

Epileptiform Activity in Traumatic Brain Injury Predicts Post-Traumatic Epilepsy

Jennifer A. Kim, MD, PhD,^{1,2}
Emily J. Boyle, BS,¹
Alexander C. Wu, MPH,³
Andrew J. Cole, MD,¹
Kevin J. Staley, MD, PhD,¹
Sahar Zafar, MD,^{1,2}
Sydney S. Cash, MD, PhD,¹ and
M. Brandon Westover, MD, PhD¹

We hypothesize that epileptiform abnormalities (EAs) in the electroencephalogram (EEG) during the acute period following traumatic brain injury (TBI) independently predict first-year post-traumatic epilepsy (PTE₁). We analyze PTE₁ risk factors in two cohorts matched for TBI severity and age (n = 50). EAs independently predict risk for PTE₁ (odds ratio [OR], 3.16 [0.99, 11.68]); subdural hematoma is another independent risk factor (OR, 4.13 [1.18, 39.33]). Differences in EA rates are apparent within 5 days following TBI. Our results suggest that increased EA prevalence identifies patients at increased risk for PTE₁, and that EAs acutely post-TBI can identify patients most likely to benefit from antiepileptogenesis drug trials.

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Severe brain trauma is a leading cause of death and disability in adults and children worldwide.¹ Post-traumatic epilepsy (PTE) is one of the most disabling complications in survivors and can be difficult to treat.² PTE rates are reported in up to 20% of patients, with increased risk based on brain injury severity, surgical intervention, time since traumatic brain injury (TBI), and younger age.^{3–6}

Although some risk factors are known, we need to better stratify patients at highest risk for PTE to better understand antiepileptogenesis and develop therapeutic agents. Although there is great interest in interventions to prevent post-TBI epileptogenesis, clinical trials have been plagued by financial and logistical barriers, with estimates upward of \$20 million.^{4,7} Efforts to prevent epileptogenesis would be greatly aided by identification of acute biomarkers that identify patients at high risk for developing

PTE, thus enriching the population eligible for clinical trials in a cost-effective manner.⁸

Epileptiform abnormalities (EAs), which include sporadic epileptiform discharges (spikes and sharp waves), periodic epileptiform discharges, and rhythmic patterns, are common following all types of acute brain injury, including TBI.⁹ Recent work from our group suggests that EAs predict risk for secondary brain injury (Kim et al 2017) and acute seizures.^{10,11} TBI serves as an excellent acute brain injury model in which to investigate the role of EAs as a marker of, and possible contributor to, secondary morbidity in the form of PTE. We aimed to determine whether EAs could be used as an early biomarker of elevated risk for first-year post-traumatic epilepsy (PTE₁). Such information could be used to specify subpopulations of TBI patients that would benefit from targeted trials of antiepileptogenic interventions with reduced cost and adverse risk exposures.

Methods

We evaluated EEG reports and medical records from 50 patients with TBI at a tertiary care center (Massachusetts General Hospital Neurosciences and Surgical ICUs) who met study inclusion criteria between 2011 and 2015. Inclusion criteria were: age ≥ 18 years, TBI on presentation, and EEG monitoring during the initial hospital admission for TBI. Retrospective collection and analysis of clinical data were performed under a protocol approved by the local institutional review board. Among patients meeting the inclusion criteria, we first evaluated consecutive (based on hospital admission) cases to identify 25 who developed PTE₁ (defined below), and subsequently evaluated consecutive cases to identify 25 controls without PTE₁, matched by age and admission Glasgow Coma Scores (GCSs).

EEG Recordings and Report Review

EEG data were recorded using conventional 10-20 scalp electrode placement. EAs were classified according to standardized nomenclature¹² as: seizures, sporadic epileptiform discharges

From the ¹Department of Neurology, Massachusetts General Hospital, Boston, MA; ²Department of Emergency Neurology and Neurocritical Care, Massachusetts General Hospital, Boston, MA; and ³Department of Environmental Health, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA

Address correspondence to Dr M. Brandon Westover, Department of Neurology, Massachusetts General Hospital, 15 Parkman Street, Wang ACC 739 L, Boston, MA 02114. E-mail: mwestover@mg.harvard.edu

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TABLE 1. Demographic Predictors of PTE₁ Development

Univariate Analysis	PTE (n = 25)	No PTE (n = 25)	OR ([95% CI])	<i>p</i>
Age	52.5 ± 20.4	49.6 ± 25.8	1.01 [0.98, 1.03]	0.36
Sex: F/M	10/15	8/17	1.42 [0.41, 4.85]	0.25
IPH	8 (32%)	3 (12%)	3.45 [0.77, > 100]	0.06
SDH	21 (84%)	15 (60%)	4.13 [1.18, 39.33]	0.02*
SAH	14 (56%)	12 (48%)	1.38 [0.40, 4.66]	0.27
EDH	5 (20%)	2 (8%)	2.88 [0.41, > 100]	0.10
Skull fracture	14 (56%)	10 (40%)	1.91 [0.62, 6.73]	0.12
Admission GCS	6.00 ± 4.66	8.00 ± 4.53	0.94 [0.81, 1.07]	0.25

P-value met our criteria for statistical significance ($P < 0.05$).

PTE₁ = first-year post-traumatic epilepsy; IPH = intraparenchymal hemorrhage; SDH = subdural hemorrhage; SAH = subarachnoid hemorrhage; EDH = epidural hemorrhage; GCS = Glasgow Coma Scale; OR = odds ratio; CI = confidence interval.

(EDs), lateralized or generalized periodic discharges (LPDs and GPDs), and lateralized rhythmic delta activity (LRDA).¹³ We also analyzed generalized rhythmic delta activity (GRDA) and polymorphic generalized and focal slowing, but consider these separate from EAs. The presence (dark bars) or absence (light bars) of these abnormalities, as documented in daily clinical EEG reports, was tallied for each patient with “day of traumatic brain injury” marked as day 0 (Fig A). A histogram representing the EEG distribution is shown in Figure B.

PTE₁ Definition

Patients with at least one seizure 2 to 12 months post-TBI, based on medical record review. Control subjects were patients meeting the inclusion criteria who had TBI without any documented seizures in the same period, matched for age and admission GCS (Table 1). Patients were excluded if there were insufficient follow-up visits in the electronic health record to determine PTE₁ status. For practicality, we analyzed up to 12 months, the highest-risk period,¹⁴ while acknowledging that this does not fully capture eventual PTE development.

Statistical Analysis

For data analysis, we used Matlab, including the Matlab Statistics Toolbox (The MathWorks, Inc., Natick, MA). We utilized uni- and multivariate logistic regression to calculate odds ratios (ORs) of the reported demographic or EEG features (candidate predictor variables for PTE₁). In addition to evaluating EA as a group, we analyzed individual EA subtypes (seizures, EDs, LPDs, GPDs, and LRDA). Bootstrapping was used to determine 95% confidence intervals (CIs) and *p* values, with a significance threshold of $p \leq 0.05$.

Results

Demographic Predictors

We calculated associations between demographic variables and PTE₁, including age, sex, admission GCS, presence of

intraparenchymal hemorrhage (IPH), subdural hemorrhage (SDH), subarachnoid hemorrhage (SAH), or epidural hemorrhage (EDH; Table 1). The only demographic variable significantly associated with PTE₁ development is SDH ($p = 0.02$; Table 1).

EEG Distribution

EEG acquisition days are shown for each individual and summarized for each cohort (Fig A,B). The PTE₁ group has more days of EEG monitoring overall, possibly attributable to the continuation of EEG monitoring when epileptiform abnormalities were found.

EEG Predictors

EAs are more common in patients with PTE₁ compared to patients without PTE₁ (64% versus 36%; $p = 0.04$; Fig C). The prevalence of each EA subtype is shown in Figure D. EAs are significant predictors of PTE₁ with an OR of 3.16 [0.99 11.68] ($p = 0.04$; Table 2).

When evaluating individual EA subtypes, only EDs ($p = 0.01$) are significantly associated with PTE₁ (Table 2). Although not classified as an EA, focal slowing ($p = 0.04$) is also significantly associated with PTE₁ (Table 2). Early seizures and LPDs show positive associations with PTE₁, but did not reach significance ($p = 0.06$ and $p = 0.10$, respectively), probably attributed to small sample size.

The difference in EDs is observed early, ≤ 5 days after TBI, with 50% occurring on day 0 after TBI (OR, 3.67 [1.02, 18.76]; $p = 0.04$; Fig E).

Multivariate Analysis

Controlling for SDH, acute EA remains significantly associated with subsequent PTE₁ (OR, 2.97 [0.91, 14.18], $p = 0.03$; Table 2). EDs alone, after adjusting for

TABLE 2. EEG Predictors of PTE₁ Development

Univariate Analysis	OR (95% CI)	<i>p</i>
Epileptiform abnormalities	3.16 [0.99 11.68]	0.042*
Early Seizures	2.95 [0.80, 24.42]	0.06
EDs	4.57 [1.60, 21]	0.007*
LPDs	2.85 [0.71, > 100]	0.10
GPDs	2.09 [<0.1, > 100]	0.25
LRDA	1.88 [0.48, 8.80]	0.19
GRDA	0.43 [<0.1, 2.30]	0.87
Generalized slowing	3.27 [<0.1, > 100]	0.15
Focal slowing	2.67 [0.97, 10.1]	0.04*
Multivariate analysis		
EAs adjusted for SDH	2.97 [0.91, 14.18]	0.03*
EDs adjusted for SDH	3.8 [1.18, 18.96]	0.016*

P-value met our criteria for statistical significance (*P* < 0.05).
 EEG = electroencephalogram; PTE₁ = first-year post-traumatic epilepsy; EDs = epileptiform discharges; LPDs = lateralized periodic discharges; GPDs = generalized periodic discharges; LRDA = lateralized rhythmic delta activity; GRDA = generalized rhythmic delta activity; EAs = epileptiform abnormalities; OR = odds ratio; CI = confidence interval.

SDH, have an even stronger effect with an adjusted OR of 3.8 [1.18, 18.96] (*p* = 0.016; Table 2).

By comparing multivariate logistic regression models of SDH + EA with the univariate regressions of EA and SDH independently, we find that SDH and EA independently contribute to increased PTE₁ risk (*p* = 0.05 and *p* = 0.03, respectively) without any direct relationship to each other (*p* = 0.17), suggesting that model (1) is the most likely relationship between the variables: SDH and ED are independent causal factors for PTE₁ (Fig F).

Discussion

Our results provide novel evidence that EAs may be a useful marker in identifying patients at high risk for PTE₁.

SDH and PTE₁

SDH is significantly associated with PTE₁ in our study, in concordance with multiple other studies.^{15,16} Past studies also find associations with other variables, such as post-TBI amnesia, alcohol, and midline shift, which we did not assess.¹⁶ Intraparenchymal hemorrhage and skull fractures are also associated with PTE₁ in other studies,¹⁵ and although neither OR ratio in our cohort is significant (*p* = 0.06 and 0.12 respectively), we are underpowered to detect such associations.

EA and PTE₁

Although the presence and prevalence of EA after TBI has been described,¹⁷ the association with PTE₁ has not been reported. Our results demonstrate that the presence of EA following TBI signals increases risk for the development of PTE₁. More specifically, EDs are associated with PTE₁ development. Other subtypes of EA in our data, including early seizures and LPDs, show weak associations with PTE₁, but do not reach statistical significance, potentially because of small sample size. Interestingly, focal polymorphic slowing is also significantly associated with PTE₁. Although often considered a non-specific EEG pattern, focal slowing has been observed in PTE previously,¹⁸ and a recent study showed focal slowing in areas corresponding to blood-brain barrier (BBB) disruption after TBI, which correlated with PTE₁.¹⁹

Our results also show that EA occur early (<5 days) after TBI, suggesting that *early* EEG could be a useful diagnostic tool to assess TBI patients for PTE₁ risk. TBI is a defined time-point event in which patients are known to be at risk for epileptogenesis, thus making this group prime for antiepileptogenesis trials. However, the large patient numbers needed to test interventions and unnecessary exposure to potential adverse effects in low-risk patients has been prohibitive. For example, for an antiepileptogenesis drug trial that enrolled severe TBI patients with an estimated incidence of PTE₁ at 7.1%,²⁰

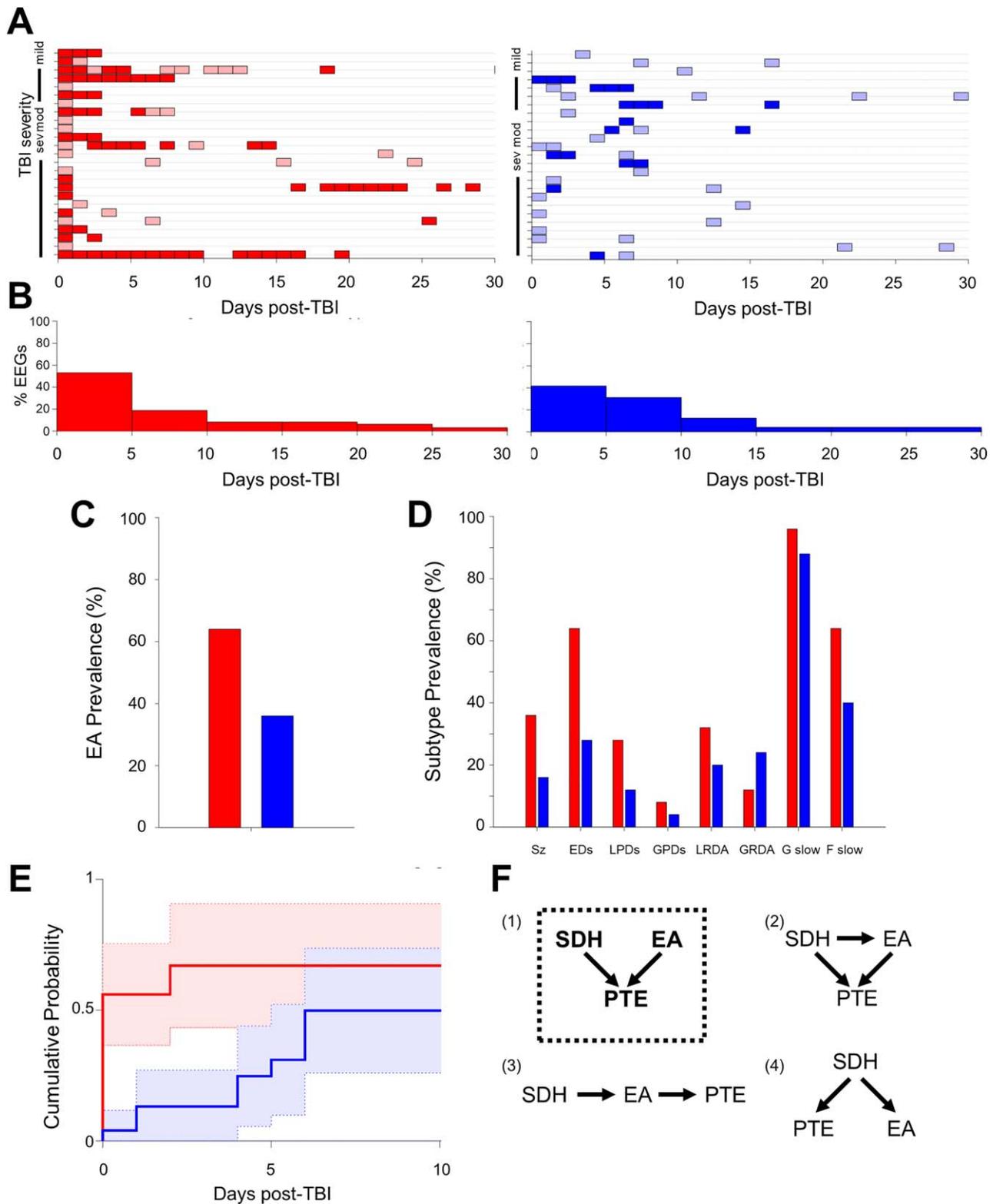


FIGURE: EEG recording distribution and prevalence in PTE₁ (red) and non-PTE₁ (blue) patients. (A) EEG recording days (colored boxes) plotted for individual patients plotted along y-axis based on TBI severity. Shading based upon presence (dark) or absence (light) of EA during that day's recording. **(B)** Histogram summarizing the proportion of EEGs during each 5-day time period. **(C)** Prevalence of EA in PTE₁ and non-PTE₁ groups. **(D)** Prevalence of EA subtypes in PTE₁ and non-PTE₁ groups. **(E)** Cumulative probability of the first appearance EDs in recordings up to the first 10 days post-TBI. **(F)** Models of possible causal relationship between SDH, EA, and PTE₁. Model (1) with dotted box outline is the most likely model based upon logistic regression. EEG = electroencephalogram; EAs = epileptiform abnormalities; EDs = epileptiform discharges; EEG = electroencephalogram; GPDs = generalized periodic discharges; GRDA = generalized rhythmic delta activity; LPDs = lateralized periodic discharges; LRDA = lateralized rhythmic delta activity; PTE₁ = first-year post-traumatic epilepsy; SDH = subdural hemorrhage; Sz = seizure; TBI = traumatic brain injury.

the sample size required to detect a 50% treatment effect is 1,364 patients (Fisher's two-sided exact test, power 0.8, alpha 0.05). By contrast, if we enroll severe TBI patients with early EAs on EEG, according to our data the incidence of PTE₁ rises to 12%, and the required sample size is only 778, a decrease of 43%.²⁰ Although our sample size is small, retrospective in design, and needs further confirmation, our results suggest that by using EA as a biomarker to identify the subset of TBI patients at highest risk for PTE₁ development, antiepileptogenesis interventions could be feasible in a cost-effective manner.

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Author Contributions

J.A.K., A.J.C., and M.B.W. contributed to the conception and design of the study. J.A.K., E.B., A.W., and M.B.W. contributed to the acquisition and analysis of data. J.A.K., A.J.C., S.Z., S.S.C., K.J.S., and M.B.W. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

Nothing to report.

References

- Wang ML, Li WB. Cognitive impairment after traumatic brain injury: the role of MRI and possible pathological basis. *J Neurol Sci* 2016;370:244–250.
- Curia G, Eastman CL, Miller JW, D'Ambrosio R. Modeling post-traumatic epilepsy for therapy development. In: Laskowitz D, Grant G, eds. *Translational Research in Traumatic Brain Injury*. Boca Raton, FL: CRC Press/Taylor and Francis Group; 2016.
- Ritter AC, Wagner AK, Fabio A, et al. Incidence and risk factors of posttraumatic seizures following traumatic brain injury: a traumatic brain injury model systems study. *Epilepsia* 2016;57:1968–1977.
- Klein P, Tyrlikova I. Prevention of epilepsy: should we be avoiding clinical trials? *Epilepsy Behav* 2017;72:188–194.
- Annegers J, Hauser W, Coan S, Rocca W. A population-based study of seizures after traumatic brain injuries. *N Engl J Med* 1998;338:20–24.
- Piccenna L, Shears G, O'Brien TJ. Management of post-traumatic epilepsy: an evidence review over the last 5 years and future directions. *Epilepsia Open* 2017;2:123–144.
- Schmidt D, Friedman D, Dichter MA. Anti-epileptogenic clinical trial designs in epilepsy: issues and options. *Neurotherapeutics* 2014;11:401–411.
- Terrone G, Pauletti A, Pascente R, Vezzani A. Preventing epileptogenesis: a realistic goal? *Pharmacol Res* 2016;110:96–100.
- Vespa P, Tubi M, Claassen J, et al. Metabolic crisis occurs with seizures and periodic discharges after brain trauma. *Ann Neurol* 2016;79:579–590.
- Shafi MM, Westover MB, Cole AJ, et al. Absence of early epileptiform abnormalities predicts lack of seizures on continuous EEG. *Neurology* 2012;79:1796–1801.
- Westover MB, Shafi MM, Bianchi MT, et al. The probability of seizures during EEG monitoring in critically ill adults. *Clin Neurophysiol* 2015;126:463–471.
- Hirsch LJ, LaRoche SM, Gaspard N, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. *J Clin Neurophysiol* 2013;30:1–27.
- Ruiz AR, Vlachy J, Lee JW, et al. Association of periodic and rhythmic electroencephalographic patterns with seizures in critically ill patients. *JAMA Neurol* 2017;74:181–188.
- Yeh CC, Chen TL, Hu CJ, et al. Risk of epilepsy after traumatic brain injury: a retrospective population-based cohort study. *J Neurol Neurosurg Psychiatry* 2013;84:441–445.
- Liesemer K, Bratton SL, Zebrack CM, et al. Early post-traumatic seizures in moderate to severe pediatric traumatic brain injury: rates, risk factors, and clinical features. *J Neurotrauma* 2011;28:755–762.
- Xu T, Yu X, Ou S, et al. Risk factors for posttraumatic epilepsy: a systematic review and meta-analysis. *Epilepsy Behav* 2017;67:1–6.
- Vespa P, Tubi M, Claassen J, et al. Metabolic crisis occurs with seizures and periodic discharges after brain trauma. *Ann Neurol* 2016;79:579–590.
- Koufen H, Dichgans J. Frequency and course of posttraumatic EEG-abnormalities and their correlations with clinical symptoms: A systematic follow up study in 344 adults. *Fortschritte der Neurologie, Psychiatrie und ihrer Grenzgebiete* 1978;46:165–177.
- Tomkins O, Shelef I, Kaizerman I, et al. Blood-brain barrier disruption in post-traumatic epilepsy. *J Neurol Neurosurg Psychiatry* 2008;79:774–777.
- Annegers JF, Grabow JD, Groover R V, et al. Seizures after head trauma: a population study. *Neurology* 1980;30(7 pt 1):683–689.