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Short report

Quantitative epileptiform burden and electroencephalography background features predict post-traumatic epilepsy

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ABSTRACT

Background Post-traumatic epilepsy (PTE) is a severe complication of traumatic brain injury (TBI). Electroencephalography aids early post-traumatic seizure diagnosis, but its optimal utility for PTE prediction remains unknown. We aim to evaluate the contribution of quantitative electroencephalograms to predict first-year PTE (PTE_1).

Methods We performed a multicentre, retrospective case–control study of patients with TBI. 63 PTE_1 patients were matched with 63 non-PTE_1 patients by admission Glasgow Coma Scale score, age and sex. We evaluated the association of quantitative electroencephalography features with PTE_1 using logistic regressions and examined their predictive value relative to TBI mechanism and CT abnormalities.

Results In the matched cohort (n=126), greater epileptiform burden, suppression burden and beta variability were associated with 4.6 times higher PTE_1 risk based on multivariable logistic regression analysis (area under the receiver operating characteristic curve, AUC (95% CI) 0.69 (0.60 to 0.78)). Among 116 (92%) patients with available CT reports, adding quantitative electroencephalography features to a combined mechanism and CT model improved performance (AUC (95% CI), 0.71 (0.61 to 0.80) vs 0.61 (0.51 to 0.72)).

Conclusions Epileptiform and spectral characteristics enhance covariates identified on TBI admission and CT abnormalities in PTE_1 prediction. Future trials should incorporate quantitative electroencephalography features to validate this enhancement of PTE risk stratification models.

INTRODUCTION

Post-traumatic epilepsy (PTE) is a devastating consequence of traumatic brain injury (TBI). Early stratification of PTE risk in patients with TBI would facilitate targeted enrollment into antiepileptogenesis treatment trials.[1]

While electroencephalography (EEG) is recommended to detect early post-TBI electrographic seizures (ESZs),[2] whether and how it benefits later PTE prediction remains unclear.[1 3 4] Early investigations suggest that classifying post-TBI (<3 month) EEG into normal/abnormal may not differentiate PTE risk.[3] Recently, we found that the presence of epileptiform abnormalities (EAs, ie, ESZs, sporadic epileptiform discharges (EDs), lateralised or generalised periodic discharges (LPDs, GPDs), lateralised rhythmic delta activity (LRDA)) and focal polymorphic slowing <1 month post-TBI is associated with first-year PTE (PTE_1).[1] Yet, accessible quantitative EEG (QEEG) tools[5–8] remain unexplored in quantifying abnormalities[1] relevant to PTE_1.

Here, we propose a quantification scheme to automatically calculate QEEG characteristics ≤14 days post-TBI. We aim to evaluate the contribution of quantitative epileptiform and spectral features to PTE_1 prediction beyond covariates identifiable on TBI admission and initial CT head abnormalities.[1 9–11]

METHODS

In this case–control study, we collected data from nine centres of the Critical Care EEG Monitoring Research Consortium: Yale School of Medicine (New Haven, Connecticut, USA), Brigham and Women's Hospital (Boston, Massachusetts, USA), Duke University Medical Center (Durham, North Carolina, USA), Emory School of Medicine (Atlanta, Georgia, USA), Henry Ford Health System (Detroit, Michigan, USA), Massachusetts General Hospital (Boston, Massachusetts, USA), University of Florida Health (Gainesville, Florida, USA), University of Miami School of Medicine/Jackson Memorial Health System (Miami, Florida, USA) and UT Southwestern Medical Centre (Dallas, Texas, USA) between 2012 and 2019.

Participants

Patients with TBI were included retrospectively if age ≥18 years, no seizure/epilepsy history, EEG monitoring data ≤14 days post-TBI and ≥12 months follow-up or developed PTE_1. Patients were excluded per signal quality inspection (online supplemental methods I). Among included

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patients, one-to-one case-control (PTE_1 vs non-PTE_1) match was performed based on admission Glasgow Coma Scale (GCS) score, age and sex (online supplemental methods II).

Outcome and exposures

We defined PTE_1 according to our prior publication[1] as an unprovoked seizure 1–12 months post-TBI. Eligible patients in this study commonly had protracted hospital courses. Hence a seizure >7 days post-TBI but during the acute hospitalisation was likely provoked by subsequent complications.[11] EEGs (21 channel, 10–20 system) were recorded for clinical indication.

Predictors

We recorded from CT reports the presence of intraparenchymal, subdural, subarachnoid, epidural haemorrhage (IPH, SDH, SAH, EDH) and skull fracture; and from EEG reports the presence of EA (ie, ESZs, EDs, LPDs, GPDs, LRDA), generalised rhythmic delta activity (GRDA), suppression, focal slowing and generalised slowing.

For QEEG analysis, we split each patient's EEG into non-overlapping, 1-hour windows of homogeneous duration (online supplemental methods I). Each feature per patient was represented by the maximum (EA, GRDA features) or median (spectra) values across all windows. We matched outputs from two algorithms for ESZ ('SPaRCNet',[8] Persyst14[6]) and ED (SpikeNet,[7] Persyst14[5]) detection to reduce false-positive rates and computed ESZ and ED presence.[1 12] We analysed EA burden ('SPaRCNet'[8]; hourly % EA presence), GRDA burden, suppression burden (hourly % signal with amplitude <3 µV lasting ≥0.5 s), global delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz) and beta (13–20 Hz) powers, theta/alpha/beta-over-delta ratios, power asymmetry (absolute hemispheric difference over global power) and power variability (hourly IQR) (Persyst14).

Statistical analysis

Univariable and multivariable (forward-selection algorithm applied) logistic regressions were used to evaluate the association of unmatched covariates and QEEG features with PTE_1. To combat overfitting, ridge logistic regressions trained and tested via 8-fold nested cross-validation were applied to compare predictive values of different feature sets (mechanism+CT, mechanism+CT+QEEG, mechanism+CT+EEG-report; online supplemental methods III). Evaluation metrics were calculated by concatenating test sets.

Area under the receiver operating characteristic curve (AUC), accuracy (optimal operating point), odds ratio and calibration error were evaluated (online supplemental methods IV). p=0.05 was the significance threshold. The 95% CIs were generated by bootstrapping (n=1000). Analysis was performed using R V.3.6.1.

RESULTS

Of 279, 205 eligible patients with high-quality EEG were included. Sixty-three PTE_1 patients were matched with 63 non-PTE_1 patients (online supplemental tables 1 and 2). 116 (92%) matched patients had CT reports.

TBI mechanism, CT and QEEG predictors of PTE_1

We used univariable logistic regression to assess potential covariates, including QEEG features, that predict PTE_1 risk independent of matched variables (table 1; figure 1A,B; online supplemental figure S1). For TBI mechanism, penetrating injury was associated with an increased odd of PTE_1 (OR=6.20, p=0.03) compared with acceleration/deceleration. For CT abnormalities, SDH (OR=3.34, p=0.01) and skull fracture (OR=2.48, p=0.03) were positively associated with PTE_1 risk (n=116; online supplemental table S3). For QEEG, ESZ presence (OR=2.79, p=0.02), greater EA burden (OR per 10%-increase ($OR_{10\%}$)=1.15, p=0.01; figure 1A), LRDA burden ($OR_{10\%}$=1.13, p=0.02) and delta asymmetry ($OR_{10\%}$=1.29, p=0.047) were associated with increased odds of PTE_1. Non-epileptiform GRDA burden[1 13] ($OR_{10\%}$=0.77, p=0.01) was negatively associated with PTE_1. QEEG findings generally agreed with EEG-report results (EA, OR=2.29, p=0.03; focal slowing, OR=2.18, p=0.04) except for ED presence (significant in EEG-report[1] (OR=2.91, p=0.02) but non-significant in QEEG analysis) (online supplemental table S3).

To examine whether QEEG predicts PTE_1 risk independent of significant covariates, we applied a forward-selection algorithm on QEEG features with p<0.1 in univariable analysis to construct a multivariable QEEG-only model, and then stepwise added penetrating injury, SDH and skull fracture. EA burden ($aOR_{10\%}$=1.17, p<0.01), suppression burden ($aOR_{10\%}$=1.41, p=0.03), and beta variability (aOR=16.17, p=0.03) jointly predicted PTE_1 with an AUC of 0.69 (95% CI 0.60 to 0.78; figure 1C). The association of forward-selected QEEG features with PTE_1 remained significant relative to penetrating injury alone (n=126), and more importantly, relative to all penetrating, SDH and skull fracture injuries combined (n=116; online supplemental table S4).

Additive benefits of QEEG in PTE_1 prediction

To avoid overfitting in small-sample cohort, we leveraged nested cross-validation and regularisation (eg, ridge) techniques to evaluate the additive benefits of QEEG beyond TBI mechanism and CT abnormalities in PTE_1 prediction (n=116). Compared with the Mechanism+CT ridge regression, Mechanism+CT+QEEG demonstrated improved discrimination (test AUC, 0.71 (95% CI 0.61 to 0.80) vs 0.61 (95% CI 0.51 to 0.72)) with a comparable calibration error (0.08 (95% CI 0.04 to 0.15) vs 0.06 (95% CI 0.02 to 0.12)) (figure 1C,D; online supplemental table S5). Per feature importance measures (figure 1E), CT abnormalities (skull fracture, SDH) were the most important positive predictors, followed by QEEG epileptiform (ESZ presence, GPD burden, ESZ burden, EA burden) and spectral (suppression burden, beta variability) features. Penetrating injury also had strong positive importance. Consistent with logistic regression, GRDA burden had strong negative importance. A ridge algorithm utilising EEG-report abnormalities, instead of QEEG, (AUC (95% CI), 0.65 (0.54 to 0.75); online supplemental table S5) demonstrated modest, but less robust improvement on the mechanism+CT model.

DISCUSSION

We demonstrate that EA burden, suppression burden and beta variability combined enhance PTE_1 risk stratification in this case–control cohort. Furthermore, QEEG provides added benefit in PTE_1 prediction beyond TBI mechanism and CT abnormalities, especially given our data suggesting potential collinearity between penetrating and skull fracture (online supplemental table S4). Taking a PTE_1 rate at 9.8% among moderate-to-severe patients with TBI,[10] our mechanism+CT ridge model would identify patients with 15% PTE_1, similar to the previously reported 1 year rates using clinical covariates.[14] Our mechanism+CT+QEEG model increases this PTE_1 identification nearly 2-fold to 27%;

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Table 1 Univariable analysis of QEEG features associated with PTE_1 development*

Univariable analysis			Univariable logistic regression	
Variable, descriptive statistics, unit	**Non-PTE_1 patients (n=63)**	**PTE_1 patients (n=63)**	**OR (95% CI)**	**P value**
Matched Variables				
Age at TBI, median (IQR), year	49 (28 to 66)	48 (28 to 65)	1 (0.98 to 1.02)	0.94
Female, no (%)	18 (29)	17 (27)	1.09 (0.50 to 2.38)	0.84
Admission GCS Score, no (%)				
13–15 (mild-TBI)	13 (21)†	13 (21)†	1 (Reference)	
9–12 (moderate-TBI)	15 (24)†	15 (24)†	1 (0.35 to 2.86)	1
3–8 (severe-TBI)	35 (56)†	35 (56)†	1 (0.41 to 2.46)	1
Injury mechanism, no (%)				
Acceleration/deceleration	31 (49)	20 (32)	1 (Reference)	
Direct impact to head	3 (5)	6 (10)	3.10 (0.69 to 13.83)	0.14
Fall from standing	16 (25)	20 (32)	1.94 (0.82 to 4.60)	0.13
Fall from >3 ft	11 (17)	9 (14)	1.27 (0.45 to 3.61)	0.66
Penetrating	2 (3)	8 (13)	6.20 (1.19 to 32.23)	0.03
EEG monitoring, median (IQR)				
Start time post-TBI, day	2.3 (1.5 to 4.7)	2.6 (1.6to 4.8)	1.01 (0.95 to 1.07)	0.71
Monitoring duration, day	0.7 (0.3 to 1.7)	1.0 (0.7 to 1.8)	1.21 (0.96 to 1.53)	0.11
QEEG Features, ≤14 days post-TBI				
ESZ Presence, no (%)	9 (14)	20 (32)	2.79 (1.15 to 6.75)	0.02
ED Presence, no (%)	41 (65)	45 (71)	1.34 (0.63 to 2.85)	0.45
Peak EA Burden, median (IQR), %1 hour	8.2 (1.4 to 31.7)	34.3 (2 to 81.3)	1.15 (1.04 to 1.27)‡	0.01
ESZ	0 (0 to 0)	0 (0 to 7.7)	1.32 (0.99 to 1.75)‡	0.06
ED	0.1 (0 to 0.7)	0.1 (0 to 0.8)	1.04 (0.79 to 1.36)‡	0.80
LPD	0.1 (0 to 1.2)	0.2 (0 to 3.3)	1.09 (0.88 to 1.35)‡	0.42
GPD	0.1 (0 to 0.5)	0.1 (0 to 1)	11.76 (0.78 to >100)‡	0.08
LRDA	3.4 (0.5 to 24.2)	9.1 (0.9 to 76.9)	1.13 (1.02 to 1.25)‡	0.02
Peak GRDA burden, median (IQR), %1 hour	8.3 (0.3 to 32.1)	1.3 (0.1 to 9.5)	0.77 (0.64 to 0.92)‡	0.01
Suppression, median (IQR), %1 hour	2.9 (0.6 to 7.1)	3.8 (0.9 to 12.5)	1.29 (0.96 to 1.73)‡	0.09
Global band power, mean (SD)				
Delta (1–4 Hz)	9.4 (2.2)	9.2 (2.4)	0.97 (0.83 to 1.13)	0.69
Theta (4–8 Hz)	7.3 (1.8)	7.0 (1.9)	0.92 (0.76 to 1.11)	0.38
Alpha (8–13 Hz)	6.3 (1.2)	6.1 (1.4)	0.94 (0.72 to 1.22)	0.63
Beta (13–20 Hz)	6.0 (1.3)	6.0 (1.5)	0.99 (0.76 to 1.27)	0.92
Global X-over-delta ratios, mean (SD)				
Theta-over-delta	0.8 (0.1)	0.8 (0.1)	0.47 (0.02 to 10.91)	0.64
Alpha-over-delta	0.7 (0.1)	0.7 (0.1)	1.82 (0.13 to 25.30)	0.66
Beta-over-delta	0.7 (0.1)	0.7 (0.2)	2.42 (0.28 to 21.02)	0.42
Power asymmetry, median (IQR), %				
Delta	8.4 (5.7 to 18.7)	13.5 (7.3to 33.1)	1.29 (1 to 1.66)‡	0.047
Theta	9.0 (4.8 to 15.2)	11.7 (6.7to 28.3)	1.25 (0.98 to 1.58)‡	0.07
Alpha	8.4 (5.6 to 14.3)	11.7 (5.3 to 23.8)	1.25 (0.98 to 1.59)‡	0.07
Beta	8.0 (4.6 to 13.8)	9.7 (5.3 to 22.1)	1.27 (0.98 to 1.64)‡	0.07
Power variability, median (IQR)				
Delta	0.6 (0.4 to 0.8)	0.7 (0.3 to 0.8)	0.96 (0.39 to 2.31)	0.92
Theta	0.3 (0.2 to 0.4)	0.3 (0.2 to 0.5)	3.08 (0.53 to 17.87)	0.21
Alpha	0.3 (0.2 to 0.4)	0.3 (0.2 to 0.4)	3.77 (0.42 to 33.93)	0.24
Beta	0.2 (0.2 to 0.3)	0.3 (0.2 to 0.4)	7.24 (0.70 to 74.49)	0.096

*Predictors were included in forward-selection algorithm if p<0.10.
†Numbers may not sum to 100% due to rounding issue.
‡OR associated with 10 unit increase of features.
EA, epileptiform abnormality; ED, epileptiform discharge; ESZ, electrographic seizure; GCS, Glasgow Coma Scale; GPD, generalised periodic discharge; GRDA, generalised rhythmic delta activity; LPD, lateralised periodic discharge; LRDA, lateralised rhythmic delta activity; PTE_1, post-traumatic epilepsy within first-year post-TBI; QEEG, quantitative electrocochleography; TBI, traumatic brain injury.

reducing the enrollments for anti-epileptogenesis trials by 50% (online supplemental table S6).

We found that a greater EA burden was associated with PTE_1, generating hypotheses on metabolic dysregulation. EA burden post-TBI may increase metabolic demand when there is decreased metabolic supply, leading to a mismatch triggering epileptogenesis. Whether interventions reducing EAs post-TBI prevent metabolic exhaustion and PTE development warrants exploration.

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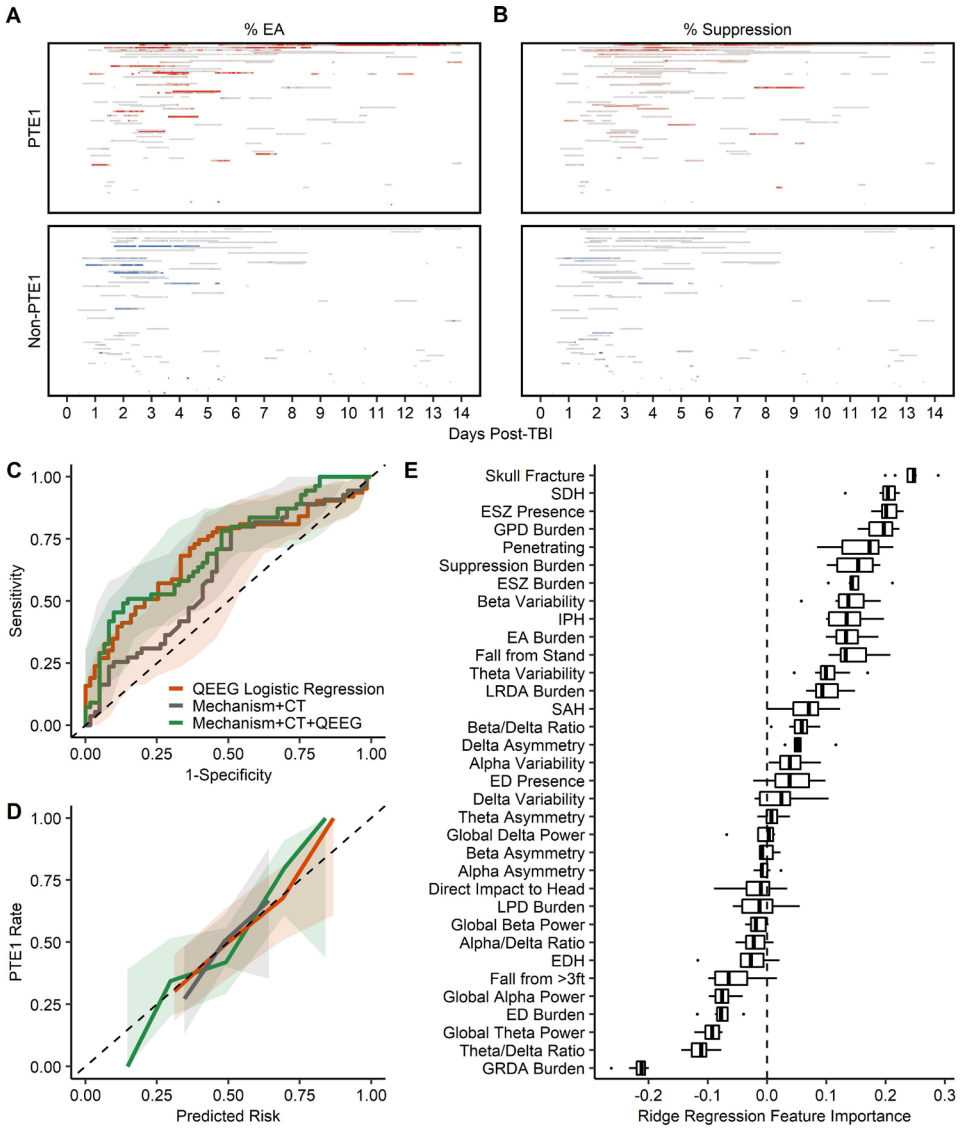

Figure 1 Quantitative electroencephalography (QEEG) prediction models for First-year post-traumatic epilepsy (PTE_1). (A) % epileptiform abnormalities (EAs) for all 1-hour windows for all patients (0% corresponds to grey, higher % corresponds to darker red/blue); each block represents an 1-hour window; y-axis represents individual patients sorted by total recording duration (top: longest duration). (B) Same as panel A but for % suppression distribution. (C) Area under the receiver operating characteristic curve (AUC) comparison; AUC for forward-selected QEEG logistic regression (orange): 0.69 (95% CI 0.60 to 0.78); test AUC for cross-validated ridge logistic regression based on TBI mechanism and CT (mechanism+CT, grey): 0.61 (95% CI 0.51 to 0.72) and test AUC for cross-validated ridge logistic regression based on TBI mechanism, CT and QEEG (mechanism+CT+ QEEG, green): 0.71 (95% CI 0.61 to 0.80); shaded areas represent the bootstrapped (n=1000) 95% CIs. (D) same as C but showing calibration errors for QEEG logistic regression: 0.06 (95% CI 0.02 to 0.12), mechanism+CT ridge regression: 0.06 (95% CI 0.02 to 0.12), mechanism+CT+ QEEG ridge regression: 0.08 (95% CI 0.04 to 0.15). (E) Feature importance for mechanism+CT+ QEEG ridge regression; features were sorted by the importance measure; each boxplot visualises the distribution of penalised coefficients across eight folds.

The larger delta asymmetry for PTE_1 versus non-PTE_1 patients suggests that focal/hemispheric network dysfunction may be relevant as reported previously.[1 4] Suppression burden predicts PTE_1, perhaps reflecting injury severity independent of GCS.

Together, our data highlight the benefits of EEG monitoring for moderate-to-severe patients with TBI.[1 2] With increased post-TBI EEG monitoring, our quantification scheme may reduce the cost of manually reviewing EEG reports without compromising PTE_1 prediction accuracy. However, ED algorithms may need further improvement in specificity (online supplemental tables S4 and 7).

Limitations

First, medication and state changes (sleep, awake and sedated) may affect EEG. These differences are highly influenced by TBI severity, and thereby more comparable among patients matched by admission GCS. However, the impacts of these and other TBI severity measures (lesion location/type, craniectomy/craniotomy) on QEEG and PTE_1 risk warrant further exploration. Second, our study is retrospective with possible selection bias toward moderate-to-severe patients with TBI and/or those at risk for ESZ. Therefore, PTE_1 incidences or prediction models here need further refinement to apply to the mild TBI population. Our findings should be validated in prospective studies. Third, some non-PTE_1 patients here might develop >12 months PTE. If such patients had QEEG similar to those of PTE_1 patients, their risk for PTE would be underestimated, and so would the contributions of QEEG in PTE prediction. Studies investigating the association of QEEG with PTE latency are warranted. Finally,

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combining QEEG with quantitative neuroimaging data[15] may improve PTE prediction.

In summary, epileptiform and spectral features quantified by QEEG tools enhance covariates identifiable on TBI admission and CT abnormalities in PTE_1 prediction. Future large-sample, prospective studies should validate our findings and could incorporate QEEG into PTE risk models.

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