BRIEF COMMUNICATION

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 criteria[6]), 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).

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		
Clinical variables							
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.	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		
Neuroimaging variables							
Vessel involved	MCA/ACA[1]	47 (65.3)	27 (75.0)	Ref.	Ref.		
	PCA	6 (8.33)	3 (8.33)	0.86 [0.13;4.67]	0.99		
	Multiple	5 (6.94)	2 (5.56)	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		50 (69.4)	28 (77.8)	1.52 [0.61;4.10]	0.36		
Side affected	Bilateral	12 (16.7)	3 (8.33)	Ref.	Ref.		
	Left	26 (36.1)	18 (50.0)	2.64 [0.70;13.6]	0.15		
	Right	34 (47.2)	15 (41.7)	1.70 [0.45;8.73]	0.43		
Lobes involved	Multilobar	28 (38.9)	16 (44.4)	Ref.	Ref.		
	Unilobar	22 (30.6)	11 (30.6)	0.88 [0.33;2.28]	0.78		
	N/A	22 (30.6)	9 (25.0)	0.72 [0.26;1.94]	0.51		
Hemorrhagic conversion		8 (11.1)	12 (33.3)	3.92 [1.43;11.3]	0.007*	6.25 [0.995, 127.3]	0.051
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.	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.	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.
[1]Only one case with ACA stroke (Therefore, combined with MCA).
*$p < 0.05$.
[†]Exact conditional logistic regression.

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 2. Comparison of electro-clinical features and seizure management between cases and controls.

Variable	Level	Control (n = 72)	Case (n = 36)	Univariable results		Multivariable results	
				Odds ratio	p-value	Odds ratio	p-value
EEG-related variables							
Pre-cEEG convulsive seizures		3 (4.17)	9 (25.0)	7.28 [1.96;36.6]	0.004*	6.23 [0.29, 423.4]	0.40
cEEG indications‡	AMS	68 (94.4)	28 (77.8)	Ref.	0.015*		
	Seizure like event	4 (5.56)	8 (22.2)	0.21 [0.05;0.75			
Duration between presentation and start of cEEG, median [25th;75th]		1.00 [0.00;2.00]	1.00 [1.00;3.00]	1.13 [0.89;1.44]	0.32		
Total Number of days on cEEG, median [25th;75th]‡		1.00 [1.00;2.00]	2.00 [1.00;4.00]	1.59 [1.20;2.11]	0.001*		
Epileptiform abnormalities		11 (15.3)	19 (52.8)	9.43 [2.73, 32.6]	<0.001*	11.9 [1.75;491.6]	0.004
Seizure management variables							
ASMs in hospital‡		8 (11.1)	15 (41.7)	5.56 [2.10;15.8]	0.001*		
IV anesthetic used for seizure control†,‡		0 (0.00)	3 (8.33)	7.70 [1.17;Inf]	0.037*		
Patient discharged on ASMs‡		5 (6.94)	15 (41.7)	9.16 [3.11;31.7]	<0.001*		

Categorical variables presented as *N* with % in parenthesis.
Inf, Infinite.
*$p < 0.05$.
†Exact conditional logistic regression.
‡Not included in multivariable regression model.

Results

A total of 36 cases and 72 controls were included in the study from a previously described cohort of stroke patients undergoing cEEG.[7] 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, as expected, 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 = 1.2–2.11). 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

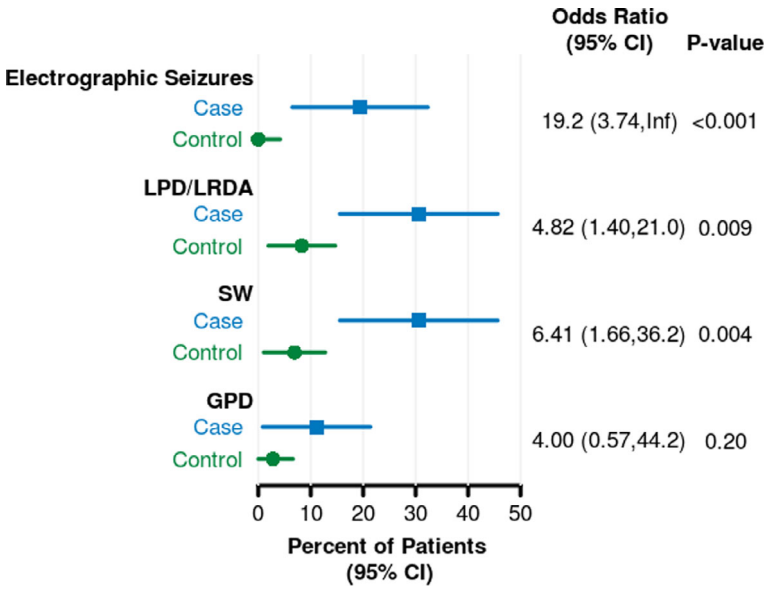

Figure 1. Comparison of individual epileptiform abnormalities in the case–control groups.

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).[5] Convulsive acute symptomatic seizures (ASyS), stroke severity, and cortical involvement are widely reported predictors of PSE.[8] 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[9]) period after stroke.[2,10] We included predictors of PSE based on the SeLECT score,[2] 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.[11] 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.[12]They found that the presence of interictal epileptiform activity (sharp waves/spikes) is an independent predictor of PSE.[12] 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.[3] These findings suggest the utility of acute EEG findings as a reliable prognostic biomarker of epileptogenesis.[4]cEEG reveals EAs in 17% of AIS patients.[13] More than 80% of cases and controls in our study had EAs on the first day of cEEG monitoring (Fig. 2). 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.[12]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.[14] 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.[7]

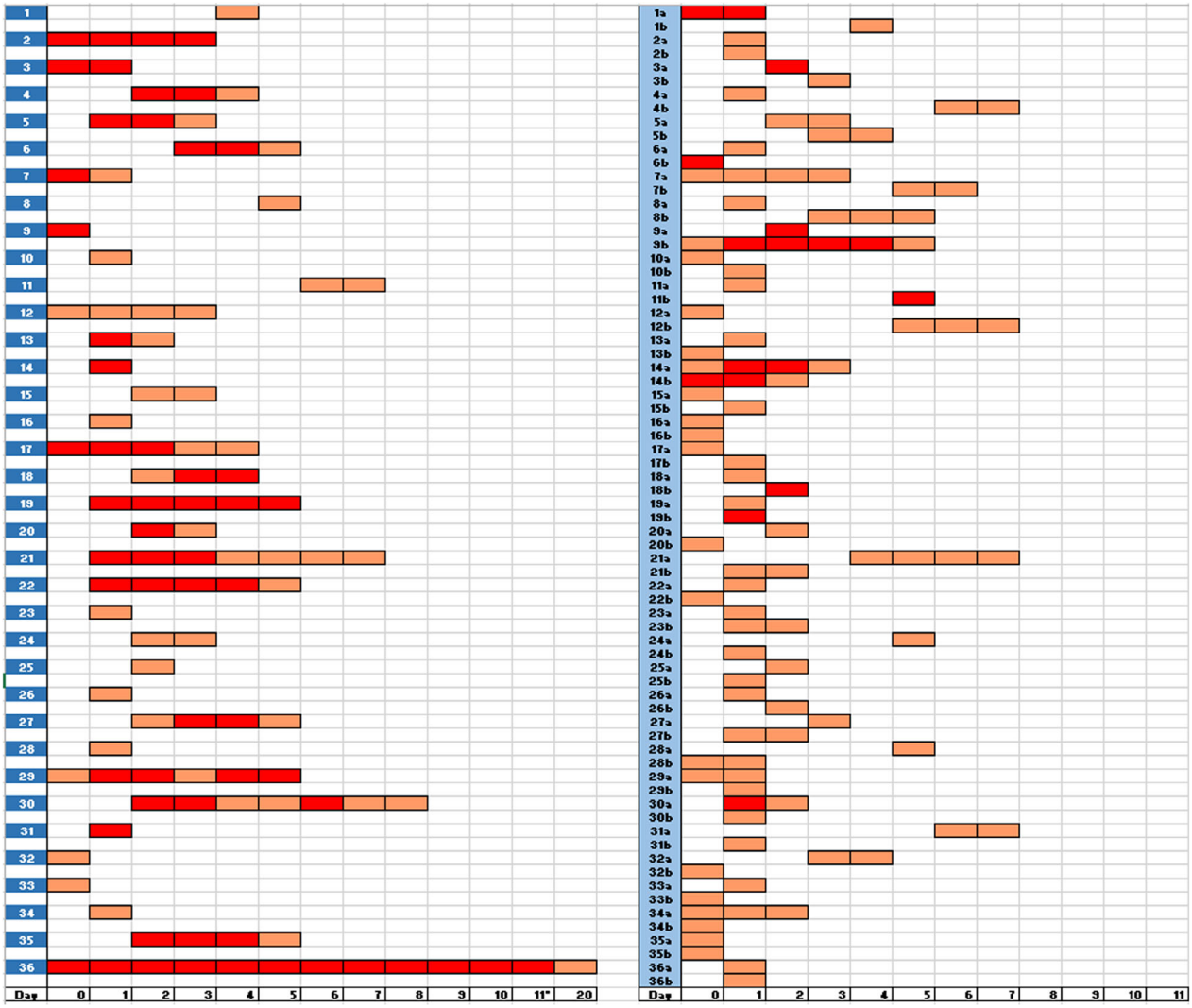

Figure 2. Cases (left side) and their controls (right side, 1:2 matched) from the day of admission (Day #0) to the day of the start of cEEG monitoring (first colored box) highlighting the day with epileptiform abnormalities on cEEG (Red color; otherwise Orange color).

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.[8] With 17% rate of EAs in unselected stroke cohort,[13] 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

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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