Acute epileptiform abnormalities are the primary predictors of post-stroke epilepsy: a matched, case–control study

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Abstract
Stroke patients who underwent continuous EEG (cEEG) monitoring within 7 days of presentation and developed post-stroke epilepsy (PSE; cases, n = 36) were matched (1:2 ratio) by age and follow-up duration with ones who did not (controls, n = 72). Variables significant on univariable analysis [hypertension, smoking, hemorrhagic conversion, pre-cEEG convulsive seizures, and epileptiform abnormalities (EAs)] were included in the multivariable logistic model and only the presence of EAs on EEG remained significant PSE predictor [OR = 11.9 (1.75–491.6)]. With acute EAs independently predicting PSE development, accounting for their presence may help to tailor post-acute symptomatic seizure management and aid anti-epileptogenesis therapy trials.

Introduction
Post-stroke epilepsy (PSE) accounts for nearly one in every eight epilepsy cases in high-income countries.1 Several stroke-related features, including stroke severity, early clinical seizure, and neuroimaging findings, are well-known predictors of PSE.2 Despite epilepsy being an electrophysiological disorder, the role of early electroencephalogram (EEG) findings in predicting PSE development remains poorly investigated. A few recent studies report association of acute EEG findings after acute brain injuries (ABIs), including trauma, to epilepsy development.3,4 Our primary aim is to test the hypothesis that acute epileptiform abnormalities (EAs) after stroke are associated with an increased risk of PSE using a case–control study design.

Methods
After IRB approval, we used prospectively maintained stroke and EEG database to identify adults presenting with acute ischemic stroke (AIS) between 04/01/2012 and 03/31/2018, who underwent continuous EEG (cEEG) monitoring (at least 12-h) within 7 days of last known well time. cEEG at our institute is typically performed for the indication of unexplained altered mental status or a motor event concerning for seizure. Each cEEG is preceded by a screening for 20-min EEG. A research associate (LE), blinded to the clinical and EEG data, reviewed the electronic medical records (EMR) of above patients to identify cases and control. We excluded patients with epilepsy prior to the AIS. Patients who had a clinical seizure after hospital discharge, as documented by their treating physician, were identified to have PSE (cases).5 We matched these cases by age at the time of AIS (±5 years) and duration of follow-up (±3 months) with controls (AIS who underwent cEEG but did not develop PSE) in a 1:2 ratio. Subsequently, EMR was reviewed to extract the acute clinical, neuroimaging, EEG, and anti-seizure medication (ASM) data (Tables 1 and 2). Epileptiform abnormalities (EAs) on EEG includes electrographic seizures (based on Salzburg criteria6), isolated sharp waves (SWs), lateralized periodic discharges (LPDs), lateralized rhythmic delta activity (LRDA), and generalized periodic discharges (GPDs) (based on American Clinical Neurophysiology Society nomenclature).
Statistical methods

Univariable logistic regression with a random effect accounting for matching was used to analyze the differences between cases and controls. Variables with zero-cells use exact conditional logistic regression to compute p-values. The variables significant in the univariable analysis (p < 0.05) were included in the multivariable analysis, except ASMs use, cEEG indication and duration because these were not considered potential predictors of PSE development. The multivariable model was fit using exact conditional logistic regression to account for zero cells. Analysis was done in SAS (v9.2, Cary, NC) and R (v 4, Vienna, Austria), and p-values less than 0.05 are considered significant.

Table 1. Comparison of various stroke-related variables between cases and control.

| Variable                      | Level                           | Control (n = 72) | Case (n = 36) | Univariable results | Multivariable results |
|-------------------------------|---------------------------------|-----------------|---------------|---------------------|----------------------|
|                               |                                 |                 |               | Odds ratio          | p-value              | Odds ratio          | p-value              |
| Age at presentation, mean (SD)| 65.8 (14.2)                     | 66.0 (14.5)     | 1.00 [0.97;1.03] | 0.96                |                      |
| Female sex                    | 35 (48.6)                       | 12 (33.3)       | 0.53 [0.23;1.22] | 0.13                |                      |
| Duration of follow-up (months)| 33.4 [17.8;58.6]                | 32.5 [16.5;58.1]| 1.00 [0.98;1.02] | 0.95                |                      |
| Initial NIHSS, median [25th;75th] | 7.00 [3.00;15.2]             | 13.5 [4.00;18.0] | 1.05 [0.99;1.10] | 0.086               |                      |
| Hypertension                  | 63 (87.5)                       | 25 (69.4)       | 0.33 [0.12;0.90] | 0.027*              | 0.41 [0.04, 2.28]    | 0.42                |
| Dyslipidemia                  | 45 (62.5)                       | 19 (52.8)       | 0.67 [0.30;1.53] | 0.33                |                      |
| Diabetes                      | 28 (38.9)                       | 11 (30.6)       | 0.70 [0.29;1.62] | 0.40                |                      |
| Current smoker                | 31 (43.1)                       | 8 (22.2)        | 0.39 [0.14;0.94] | 0.037*              | 0.22 [0.05, 1.19]    | 0.099               |
| Prior stroke                  | 14 (19.4)                       | 7 (19.4)        | 1.01 [0.34,2.74] | 0.99                |                      |
| Atrial fibrillation           | 25 (34.7)                       | 13 (36.1)       | 1.06 [0.45,2.46] | 0.89                |                      |
| Cause of stroke               | Cadioembolism                   | 31 (43.1)       | 10 (27.8)     | Ref.                |                      |
|                               | Large artery atherosclerosis    | 10 (13.9)       | 9 (25.0)      | 3.02 [0.78;13.1]    | 0.13                |
|                               | Other                           | 31 (43.1)       | 17 (47.2)     | 1.83 [0.64,5.74]    | 0.32                |
| Vessel involved               | MCA/ACA1                        | 47 (65.3)       | 27 (75.0)     | Ref.                |                      |
|                               | PCA                             | 6 (8.33)        | 3 (8.33)      | 0.86 [0.13,4.67]    | 0.99                |
|                               | Multiple                        | 5 (6.94)        | 2 (5.65)      | 0.69 [0.06,4.34]    | 0.99                |
|                               | Small vessel                    | 14 (19.4)       | 4 (11.1)      | 0.52 [0.12,1.80]    | 0.40                |
| Cortical involvement          | Bilateral                      | 50 (69.4)       | 28 (77.8)     | 1.52 [0.61,4.10]    | 0.36                |
| Side affected                 | Left                            | 12 (16.7)       | 3 (8.33)      | Ref.                |                      |
|                               | Right                           | 26 (36.1)       | 18 (50.0)     | 2.64 [0.70,13.6]    | 0.15                |
| Lobes involved                | Multilobar                      | 34 (47.2)       | 15 (41.7)     | 1.70 [0.45,8.73]    | 0.43                |
|                               | Unilobar                        | 28 (38.9)       | 16 (44.4)     | Ref.                |                      |
|                               | N/A                             | 22 (30.6)       | 11 (30.6)     | 0.88 [0.33,2.28]    | 0.78                |
| Hemorrhagic conversion        |                                 | 22 (30.6)       | 9 (25.0)      | 0.72 [0.26,1.94]    | 0.51                |
| Stroke therapies and outcome  |                                 |                 |               |                     |                      |
| Reperfusion therapy           | 14 (19.4)                       | 6 (16.7)        | 0.84 [0.27,2.36] | 0.99                |
| Secondary prevention therapies| Anticoagulation                 | 5 (6.94)        | 4 (11.1)      | Ref.                |                      |
|                               | Antiplatelet                    | 53 (73.6)       | 26 (72.2)     | 0.71 [0.15,3.67]    | 0.86                |
|                               | Combination                     | 14 (19.4)       | 4 (11.1)      | 0.45 [0.06,2.99]    | 0.54                |
|                               | None                            | 0 (0.00)        | 2 (5.56)      | 2.32 [0.25,Inf]     | 0.27                |
| Glasgow outcome scale at the time of discharge | Poor outcome | 35 (48.6) | 19 (52.8) | Ref. |                      |
|                               | Good outcome                    | 37 (51.4)       | 17 (47.2)     | 0.85 [0.38,1.90]    | 0.68                |

Categorical variables presented as N with % in parenthesis.
Inf, Infinite.
1Only one case with ACA stroke (Therefore, combined with MCA).
*p < 0.05.
ªExact conditional logistic regression.
Results

A total of 36 cases and 72 controls were included in the study from a previously described cohort of stroke patients undergoing cEEG. Among the 38 (11.1%) out of 341 AIS patients who developed PSE, two were excluded due to lack of matching controls. The included cases and controls were well matched by age at the time of AIS (66 years, \(p = 0.96\)) and duration of follow-up (33 months; \(p = 0.95\)). Tables 1 and 2 compare the distribution of various stroke-related (demographics, clinical, neuroimaging, and stroke therapies) and the electro-clinical variables, respectively, between the cases and controls. Two separate tables are provided for ease visualization.

**Univariable analysis**

As noted in Table 1, cases at the time of AIS were less likely to have hypertension (OR = 0.33, 95%CI = 0.12–0.9), and ongoing smoking (OR = 0.39, 95%CI = 0.14–0.94), and more likely to have a hemorrhagic conversion of the stroke (OR = 3.92, 95%CI = 1.43–11.3). Table 2 shows that convulsive seizures prior to cEEG (OR = 7.28, 95%CI = 1.96–36.6). Overall, EAs were significantly more common among cases (21/36, 58.3%) compared to controls (11/72, 15.3%) (OR = 15.4, 95%CI = 3.63–137.5). Except for GPDs, all individual EAs, including electrographic seizures, LPDs/LRDA, SWs, were significantly more common in cases (Fig. 1).

**cEEG and EAs**

Figure 2 provides a representation of cEEG start in relation to the day of admission, number of days of monitoring, and presence/absence of EAs on each day of cEEG monitoring. Ten (27.8%) cases and 23 (31.9%) controls were started on cEEG on the day of admission. Cases and controls were comparable in terms of the median day of the start of cEEG monitoring after AIS (Table 2 and Fig. 2). However, due to the higher prevalence of EAs among cases, the duration of cEEG was significantly longer in them compared to controls (OR = 1.59, 95%CI = 1.20–2.11). Among patients with EAs on cEEG, these findings were present on the first day of monitoring in 18 (85.7%) cases and nine (81.8%) controls. A total of 16 patients had EAs on their initial 20-min screening EEG. Overall, EAs were noted at a median of 1.65 (interquartile range = 0.3–10) h after the start of EEG monitoring.

**Multivariable analysis**

The variables included in the final exact conditional logistic regression model included EAs, hypertension, smoking status, hemorrhagic conversion of stroke, convulsive...
seizures prior to cEEG, and ongoing smoking status. The fully adjusted model found that only the presence of EAs significantly increased epilepsy development odds by 11.9 (95%CI = 1.75–491.6, \( p = 0.004 \)) (Table 2).

**Discussion**

Widespread use of EEG monitoring in modern neurocritical care warrants investigation of acute EEG findings’ association to late seizures (>7 days) after stroke (PSE). Convulsive acute symptomatic seizures (ASyS), stroke severity, and cortical involvement are widely reported predictors of PSE. Using a case–control design and a deeply phenotyped stroke population (demographical, clinical, neuroimaging, therapeutics, and electrophysiological data), we found that acute EAs on the EEG are associated with almost 12-times increased odds of PSE after adjusting for a multitude of potential risk factors, including convulsive seizures prior to EEG. Remarkably, acute EAs on EEG are the only significant predictors of PSE. Prior PSE prognostication models did not include electrophysiological findings from the acute ictogenesis (ASyS) period after stroke. We included predictors of PSE based on the SeLECT score, but some of them were not significantly different between cases and controls on univariable analysis. Therefore, it is notable that when acute EEG findings are analyzed alongside established clinical and neuroimaging predictors, only the former remains significantly associated with PSE development.

A few primarily pre-cEEG era studies investigating the correlation of acute EEG with PSE reveal conflicting results. A recent prospective study of consecutive anterior circulation stroke patients analyzed a limited set of clinical and neuroimaging predictors alongside findings from a short-duration (<60 min) EEG performed within 72-h of admission. They found that the presence of interictal epileptiform activity (sharp waves/spikes) is an independent predictor of PSE. A case–control study analyzed post-traumatic epilepsy (PTE) patients and found that patients with PTE had three times increased odds of presence of acute EAs compared to TBI patients who did not develop epilepsy. These findings suggest the utility of acute EEG findings as a reliable prognostic biomarker of epileptogenesis. cEEG reveals EAs in 17% of AIS patients. EEGs of up to 1-h duration performed almost daily during the first 7 days after stroke show LPDs, isolated SWs, and electrographic seizures in around 25%, 12%, and 4% of stroke patients, respectively. Therefore, the timing of the EEG, rather than the duration, may be more important in providing critical information for PSE prognostication.

Our findings have direct clinical and research implications. ASMs lack definitive anti-epileptogenesis (AEG) properties. Yet, they prevent ASyS recurrence and delay recurrence 1–2 years after the first seizure. Therefore, their use in patients at high risk of PSE, individualized based on the identification of acute EAs, could potentially prevent seizures in the immediate post-hospitalization period and aid in uninterrupted rehabilitation. Conversely, the absence of acute EAs could help to avoid the indiscriminate long term use of ASMs after hospital discharge.

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Figure 1. Comparison of individual epileptiform abnormalities in the case–control groups.
Additionally, the 12-times increased odds of PSE in stroke patients with acute EAs can help to select a highly enriched, at-risk cohort for PSE development. Such high-risk cohort selection is critical to improve feasibility of AEG therapy trials because only 6% of unselected stroke patients develop PSE. With 17% rate of EAs in unselected stroke cohort, using the 95% lower confidence bound of the EA rate in cases [52.8% (37%–68%)] as a conservative estimate of their probability among cases, a study focused on just those with EAs would increase expected event rate (PSE) to 13.1%, using Bayes’ Rule. Thus, an AEG therapy trial focusing on a stroke population with EAs, would reduce the total sample size required to detect a 50% treatment effect in a clinical trial with 80% power based on a two-sided test with alpha = 0.05 by 57% (1498 to 646).

Although our study shows a clear association between acute EAs and PSE, the small study population and overlap in occurrence between various EAs prevented us from analyzing their individual, independent association with PSE. We relied on the treating physician’s judgment to determine PSE, which overcomes the patients’ potential misclassification of events as seizures. However, the selection bias inherent in case-control studies and the dependence on EMR for outcome documentation are relevant limitations to consider in the interpretation of our study.

In conclusion, using a case-control design with deep, multi-modal phenotyped stroke patients, we show that acute EAs are the only significant PSE predictor after adjusting for many potential risk factors. Our findings may guide ASM management in the posthospital

**Figure 2.** Cases (left side) and their controls (right side, 1:2 matched) from the day of admission (Day #0) to the day of the start of cEEG monitoring (first colored box) highlighting the day with epileptiform abnormalities on cEEG (Red color; otherwise Orange color).
discharge course. With the caveat of a small sample size, we provide evidence for acute EAs as prognostic biomarkers of PSE development, which can enhance the feasibility of clinical trials testing anti-epileptogenesis therapies.

**Conflict of Interest**

None of the authors has any conflict of interest to disclose.

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