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Seizures Following Ischemic Stroke: Frequency of Occurrence and Impact on Outcome in a Long-Term Population-Based Study

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Abstract

Background & Purpose—Seizures are a known complication of ischemic stroke. This study assesses the long-term incidence and characteristics of post-stroke seizures in a well-defined population.

Methods—Utilizing the Rochester Epidemiology Project medical record linkage system, we identified all incident cases of ischemic stroke (IS) among Rochester, MN residents from 1990-1994, and followed the patients in the comprehensive medical record through March 2014. All patients with post-stroke seizures were identified, and data regarding incident IS, seizures, and status at last follow-up were analyzed.

Results—We identified 489 patients with first IS. Mean follow-up was 6.5 (SD 6.3) years. New onset seizures occurred in 35 patients (7.2%). Patients with post-stroke seizure did not differ from those without in terms of IS etiologic subtype ($p=0.44$) or IS risk factors ($p>0.05$). Early seizures (within 14 days of index stroke) developed in 14 patients (40%), the majority within the first 24 hours ($n=9$; 64.3%). The median time of seizure onset for the remaining 21 patients was 13.8 months. Functional outcome, as measured by modified Rankin scale, was worse following development of post-stroke seizures (mean mRS 2.9 after IS, 3.3 following index seizure; $p=0.005$), and mortality was higher as well, even after adjusting for IS etiologic subtype (HR 1.52; 95% CI 1.07-2.16; $p=0.02$).

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Conclusion—Development of post-stroke seizures is an infrequent, but significant complication of ischemic stroke, portending a worse short-term functional outcome and a higher long-term mortality rate. Seizure occurrence did not differ based on IS etiologic subtype or stroke risk factors.

Keywords

stroke; seizure; TOAST; epidemiology

Introduction

Seizures have been long recognized as a potential complication of ischemic stroke,^{1, 2} and many studies have been conducted assessing their epidemiology.³⁻²⁰ However, the data regarding the incidence of post-stroke seizures, risk factors for their development, and their effect on mortality and functional outcome of stroke survivors vary substantially across studies.²¹⁻²⁵ Differing study designs, definitions of early and late seizures and epilepsy, varying lengths and completeness of follow-up all contribute for this variability. Additionally, there are no recent randomized controlled trials that would answer the question whether antiepileptic drugs (AEDs) have any benefit for primary and secondary prevention of post-ischemic stroke seizures.²⁶ Seizures thus remain a problematic complication of stroke due to their unpredictability, unclear effect on prognosis, and lack of specific treatment guidelines.

In spite of all differences in study design and patient cohort, previously published studies have consistently shown a few patterns. There are two peaks in post-stroke seizure occurrence – the first is usually within the first day after a stroke, and the second is between six to twelve months.²¹ Early seizures (ES), variously defined as occurring within the first hours or days after stroke (24 hours up to 30 days),^{23, 25} occur in 1.8% to 16.6%.^{21, 23} Late seizures (LS), usually defined as occurring after the ES period (varying from after 24 hours to after 30 days) occur in 3% to 7.3% of stroke survivors.^{21, 23} Epilepsy (although variously defined), develops in only 2% to 4% of patients after stroke.²¹⁻²³ Data on risk factors for development of post-stroke seizures are equivocal.²¹⁻²⁴ However, a recently published meta-analysis reported hemorrhagic transformation of ischemic stroke, stroke severity, and alcoholism are risk factors for the development of ES, while cortical involvement and stroke severity are risk factors for LS development.²⁵ The data concerning the effect of post-stroke seizures on long-term outcome are not consistent - some studies have reported higher mortality and worse functional outcomes,^{8, 9, 27} whereas other studies have shown no such effect.^{5, 18, 20}

The aim of this long-term retrospective population-based study is to provide comprehensive data on the incidence and characteristics of post-stroke seizures, risk factors for their development, and their effect on long-term patient outcome.

Methodology

Design

We performed a retrospective medical record review utilizing the resources of the Rochester Epidemiology Project Medical Record Linkage System (REP).²⁸ All medical institutions in Rochester, Minnesota, participate in the REP, and therefore it allows for identification of virtually all new cases of incident stroke occurring among Rochester residents. The comprehensive medical records include inpatient and outpatient data, emergency department visits, skilled nursing home care, and autopsy and death certificate information.

Index ischemic stroke

The identification of index stroke cases was completed using methods described in previous epidemiology studies of stroke and transient ischemic attack (TIA) in Rochester, Minnesota.²⁹⁻³¹ In short, medical records of all residents of Rochester, Minnesota, who had a potential diagnosis of first-ever ischemic stroke or TIA during the five-year period starting January 1, 1990, through December 31, 1994, were screened by cerebrovascular nurses, and then all cases were confirmed by a cerebrovascular neurologist. Patients with a previous ischemic stroke were excluded. Verification of residence was done for all identified cases using information from city and county directories and earlier medical records.

All medical information, including patient demographics, cardiac and other medical comorbidities, medications, imaging reports, and outcome data were reviewed through March 31, 2014. Assessment of location of IS and vascular territory involved was based on available radiographic records. If these were not available, this assessment was based on a neurologist's clinical localization of the lesion and/or documented neurologic deficits. A group of cerebrovascular neurologists reviewed the medical records, and based on clinical history, documented neurologic examination, and the results of diagnostic and radiographic studies assigned ischemic stroke subtype classification using the criteria from the Trial or Org 10172 in Acute Stroke Treatment (TOAST).³² For patients with a post-stroke seizure, stroke severity was assessed as modified Rankin Scale score (mRS) at discharge from hospital by reviewing in detail the medical records available, with discharge notes being the principal source of information for this assessment.³³ Functional outcome after the first stroke data for patients that did not have a post-stroke seizure were not available for our analysis.

Index seizure

A post-stroke seizure was defined as any seizure occurring after the index stroke. A patient was determined to have had a seizure if he/she had a diagnosis by a physician (in almost every case by a neurologist) or, when available, an electroencephalographic (EEG) report of seizure activity. Patients with a pre-existing seizure disorder, defined as previous documented seizure (not including febrile seizures) or diagnosis of epilepsy, were excluded. We recorded the date of the first seizure, and also the dates of subsequent seizures. Records were reviewed for any episode of status epilepticus (SE) and reported complications of the seizures. Seizures were classified as generalized or partial (focal), based on the clinical history and EEG findings. Seizures were classified as ES if they occurred within two weeks

(14 days) of the index stroke. Seizures occurring more than 14 days after the index stroke were classified as LS. Functional status after the first seizure (also as mRS) was assessed in a fashion similar to the assessment of post-stroke functional status, using the medical records after the first recorded seizure.³³ The type, number, and side effects of AEDs used for seizure management were recorded.

Statistical analysis

Descriptive summaries were reported as mean (standard deviation) for continuous variables and as frequencies (percentages) for categorical variables. Incidence rate of seizures post-stroke was calculated as number of seizures divided by the sum of the follow-up times for each individual and was reported as incidence rate per 1,000 person years. Association between variables of interest and post stroke seizure status as outcome were assessed using Wilcoxon rank sum test or Fisher's exact test as appropriate. Magnitude of association was reported as odds ratio and 95% confidence intervals using logistic regression analysis. Association of post-stroke seizure (yes, no) with mortality was assessed using Cox proportional hazards regression model adjusting for TOAST subtype. P-values from Wald test were reported along with hazards ratio and 95% confidence intervals. All statistical analysis was performed using SAS version 9.3 software (SAS Inc., Cary, NC). All tests were 2 sided and p-values less than 0.05 were considered statistically significant.

The study was approved by the Institutional Review Board.

Results

Demographics

A total of 489 residents of Rochester, MN had a first-ever ischemic stroke between January 1, 1990, and December 31, 1994. Of these, 194 were males (39.7%). Mean follow up to death or final follow-up was 6.5 (SD 6.3) years, median follow-up was 4.6 years (range, 0–24 years) (Q1, Q3: 1.2, 10.3 years). Of the 489 patients, 35 (7.2%) developed a post-stroke seizure (males, 15; females, 20). Overall incidence rate of seizure post-stroke was 11.05 per 1,000 person years, and 11.63 and 10.66 per 1,000 patient year for males and females, respectively. The mean age at index stroke was 76.6 years (SD 12.9) overall, 77.0 years (SD 13.0) in patients without post-stroke seizure and 72.7 years (SD 10.8) in the seizure group ($p = 0.017$) (Table 1).

Stroke

The ischemic stroke most often involved the frontal lobe (23.1%), followed by parietal lobe (21.2%). Middle cerebral artery territory was the most common vascular territory involved (48.7%). Neither location of stroke nor vascular territory involved differed significantly between patients with and without post-stroke seizure ($p > 0.05$).

The most common TOAST ischemic stroke subtype was stroke of undetermined etiology (cryptogenic; 46.8%), followed by cardioembolic (24.9%). There was no significant difference in TOAST stroke subtypes between patients who developed post-stroke seizures and those who did not ($p = 0.44$) (Table 1). There was also no difference between the two

groups when comparing combined cardioembolic and large-artery atherosclerosis to small-vessel occlusion ($p = 0.32$), or cryptogenic to small-vessel occlusion ($p = 1.00$) (Table 1). Similarly, there was no difference in TOAST subtypes between patients who developed ES and LS ($p = 0.19$).

Risk factors for stroke and seizures

No differences were identified between those with and without post-stroke seizures in terms of pre-morbid stroke risk factors. Those studied included the following: hypertension ($p = 0.22$), total cholesterol ($p = 0.95$), diabetes mellitus type 2 ($p = 0.13$), tobacco use ($p = 0.27$), atrial fibrillation ($p = 0.91$), and a history of myocardial infarction ($p = 0.67$) (Table 1). Three of the 489 stroke patients had a history of traumatic brain injury, however, none of these patients developed post-stroke seizures.

Univariate regression analysis

Univariate logistic regression analysis regarding patient demographics, TOAST stroke subtypes, and pre-morbid ischemic stroke risk factors did not identify any independent predictors for the development of post-stroke seizure (Table 2).

Seizures

Of the 35 patients that developed post-stroke seizures, ES developed in 14 patients (40%). Half of ES occurred within the first 24 hours after the index stroke ($n = 7$; 50%). Of the other patients with ES, five had a seizure between 24 hours and 7 days following the stroke, and two patients had a seizure during the second week following the stroke. Late seizures developed in the remaining 21 patients (60%). Median time of onset of LS was 13.8 months (range 0.6 – 234 months) (Figure 1).

An EEG result was available in 19 patients (54.3%). Diffuse slowing ($n = 7$; 36.8%) and focal slowing ($n = 7$; 36.8%) were the most commonly found abnormalities. Two patients had normal EEGs. Based on EEG reports and seizure semiology, the majority of patients had partial (focal) onset seizures ($n = 23$; 65.7%) with or without secondary generalization. The other 12 patients had generalized seizures at onset (34%).

Thirteen patients (37.1%) had recurrent seizures (>1 seizure). Of these, seven had only one additional seizure following the index seizure (one case due to a temporary discontinuation of AED treatment, and one case due to difficulty administering AED treatment). Of the other patients with recurrent seizures, five had at least two additional seizures following the index seizure (one of these had subtherapeutic levels of AED recorded due to non-compliance), and one patient had repeated and frequent seizure activity. There was no significant differences in seizure recurrence between patients with ES versus LS ($p = 0.89$). Four patients (11.4%) developed status epilepticus (SE), with no difference regarding the timing of seizure onset, (ES, 2; LS, 2). For one patient, SE was the initial presentation of index seizure.

Medical complications immediately following the onset of post-stroke seizure were noted in 6 patients (17.1%): one patient developed pneumonia, one patient died as a direct result of a seizure, and four patients had tongue injuries, presumably as a result of tongue biting.

Treatment with AEDs was initiated in 32 patients (91.4%). Only one AED was necessary for seizure control in the 32 patients. Of the three untreated patients, one died shortly after the seizure and had no treatment started, and the other two patients did not require antiepileptic medication for seizure control. Phenytoin was the most commonly prescribed drug (n = 24 patients, 70.6%). Side effects of AEDs were noted in 7 patients (21.9%). One patient had increased somnolence along with fluctuations between agitated behavior and extreme drowsiness, one had increased somnolence with cognitive and memory problems, one had anorexia, one had diffuse slowing on EEG attributed to medication, two had purple glove syndrome, and one had signs of Depakote toxicity.

Outcomes

Functional outcome of patients with post-stroke seizures was assessed by mRS score. Following index stroke, the mean mRS was 2.9 (SD 1.5; median 3.0), compared to 3.3 (SD 1.4; median 3.0) at time of hospital discharge after development of post-stroke seizures (p = 0.005). Mortality at the last follow-up was higher in the seizure group compared to the non-seizure group overall (HR 1.54; 95% CI 1.08-2.19; p=0.02), and after adjusting for TOAST IS subtype (HR 1.52; 95% CI 1.07 - 2.16; p = 0.02).

Discussion

The current study provides population-based data with long-term comprehensive follow-up to the existing information regarding the epidemiology of seizures following incident ischemic stroke. The overall incidence of epilepsy in Rochester, MN has been reported to be 44 per 100,000 person-years, with cerebrovascular diseases being the most common antecedent to the onset of seizures.³⁴ The incidence of seizures following ischemic-stroke in our study (7.1%) is consistent with other previously published reports,^{5, 7, 9, 12} with this study having the longest mean follow up period.

TOAST stroke subtype, stroke location, vascular territory, and pre-morbid cerebrovascular risk factors did not differ significantly between those with and without post-stroke seizures, even when comparing patients with ES versus LS. Previous reports, however, have identified cortical infarction and stroke severity (both infarct size and disability) as predictors of seizures after an ischemic stroke.^{20, 22} Although strokes related to embolization tend to cause larger, more severe strokes with cortical involvement, there was no difference in TOAST stroke subtypes, even when combining cardioembolic and large-artery atherosclerosis mechanisms. Conceptually this is surprising, but other studies have also failed to demonstrate an increased seizure risk.^{5, 8, 20, 23, 35, 36}

The hypothesized pathophysiology for post-stroke seizures differs between ES and LS. The ictus for ES has been attributed to metabolic dysfunction and excitatory neurotransmitter release secondary to acute ischemia.²² Supporting this hypothesis is that the majority of patients with ES in this study and in previous studies had a seizure within 24 hours of the

ischemic event.^{22, 35} Development of variably defined ES would be distributed more evenly over the initial two weeks if the seizure ictus was due to cortical ischemia or structural damage alone. Conversely, the ictus for the development of LS is likely due to structural damage and gliosis.²² Despite the arbitrary cut-off of two weeks for patients with LS, this group had a delayed median seizure onset of 13.8 months after the stroke. The bimodal distribution suggests that the risk of post-stroke seizures declines rapidly after the initial 24 hours, only to increase roughly a year later.

Another commonly reported difference between patients with ES and LS is the development of recurrent seizures/epilepsy. The risk of recurrent post-stroke seizures has been reported to be between 3-10% overall, but as high as 55-90% in patients with LS, and in the SASS, the development of LS was an independent predictor for seizure recurrence.^{4, 9} In our study, 37.1% of patients developed recurrent seizures, with no significant difference between the patients with ES versus LS. The reason this difference was not observed is unclear, especially given the long period of follow-up, but it may be related to a relatively small sample size. Four patients (11.4%) developed SE. This frequency is similar to the previous studies,³⁷ and there was also no significant difference regarding the timing of the initial seizure and development of SE.

Post-stroke seizures are typically readily controlled by AEDs. AED monotherapy was enough to control seizures in all patients that were treated in our group. This high rate of monotherapy is similar to other previously published studies.^{3, 5} There is no consensus, though, on the appropriate use of AEDs in post-stroke seizures. Some experts advocate that patients that develop LS should be started on AEDs given the reported risk of seizure recurrence. However, patients with post-stroke seizures are often elderly and at greater risk of medication side effects or drug-drug interactions.²² More than one-fifth of the patients in this study developed side effects. This may not be as applicable today, as many of the side effects reported were attributable to phenytoin, which was the most commonly prescribed AED in this study. Additionally, the use of AEDs following stroke has been associated with slower motor recovery, worse functional independence, and poorer cognitive outcomes.^{38, 39} The newer AEDs have less drug-drug interactions and may be better tolerated, however, data from randomized controlled trials for ischemic stroke survivors are not available.²⁶ The risk of medication use needs to be weighed against the risk and morbidity associated with recurrent seizures. In our study, there was a statistically significant difference in functional outcome following the initial seizure (measured by mRS score). This finding needs to be interpreted with caution though, as we assessed the post-seizure mRS at discharge from hospital, which does not necessarily reflect the long-term functional outcome. Still, the patients with post-stroke seizures had higher overall mortality, even after adjusting for stroke subtype.

Our study's key limitations are its retrospective design and a relatively small sample size. The availability of a comprehensive medical record with long-term data availability for essentially all patients lessens, but does not eliminate, the retrospective design limitation. As outlined, the sample size limits our ability to define predictive risk factors for seizure occurrence. The retrospective design did allow for longer-term follow-up than is typically feasible for a prospective study. Another advantage of our study is that it is a population-

based study as opposed to previous single or multi-center hospital-based studies, thereby lessening the impact of referral or survival bias. Another limitation that is common to all post-stroke seizure studies is a possible underreporting and/or under recognition of seizures.

Conclusion

The development of post-stroke seizures is an infrequent, but significant complication of ischemic stroke, portending a worse short-term functional outcome and a higher long-term mortality rate. The frequency of seizure occurrence was not dependent on ischemic stroke etiologic subtype, location or, on pre-stroke risk factors. Therefore, clinicians need to be vigilant to the potential occurrence of seizures in all patients with ischemic stroke, especially since post-stroke seizures appear to be relatively easily controlled with a single medication.

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Figure. Timing of index seizure following ischemic stroke

Table 1

Patient demographic, TOAST stroke subtype, and pre-morbid ischemic stroke risk factors among patients with and without post-stroke seizure.

Variable	Source population (N=489)	No seizure [N (%) or Mean (SD)] (N=454)	Post-stroke seizure [N (%) or Mean (SD)] (N=35)	p-value
Demographics				
Age (years)	76.6 (13.0)	77.0 (13.0)	72.7 (10.8)	0.017
Male	194 (39.7%)	179 (39.4%)	15 (42.9%)	0.72
TOAST stroke subtype				0.44
Large-artery atherosclerosis	48 (9.8%)	43 (9.5%)	5 (14.3%)	
Cardioembolic	121 (24.7%)	110 (24.2%)	11 (31.4%)	
Small-vessel occlusion (lacunar)	75 (15.3%)	71 (15.6%)	4 (11.4%)	
Undetermined etiology (cryptogenic)	241 (49.3%)	214 (47.1%)	13 (37.1%)	
Combined cardioembolic & large artery v. small-vessel	169/244 (69.2%)	153/224 (68.3%)	16 / 20 (80%)	0.32
Cryptogenic v. small-vessel	227/302 (75.2%)	214/285 (75.1%)	13 /17 (76.5%)	1.00
Pre-morbid stroke risk factors				
Hypertension	365 (74.6%)	342 (75.3%)	23 (65.7%)	0.22
Total cholesterol	209.3 (48.5)	209.3 (48.6)	209.6 (48.2)	0.95
Diabetes mellitus	98 (20%)	92 (20.3%)	6 (17.1%)	0.83
Tobacco use	179 (36.6%)	163 (35.9%)	16 (45.7%)	0.25
Atrial fibrillation	117 (23.9%)	109 (24.0%)	8 (22.9%)	0.91
Previous myocardial infarction	124 (25.4%)	115 (25.3%)	9 (25.7%)	0.67

Table 2

Results of univariate logistic regression analysis assessing potential risk factors for the occurrence of post-stroke seizure.

Variable	Odds Ratio (95% CI)
Demographics	
Age	0.98 (0.95-1.00)
Male	1.16 (0.58-2.32)
TOAST ischemic stroke subtype	
Large artery-atherosclerosis	1
Cardioembolic	0.86 (0.28-2.62)
Small-vessel occlusion (lacunar)	0.49 (0.12-1.90)
Undetermined etiology (cryptogenic)	0.52 (0.18-1.54)
Combined cardioembolic & large artery	
Cardioembolic, Large-artery	1
Small-vessel, cryptogenic	0.57 (0.28-1.16)
Cryptogenic compared to small-vessel	
Cryptogenic	1
Small-vessel	0.68 (0.33-1.40)
Pre-morbid stroke risk factors	
Hypertension	0.60 (0.29-1.25)
Total cholesterol	1.00 (0.99-1.01)
Type 2 diabetes mellitus	1.04 (0.64-1.67)
Tobacco use	1.22 (0.98-1.52)
Atrial fibrillation	0.99 (0.59-1.68)
Previous myocardial infarction	1.10 (0.79-1.54)

Note: p-values not included in the table as all p-values >0.05