIIMS), New Delhi. The data were collected prospectively from the database of an ongoing Investigator-initiated randomized controlled trial (PROLEVIS: A randomized, double-blind study of prophylactic Levetiracetam for the prevention of post-stroke seizures, CTRI/2018/02/011926) funded by Department of Science and Technology, Government of India. AIIMS Institute Ethics Committee approved the study. Approval from the ethics committee was obtained. Date of approval: 25.07.2017.

Definitions

ES were classified as spontaneous seizures occurring within 1 week of the stroke event. Seizures occurring after 7 days of stroke were considered as LS. The NIHSS was used to assess the stroke severity and classified into mild (≤3), moderate (4–10), and severe (>10); and mRS was used to assess stroke disability. Stroke subtyping was done according to the TOAST criteria.

Inclusion and exclusion criteria

We screened all acute stroke patients and included consecutive patients older than 18 years of age, presenting with acute, first-ever neuroimaging-confirmed ischemic stroke. We excluded patients with a previously confirmed clinical history of stroke, transient ischemic attacks, primary hemorrhagic stroke, cerebral venous thrombosis, prior history of seizures/epilepsy, or any other potential epileptogenic comorbidities like brain tumors, arteriovenous malformations, primary central nervous system vasculitis, or hydrocephalus.

Data collection

A neurologist assessed all patients in the cohort, and baseline characteristics were gathered through a structured questionnaire. Patients were requested to report the use of any prescription drugs. Diagnosis of stroke was confirmed by brain imaging (MRI Brain/CT head). All participants were followed up with a face-to-face interview or telephonically in the outpatient services for a minimum period of 1 year, at three monthly intervals, to document recovery from stroke (mRS) and inquire about the occurrence of a seizure. The characteristics of seizures (type, severity, timing, and antiepileptic drugs) were recorded. All patients who reported seizures had a face-to-face interview. EEG was done only to rule out non-convulsive status epilepticus in patients with altered sensorium. For participants who were unable to answer our questions directly, their primary caregivers were interviewed. For patients where the consulting neurologist suspected an alternative cause for seizures other than the index ischemic stroke, relevant investigations were ordered to rule out any other pathology/stroke recurrence.

Outcomes

The main outcome assessed was the occurrence of early seizures. The secondary outcome was to determine the predictors of early seizures after acute ischemic stroke and to create an early seizure prediction score.

Statistical analysis

Statistical analysis was done using STATA, Version 14.0. Continuous variables are depicted as median with interquartile range or mean with standard deviation. Categorical variables are expressed as numbers and percentages. Student *t*-tests and Chi-square test were used as appropriate. The variables considered as possible predictors of early seizures were NIHSS and mRS at admission, stroke lateralization, cortical involvement, supratentorial location, age, sex, stroke risk factors, TOAST classification, recanalization procedures (thrombolysis/thrombectomy), hyponatremia and the use of antiplatelet/anticoagulants. Variables that were significant in univariate analysis were included in a multivariate analysis to determine risk factors for early seizures.

Results

We screened 432 patients and included 291 consecutive patients with acute ischemic stroke who fulfilled the inclusion criteria during our study period [Figure 1]. Ninety-eight patients were recruited from the PROLEVIS trial, and they did not have early seizures. No patients were lost to follow-up. Thirty-seven of the 291 patients (12.7%) had early seizures (<1 week). Unknown onset to bilateral tonic-clonic seizures was the most common seizure type (94.6%) followed by right focal seizures (5.4%). None of the patients had status epilepticus. The seizure occurred at the onset of stroke in one patient (2.7%) and within 24 h in 34 (91.9%) patients. Two patients had ES on the second day of stroke. Twenty-eight of these patients were started on an antiseizure drug (ASD) after the ES, with Levetiracetam being the most commonly prescribed drug. The baseline characteristics of all patients with and without ES are mentioned in Table 1.

Patients with ES were younger, had a more severe stroke at presentation (NIHSS and mRS), had a supratentorial and cortical location of the infarct, involving the MCA territory, and underwent lesser recanalization procedures (thrombolysis or mechanical thrombectomy). Large artery disease and cardioembolic subtypes were more common in patients with ES. Risk factors for stroke were similarly distributed except hypertension, which was less common in patients with early seizures.

Cortical location, large artery disease subtype, stroke disability (mRS) at presentation, the use of anticoagulants, and hypertension were significantly associated with the occurrence of early seizures by multivariate analysis [Table 2]. Cortical location was the strongest predictor for ES with an OR of 4.2, followed by large artery stroke subtype (OR: 2.9) and anticoagulant use (OR: 2.6). Stroke disability (defined by mRS) had an OR of 1.4 for ES. Hypertension was associated with a lower risk of ES (OR: 0.3).

Age at presentation had an inverse correlation and stroke severity (gauged by NIHSS score) had a direct correlation with early seizure occurrence and trended towards statistical significance.

Patients with ES had a statistically significant worse clinical outcome at 3 months follow-up compared to those without (mRS 3 vs 2; *P* = 0.0072).
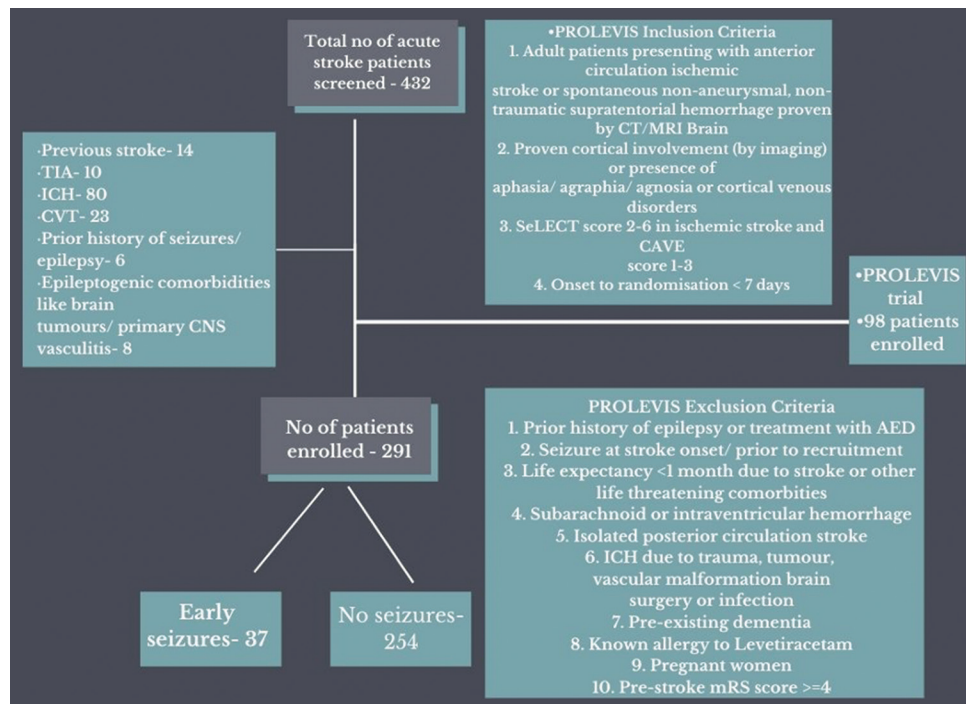
Figure 1: Enrolment of patients based on the inclusion and exclusion criteria

DISCUSSION

Early seizures occurred in 37 (12.7%) of acute ischemic stroke patients in our cohort. This is similar to the reported incidence of early seizures (2–20%) throughout the world. So *et al.*[5] and Gupta *et al.*[19] in their retrospective analysis found early seizures in 6% (33/535) and 33% (30/90) of their patient populations, respectively. The latter designated seizures occurring up to 2 weeks after stroke as early seizures. Prospective studies by Burn *et al.*[20] and Labovitz *et al.*[21] found early seizures in 1.8% (10/545) and 3.1% (22/704) of the studied populations, respectively. However, Burn *et al.*[20] considered early seizures as those that occurred within the first 24 h. The recently published SeLECT score study[22] found early seizures in 37 of their 1200 patients (3%). The majority of early seizures occurred within 24 h of the onset of stroke, which supports the hypothesis of local cellular or electrical dysfunction immediately after stroke, triggering a seizure.[23]

Younger age of patients with early seizures may be possibly due to reduced cortical excitability with aging.[24,25] A review by Feyissa *et al.*[23] found a 10.7% prevalence of stroke-related epilepsy in individuals <65 years of age compared to 1.6% over the age of 85 years ($P < 0.001$). The occurrence of early seizures significantly depended upon the location of the infarct, with cortical location predisposing to the same. This is in agreement with the study by Misirli *et al.*[25] who found it to be the most important risk factor for the development of PSS, with an OR of 4.25. It was also associated with large artery disease stroke subtype. This might be because large artery disease tends to have larger infarct volumes and involves cortical brain tissue, increasing the probability for PSS.[6,16,26] It also corroborated with the stroke severity based on the NIHSS

and the functional disability measured by mRS. Thrombolysis was not found to be associated with the development of PSS. This could be because thrombolytics tend to decrease infarct volume, thereby protecting against PSS, which may hypothetically balance out the epileptogenicity due to their postulated neurotoxicity.[27,28]

All stroke risk factors were found to be equally distributed between both the groups except hypertension, which was present in significantly lesser frequency in those with ES. This is in concordance with findings of decreased PSSs in patients with hypertension,[29,30] although the exact pathophysiology is not clear. The ischemic penumbra is electrically irritable, and may be the focus for seizure activity.[30] Elevated blood pressures might maintain its perfusion, thereby preventing seizure activity. A lesser prevalence of atherosclerotic risk factors in this subgroup of hypertensive individuals might also be responsible.[29]

The use of anticoagulants was also found to be associated with an increased risk of ES. This could be because of increased hemorrhagic transformation tendencies associated with their use, which can act as an added irritant predisposing to seizures.[29] Recent studies have revealed thrombin to be the major driving force not only for ES but also for LS by predisposing to maladaptive plasticity.[31]

Early seizure patients were found to have a significantly worse functional outcome at 3 months. This is concordant with the findings of Arnst *et al.*[32] who found a greater proportion of patients with mRS>2 in patients with PSSs than those without (27.5% vs 9.8%; $P = 0.001$).

Based on our findings, we would like to propose a model for predicting early seizures after an acute ischemic stroke.

Table 1: Baseline characteristics in ischemic stroke patients with and without early seizures

Characteristic	Patients without ES (*n*=254)	Patients with ES (*n*=37)	*P*
Median age (in years)	54±14	49±15	0.0243
Median NIHSS at presentation	6	8	0.0431
Stroke severity (%)			
Mild (NIHSS ≤3)	16.1	5.3	0.32
Moderate (NIHSS 4-10)	55.1	52.6	
Severe (NIHSS >10)	28.8	42.1	
Cortical location (%)	38.9	72.9	0.000
MCA territory involvement (%)	79.5	83.8	0.545
Supratentorial location	83.1	91.9	0.169
Stroke subtype (%)			0.028
Large artery	32.3	43.2	
Cardioembolic	14.2	18.9	
Small vessel	29.1	8.1	
Other determined	5.1	13.5	
Undetermined	19.2	16.2	
Stroke risk factors (%)			
Diabetes mellitus	31.1	21.6	0.239
Hypertension	66.9	37.8	0.001
Dyslipidemia	2.4	0	–
Coronary artery disease	11.0	8.1	0.591
Atrial fibrillation	5.1	2.7	0.521
Smoking	36.2	21.6	0.081
Alcohol intake	16.1	13.5	0.682
Stroke laterality (%)			0.364
Right	47.6	40.5	
Left	50.4	54.0	
Bilateral	2	5.5	
Sodium levels (%)			0.676
Hyponatremia (<135 mmol/L)	14.8	11.1	
Thrombolysis (%)			0.232
Yes	8.3	2.7	
No	91.7	97.3	
Mechanical thrombectomy (%)			0.900
Yes	2.4	2.7	
No	97.6	97.3	
Antiplatelet use			0.076
Yes	84.6	73.0	
No	15.4	27.0	
Anticoagulant use			0.023
Yes	11.0	24.3	
No	89.0	75.7	
Median mRS			
Presentation	2	3	0.0096
3-month follow-up	2	3	0.0072

The present models like PoSERS[33] and SeLECT[22] are only applicable to the prediction of late seizures. Strzelczyk *et al.* formulated post-stroke epilepsy risk scale (PoSERS) after evaluating 264 consecutive stroke patients and identifying seven risk factors [Table 3] prospectively.[33] It had high specificity and negative predictive value (99.6% and 98.8%, respectively) and moderate sensitivity and positive predictive value (70% and 87.5%, respectively). SeLECT score [Table 4] was developed and validated by Galovic M *et al.*[22] [Table 4] as a prediction tool for late seizures after an ischemic stroke. A six-point score indicates a late seizure risk of 18% in 1 year and 29% in 5 years after a stroke. A large artery stroke in the MCA territory with cortical involvement is likely to have a minimum score of 5, which translates to 11% (CI 8–13) at 1 year. In our cohort, even if we exclude the three points attributed to early seizure, still the total SELECT score is higher in patients with early seizure due to the cortical involvement and large artery stroke.

Our early seizure predictive model incorporates the five significant risk factors revealed in our prospective study (cortical location, large vessel stroke, mRS at admission, anticoagulant use, and presence of hypertension). Through this model, we

Table 2: Multivariate analysis

Index	P	Odds ratio	95% Confidence Interval
Cortical location	0.000	4.22	1.96–9.11
Hypertension	0.001	0.30	0.14–0.61
Anticoagulant use	0.027	2.59	1.11–6.05
Age	0.050	0.97	0.95–1.00
NIHSS at presentation	0.048	1.08	1.00–1.18
mRS at presentation	0.004	1.38	1.10–1.73
Large vessel disease	0.008	2.92	1.32–6.44

Table 3: Post-Stroke Epilepsy Risk Scale (PoSERS)[33]

Item	Risk
Supratentorial stroke	2
ICH involving cortical areas	2
Ischemia involving cortical or sub-cortical areas	1
Ischemia + ongoing neurological deficit	1
Stroke caused neurological deficit with mRS>3	1
Seizure occurred up to 14 days after stroke	1
Seizure occurred 15 days or later after stroke	2

Table 4: SeLECT score[22]

Variable	Score
Severity of stroke (Se)	
Mild (≤3)	0
Moderate (4-10)	1
Severe (≥11)	2
Large artery atheroscleorosis (L)	
Yes	1
No	0
Early seizures (≤7 days) (E)	
Yes	3
No	0
Cortical involvement (C)	
Yes	2
No	0
Territory of MCA (T)	
Yes	1
No	0

seek to determine those individuals who would be at high risk for ES, and therefore, can be given prophylactic antiseizure drugs (ASD) in the window period along with the standard of care. By preventing a seizure, we will not only decrease their infarct volume but also reduce the morbidity, mortality and duration of hospital stay for the patient.[34] We shall validate the same in a prospective study on a similar patient cohort.

STRENGTHS AND LIMITATIONS

Our study has various strengths. The data were collected prospectively with regular in-person follow-up interviews and no losses to follow-up. Stroke was identified by neuro-imaging (with a majority of patients having undergone MRI of the brain as well, which makes delineation of cortical involvement more precise) and a neurologist verified the diagnosis of seizures. We only included the patients with the first imaging-identified stroke (previous strokes can predispose to seizures due to the presence of gliosis) and those who were antiseizure drug-naive. Symptomatic causes for seizures like hyponatremia were also analyzed for imparting additional early seizure risk. Twenty-eight (75.6%) of our patients with early seizures were prescribed an antiseizure drug, which is in keeping with the general practice of giving an antiepileptic after an early seizure (SeLECT study – ASD after ES – 52% in Swiss cohort, 67% in Austria cohort, 92% in German cohort, and 27% in Italian cohort). Moreover, the SeLECT study cohort included patients recruited until 2014, during which time, mechanical thrombectomy was only being done in Austria. Our cohort included seven patients who underwent a mechanical thrombectomy and data from novel stroke cohorts are needed to address the effect of these newer modalities of stroke treatment on post-stroke epilepsy.

As our study was conducted in a tertiary care center there is likely to be a referral bias. The sample size is also small. The patients recruited from the outpatient also had some missing data like NIHSS at the time of stroke onset, leading to an incomplete evaluation of some potential risk factors.

CONCLUSION AND IMPLICATIONS FOR THE FUTURE

Identification of predictors of early seizures poses three major clinical questions at two ends of a spectrum:

1. Should acute ischemic large artery stroke patients with cortical involvement be given prophylactic short-term antiseizure drug therapy for 24 h? Since the majority of early seizures occur within 24 h, should loading antiepileptic drug be a part of the initial drug treatment of stroke with cortical involvement?

2. Unlike late seizures, early seizures after stroke do not qualify for the definition of epilepsy. Hence, the decision to treat early seizures and duration of treatment is still a clinical equipoise, even though early seizures are an important risk factor for late seizures.

3. If an analogy can be drawn between acute symptomatic seizures following traumatic brain injury and development in some head-injured patients of post-traumatic epilepsy; then an acute stroke may also be considered and used as a model to study if ASDs or any other therapeutic manipulation can prevent the development of post-stroke epilepsy in these patients.

All three questions can be answered only by a high-quality multi-center randomized controlled trial.

Through our study we have formulated an early seizure prediction tool using the following components: (a) cortical location, (b) large vessel stroke, (c) mRS at admission, (d) anticoagulant use, and (e) the presence of hypertension. The prediction tool might help in segregating and treating patients at high risk for early seizures with prophylactic antiseizure drugs, thereby preventing seizures and their associated

complications. Our model is presently being validated in another similar prospective cohort.

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Conflicts of interest

There are no conflicts of interest.

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