FULL-LENGTH ORIGINAL RESEARCH

Subclinical early posttraumatic seizures detected by continuous EEG monitoring in a consecutive pediatric cohort

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Summary

Purpose: **Traumatic brain injury (TBI) is an important cause of morbidity and mortality in children, and early posttraumatic seizures (EPTS) are a contributing factor to ongoing acute damage. Continuous video-EEG monitoring (cEEG) was utilized to assess the burden of clinical and electrographic EPTS.**

Methods: **Eighty-seven consecutive, unselected (mild – severe), acute TBI patients requiring pediatric intensive care unit (PICU) admission at two academic centers were monitored prospectively with cEEG per established clinical TBI protocols. Clinical and subclinical seizures and status epilepticus (SE, clinical and subclinical) were assessed for their relation to clinical risk factors and short-term outcome measures.**

Key Findings: **Of all patients, 42.5% (37/87) had seizures. Younger age ($p = 0.002$) and injury mechanism (abusive head trauma – AHT, $p < 0.001$) were significant risk factors. Subclinical seizures occurred in 16.1% (14/87), while 6.9% (6/87) had only subclinical seizures. Risk factors for subclinical seizures included younger age ($p < 0.001$), AHT ($p < 0.001$), and intraaxial bleed ($p < 0.001$). SE occurred in 18.4% (16/87) with risk factors including younger age ($p < 0.001$), AHT ($p < 0.001$), and intraaxial bleed ($p = 0.002$). Subclinical SE was detected in 13.8% (12/87) with significant risk factors including younger age ($p < 0.001$), AHT ($p = 0.001$), and intraaxial bleed ($p = 0.004$). Subclinical seizures were associated with lower discharge King's Outcome Scale for Childhood Head Injury (KOSCHI) score ($p = 0.002$). SE and subclinical SE were associated with increased hospital length of stay ($p = 0.017$ and $p = 0.041$, respectively) and lower hospital discharge KOSCHI ($p = 0.007$ and $p = 0.040$, respectively).**

Significance: **cEEG monitoring significantly improves detection of seizures/SE and is the only way to detect subclinical seizures/SE. cEEG may be indicated after pediatric TBI, particularly in younger children, AHT cases, and those with intraaxial blood on computerized tomography (CT).**

KEY WORDS: **Clinical neurophysiology, Children, Epilepsy, ICU.**

Traumatic brain injury (TBI) is the number one cause of death and disability in children, annually affecting nearly half a million in the United States alone (Langlois et al., 2005; Faul et al., 2010). Early posttraumatic seizures (EPTS) may indicate more severe primary injury or could cause secondary brain injury by increasing metabolic requirements and cerebral blood flow, elevating intracranial pressure, inducing relative cerebral hypoxia/ischemia, exacerbating indiscriminate neurotransmitter release, and elevating temperature (Mansfield, 1997; Vespa et al., 2007a, b). Posttraumatic seizures (PTS) may indicate an ongoing cerebral injury process such as intracranial hemorrhage, cerebral edema, or hypoxia, alerting clinicians to prompt additional investigation. In addition, prolonged PTS should

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be considered in the differential diagnosis for both a child deteriorating after a lucid interval or the etiology for persistent, unexplained coma (Snoek et al., 1984).

EPTS is classically defined as any PTS occurring <7 days postinjury (Jennett & Lewin, 1960). In studies reporting clinical seizure occurrence after pediatric TBI of all severities *without utilizing continuous video-electroencephalography* (cEEG) monitoring, EPTS incidence ranges from 2.6% to 20% (Jennett & Lewin, 1960; Hendrick & Harris, 1968; Jennett, 1973; Annegers et al., 1980; Desai et al., 1983; Pagni, 1990; Ong et al., 1996; Ratan et al., 1999; Chiaretti et al., 2000). More specifically, EPTS incidence ranges from 1% to 27% in pediatric moderate TBI, and from 22% to 45% in pediatric severe TBI. Reportedly, 59–95% of clinically detected pediatric EPTS occurs within the first 24 h postinjury (Hendrick & Harris, 1968; Jennett, 1973; Annegers et al., 1980; Pagni, 1990; Ong et al., 1996; Chiaretti et al., 2000). Studies report that children are more prone to EPTS than adults are, and in some cases with a twofold higher incidence (Jennett & Lewin, 1960; Annegers et al., 1980; Desai et al., 1983; Pagni, 1990). Furthermore, younger children appear more prone to EPTS than older children do (Hendrick & Harris, 1968; Ong et al., 1996; Ratan et al., 1999). To date, cEEG has not been utilized prospectively in pediatric cohorts to characterize EPTS incidence or time of onset postinjury.

In a pediatric intensive care unit (PICU) in patients with TBI, many factors can confound the ability to detect seizures clinically including high frequency of altered mental status/coma and the use of sedatives, paralytics, and even anticonvulsants. Therefore, the current practice of relying on clinical markers such as mental status and physical examination to monitor for seizures is insufficient. cEEG monitoring has significantly increased the detection rates of seizures and epileptiform abnormalities following moderate to severe adult TBI; 22% of patients in one study had EPTS and more than half were nonconvulsive or subclinical (Vespa et al., 1999b). High rates of epileptiform discharges have also been reported in nonseizure groups (Vespa et al., 1999b; Ronne-Engstrom & Winkler, 2006). Furthermore, cEEG was shown to improve daily management decisions, reduce cost, and improve outcome in a mixed retrospective/prospective adult ICU brain injury cohort (Vespa et al., 1999a).

The use of cEEG has become more widespread in the PICU, revealing the relatively high rate of subclinical seizures in critically ill children, and identifying younger age as a risk factor. However, these reports included relatively small numbers of TBI patients, and relied on a single EEG reader or multiple readers without validation between readers (Shahwan et al., 2010; Abend et al., 2011; Williams et al., 2011).

TBI outcome depends on the severity of *primary* brain injury, and the efficacy of preventing/limiting *secondary* brain injury in TBI patients. Both clinical and subtle/subclinical seizures are reported to be associated with TBI morbidity/outcome (Desai et al., 1983; Hahn et al., 1988; Ong et al., 1996; Chiaretti et al., 2000; Vespa et al., 2007a). The current study is the first prospective multicenter investigation of the incidence and risk factors for EPTS as detected using standardized cEEG monitoring in consecutive children requiring admission to the PICU for acute, unselected (mild – severe) TBI.

Methods

Institutions and subjects

The study was reviewed and approved by respective institutional review boards (UCLA IRB, Colorado Medical IRB). Consecutive, acute TBI patients of all severities (Glasgow Coma Scale [GCS] 3–15) requiring PICU admission at two institutions (Mattel Children's Hospital – UCLA, Children's Hospital of Colorado – CHC) were identified. Determination of PICU admission was made by the attending emergency physician in consultation with the attending PICU physician. All moderate-severe TBI patients were admitted to the PICU at each institution. No mild TBI patients were admitted to the PICU at CHC, whereas eight mild TBI patients deemed to require frequent neurologic checks required nursing staffing levels only provided in the PICU at UCLA. Of 99 eligible patients, 87 were prospectively consented and enrolled from 10/2008 to 10/2011 (100% consent rate at CHC and 83.3% at UCLA; overall 87.9%); the 12 that did not consent (all from UCLA) were demographically similar to those consented. Five consented patients did not receive monitoring because two were admitted >48 h after the injury and three were missed. Patient management followed PICU standards of care. Continuous EEG monitoring was initiated after patient identification. cEEG readings were reported once or twice daily. Injury severity was defined using postresuscitation GCS; by convention GCS 13–15 was classified as mild, 9–12 as moderate, and 3–8 as severe (Teasdale & Jennett, 1974) (Maas & Stocchetti, 2011). Patients with GCS of 13–15 and intracranial abnormalities on noncontrast brain computerized tomography (CT) were classified as moderate, considering recent studies suggesting that GCS is only a partial factor in characterizing TBI severity, and that underlying pathology as detected by acute CT may be valuable in considering risks for long-term sequelae (Saatman et al., 2008; Maas & Stocchetti, 2011). Such abnormalities included contusions, hematomas, or edema but excluded nondisplaced linear skull fractures. Injury mechanism was classified as nonabusive (falls, blunt trauma, motor vehicle accidents [MVAs] including bicycle versus motor vehicle or bicycle only) or abusive head trauma (AHT). AHT was diagnosed clinically after consultation with the neurology and child abuse teams. King's Outcome Scale for Childhood Head

Injury (KOSCHI) scores upon PICU and hospital discharge were utilized to classify global outcome following TBI. The KOSCHI score was obtained by patient examination and interview in a prospective fashion or by chart review (Crouchman et al., 2001). Secondary outcomes were analyzed, including PICU and hospital length of stay.

Inclusion and exclusion criteria

All consecutive pediatric patients (ages 1 month–18 years) admitted to the PICU with a diagnosis of acute TBI were eligible. Eight patients, all at UCLA, were admitted with mild TBI and were monitored in the PICU for frequent neurologic examinations throughout the night that was not available on the pediatric ward. Patients were included without regard to prior history of febrile seizures, family history of epilepsy, or prior history of seizures and/or epilepsy.

Continuous EEG protocol

Institutional protocols initiated cEEG monitoring as soon as possible for any patient admitted to the PICU for acute TBI. Patients were monitored for a minimum 24 h unless clinical needs necessitated shorter or longer monitoring (i.e., death, hospital discharge, ongoing seizures, and so on). All studies utilized standard international 10–20 system placement of gold-plated or plastic electrodes with standard filter settings and sampling rate. Digital EEG studies were completed on XLTEK and Stellate Harmonie (Natus Medical Incorporated, San Carlos, CA, U.S.A.) at CHC and UCLA, respectively. Both a pediatric epilepsy fellow and board certified pediatric electroencephalographer at each institution reviewed all studies in their entirety during clinical review. Studies were read remotely when clinically indicated.

Seizure classification

The seizures were classified as the following: any seizure, subclinical seizures, status epilepticus (SE), and subclinical SE. Seizures ("any seizures") were counted if they were observed in the field, in the emergency department, in the hospital prior to hookup of the cEEG or after cEEG was started. Clinical events prior to cEEG hookup were reviewed and included as "any seizure" if episodic alteration in mental status, convulsive activity, tonic motor activity, or seizure was reported in the medical record. Electrographic criteria for seizure was rhythmic repetitive sharp/spike waves with an electrographic field lasting >10 s and showing evolution in frequency, morphology, and/or amplitude. *Subclinical seizures* were defined as either electrographic seizures without clinical correlate or seizures with subtle clinical findings only apparent upon video review of EEG-detected seizures. This represents the subset of seizures that would be missed without cEEG monitoring. *SE* was classified as an ongoing seizure duration of >15 min, or repeated seizures occurring at a rate of >3 per hour; similar standards are utilized in adult TBI prospective cEEG data (Vespa et al., 1999b). *Subclinical SE* was defined as a combination of subclinical seizures and SE. Interictal/background EEG features will be addressed in a future manuscript. The exact breakdown of subjects by seizure classification is outlined in Fig. 1.

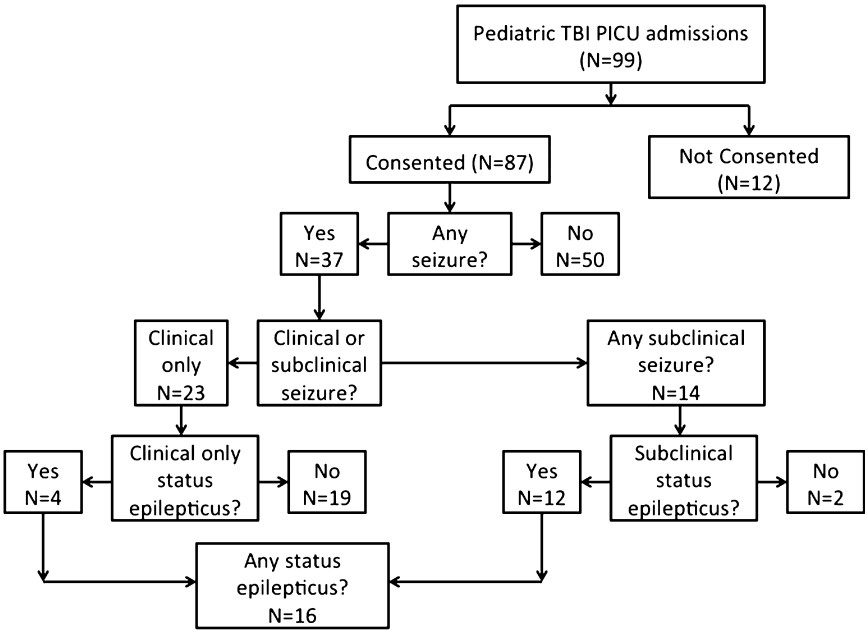

Figure 1.
Patient flow diagram.
Epilepsia © ILAE

Antiepileptic medications

Antiepileptic therapy was recorded as a therapy given on the scene, in the ambulance, in the emergency department, or in the PICU. Specific therapies included benzodiazepines, fosphenytoin, phenytoin, phenobarbital, levetiracetam, or topiramate.

Interobserver validation

Four reviewers independently appraised 40 unique 30-min unselected pediatric cEEG recordings using the standardized definitions of seizures listed earlier. A single EEG technologist created the EEG epochs, which were taken from an existing database of >5,000 studies (not including any of the present study's participants). All identifying information was removed. The age range of the patients in this selection was between 6 months and 18 years; this selection did not contain neonates. Approximately half of the epochs contained one or more seizures commencing at a random time within each study. Each reviewer recorded the presence or absence of seizure and the lateralization of the seizure (right or left hemisphere or generalized). Interobserver validation was calculated as a percent concordance between the different EEG reviewers and using a Kappa coefficient.

Analysis/statistics

All statistical calculations were conducted using R software (version 2.15.2) (R Core Team [2013]). For the continuous variables of age-at-injury, means were compared using a Welch two-sample test, and because the distributions were not normal, the analogous robust statistic (Yuen test) (Wilcox, 2012). Categorical variables were compared between centers or between the presence or absence of a particular seizure type, using Pearson's chi-square tests or Fisher exact tests when cell sizes were small. Significance was set at a $p < 0.05$. Variances were expressed as standard deviations (SDs). Conventional linear regression models were examined, in concert with multimodal inference (Burnham & Anderson, 2010) using R package MuMIn (Bartoń, 2012) to determine best fitting model subsets by rigorous statistical criteria.

Results

Demographics

Eighty-seven subjects were enrolled (UCLA 60, CHC 27; Table 1). The average age at injury was 6.2 ± 5.8 years (range 6 weeks–17 years). No age or gender differences between centers were identified. Institutional differences were noted for injury characteristics including severity, mechanism of injury, CT findings, and seizures (Table 1).

EEG validation

Four reviewers (three from UCLA [J.T.L, J.H.M., and J.Y.W.] and one from CHC [D.H.A]) demonstrated 98.8% agreement on the presence/absence of seizures, and 96.3% agreement on the hemisphere of onset of the seizures recorded. Kappa values calculated for the presence of a seizure and for both presence of a seizure and hemispheric location were 0.949 ($p < 0.001$) and 0.878 ($p < 0.001$), respectively (Kappa 95% confidence interval [CI] 0.680–1.000).

Table 1. Clinical characteristics of the two observational cohorts

	Combined n = 87 (%)	UCLA n = 60 (%)	CHC n = 27 (%)	p-Value
Gender (M:F)	56:31	39:21	17:10	NS
Age (years) ± SEM	6.2 ± 5.8	6.7 ± 5.9	5.02 ± 5.4	NS
Severity				
Mild	8 (9.2)	8 (13.3)	0	<0.001
Moderate	47 (54)	42 (70)	5 (18.5)	
Severe	32 (36.8)	10 (16.7)	22 (81.5)	
Mechanism of injury				
Fall	37 (42.5)	35 (58.3)	2 (7.4)	<0.001
MVA	20 (33.3)	10 (16.7)	10 (37.0)	
AHT	22 (25.3)	9 (15)	13 (48.1)	
Bicycle	3 (3.4)	3 (5)	0	
Blunt	5 (5.7)	3 (5)	2 (7.4)	
CT findings				
Skull fracture	44 (50.6)	33 (55)	11 (40.7)	NS
EDH	15 (17.2)	15 (25)	0	0.004
SDH	39 (44.8)	19 (31.7)	20 (74.1)	<0.001
SAH	33 (37.9)	22 (36.7)	11 (40.7)	NS
Intraaxial bleed	45 (51.7)	22 (36.7)	23 (85.2)	<0.001
Any bleed	68 (78.2)	43 (71.7)	25 (92.6)	0.047
Any seizure	37 (42.5)	22 (36.7)	15 (55.5)	NS
Subclinical seizure	14 (16.1)	4 (6.7)	10 (37.0)	<0.001
Status epilepticus	16 (18.4)	4 (6.7)	12 (44.4)	<0.001
Subclinical status epilepticus	12 (13.8)	3 (5)	9 (33.3)	<0.001

Any seizures

Seizures of any type occurred in 43.7% (37/87) for the combined cohort: 38.3% (23/60) at UCLA and 55.5% (15/27) at CHC. Age at injury was a risk factor for seizures ($p = 0.002$) as was presence of fracture on CT ($p = 0.039$). Patients with seizures were younger (mean = 3.8 ± 5.1 years) than those without seizures (mean = 7.7 ± 5.8) ($p = 0.002$). This also held true when patients were stratified into two groups; 61.5% (16/26) of children <1 year had seizures, whereas only 29.5% (18/61) of patients >1 year had seizures ($p = 0.010$). Seizures were most likely to be present in AHT (77.3%, 17/22) and less likely in blunt trauma (20.0%, 1/5), falls (27.0%, 10/37), bicycle accidents (33.3%, 1/3), and MVAs (25.0%, 5/20) ($p < 0.001$). Other findings on CT scan, severity of injury, and gender were not related to any seizures (Table 2). If patients with seizures occurring only in the field were excluded from the cohort, similar results were found with age and mechanism, which were also statistically significant. When patients with severe injury were evaluated as a subgroup, there was no relationship between the presence of seizures and KOSCHI score, hospital length of stay, or PICU length of stay.

Subclinical seizures

Subclinical seizures were detected in 16.1% (14/87) of all patients studied; 42.9% (6/14) of these patients—6.9% of the total population—had only subclinical seizures. Patients with any subclinical seizure had a mean age of 5.6 ± 3.7 months and all patients with only subclinical seizures were <1 year old (mean age 3.7 ± 1.8 months). Subclinical seizures occurred more often in younger children ($p < 0.001$) (Table 2) and those with AHT ($p < 0.001$). Subclinical seizures were found more often in children with subdural hematomas (SDHs) ($p = 0.008$), or intraaxial hemorrhage ($p < 0.001$), but not with epidural hematoma (EDH), subarachnoid hemorrhage (SAH), or skull fractures. No relationship was found between subclinical seizures and gender or injury severity. Only 4 of 33 patients given neuromuscular blocking agents were found to have subclinical seizures. The presence of this medication was not significantly related to the presence or absence of subclinical seizures. Regression analysis evaluating the relationship between subclinical seizures and age at injury, mechanism, intraaxial hemorrhage, and severity was not significant. In this initial model, age at injury ($p = 0.181$) and intraaxial hemorrhage ($p = 0.057$) approached significance. However, additional statistical modeling following Bartoń (2012) indicated that when considered together, injury age, and intraaxial hemorrhage (omitting mechanism and severity all together) yielded the best fitting predictors. The reduced regression analysis using only those two predictors found that intraaxial hemorrhage was significant ($p = 0.006$), whereas injury age was not ($p = 0.113$).

Table 2. Risk factors for seizure types.

	Age	Gender	Severity	Mechanism	Skull fracture	EDH	SDH	SAH	Intraaxial bleed	Any bleed	KOSCHI	Hospital LOS	PICU LOS	AED in field
Any seizure	$p = 0.002$	NS	NS	$p < 0.001$	$p = 0.04$	$p = 0.004$	NS	NS	NS	NS	NS	NS	NS	NS
Subclinical seizure	$p < 0.001$	NS	NS	$p < 0.001$	NS	NS	$p = 0.008$	NS	$p < 0.001$	NS	$p = 0.002$	NS	NS	$p = 0.021$
Status epilepticus	$p < 0.001$	NS	NS	$p < 0.001$	$p = 0.029$	NS	NS	NS	$p = 0.002$	NS	$p = 0.002$	$p = 0.022$	NS	$p < 0.001$
Subclinical status epilepticus	$p < 0.001$	NS	NS	$p < 0.001$	NS	NS	NS	NS	$p = 0.004$	NS	$p = 0.001$	$p = 0.049$	NS	$p = 0.002$

Status epilepticus

Status epilepticus was seen in 12.5% (1/8) of patients with mild injuries, 10.6% (5/47) of patients with moderate injuries, and 31.3% (10/32) of patients with severe injuries. Although not significant, there was a trend toward SE with severe injuries ($p = 0.075$). Age was strongly associated with presence of SE. The mean age of patients who had SE was 1.5 ± 3 years and the mean age of those without SE was 7.2 ± 5.8 years ($p < 0.001$). Mechanism of injury was related to SE; 54.5% of patients with AHT had SE, whereas it occurred in <10% of patients with all other mechanisms of injury ($p < 0.001$). In regard to CT imaging, only skull fracture ($p = 0.029$) and intraaxial bleed ($p = 0.002$) were related to SE.

Subclinical status epilepticus

Subclinical status epilepticus was seen in 13.8% (12/87) of all patients studied. Similar to any seizures and SE, patients with subclinical SE were younger ($p < 0.001$), with 10/11 patients under the age of 1 year. Mechanism of injury was related to subclinical SE; 45.5% (10/22) of patients with AHT had subclinical SE, whereas patients with other mechanisms of injury had rates of 17% (11/65) ($p < 0.001$). Subclinical status was seen more frequently in patients with intraaxial blood on CT scan ($p = 0.004$). No relationship was found between subclinical SE and severity of injury, gender, SAH, EDH, SDH, or fracture. The presence of a neuromuscular blocking agent was not significantly related to the presence or absence of subclinical SE. Regression analysis evaluating the relationship between subclinical status epilepticus and age at injury, mechanism, intraaxial hemorrhage, and severity was not significant. In this initial model, age at injury ($p = 0.216$) and intraaxial hemorrhage ($p = 0.083$) approached significance. However, additional statistical modeling following Bartoń (2012) indicated that when considered together, age at injury, and intraaxial hemorrhage (omitting mechanism and severity altogether) yielded the best fitting predictors. The reduced regression analysis using only those two predictors found that intraaxial hemorrhage was significant ($p = 0.006$), whereas injury age was not ($p = 0.113$).

Antiepileptic therapy

Patients who received antiepileptic therapy in the field, on the way to the emergency room, or in the emergency room were older (mean 7.9 ± 6.2 years vs. 4.5 ± 4.8 years, $p = 0.006$), and more likely to have severe injuries ($p < 0.001$), any type of bleed on CT scan ($p = 0.001$), subclinical seizures ($p = 0.021$), SE ($p < 0.001$), or subclinical SE ($p = 0.002$) during their hospital course. Further analysis is required to screen for electrical-clinical dissociation effects known to occur with some antiepileptic drugs.

Outcomes

Patients with SE and subclinical SE had on average a longer length of hospital stay than those without (SE 23.6 ± 4.7 standard error of the mean [SEM] days vs. no SE 11.2 ± 2.1 days, $p = 0.022$ and subclinical SE 22.6 ± 4.7 [SEM] days vs. no subclinical SE 12.0 ± 2.1 days, $p = 0.049$); however, there was no difference in the length of stay in the PICU. Finally, KOSCHI scores at hospital discharge were not related to *any seizures* (NS) but were significantly lower in patients with subclinical seizures ($p = 0.001$), SE ($p = 0.002$) and subclinical SE ($p = 0.001$). Univariate regression analysis was performed evaluating the relationship between KOSCHI score and age at injury, mechanism, intraaxial hemorrhage, severity, any seizure, and subclinical seizures. The only significant predictor found was severity of injury ($p = 0.009$).

Discussion

The incidence of 42.5% (37/87) for EPTS and 16.1% (14/87) for subclinical seizures in this study are higher than those reported in a comparable adult cohort (22.3% and 11.7%, for EPTS and subclinical seizures, respectively) (Vespa et al., 1999b). This suggests a greater risk for EPTS in pediatric patients. The rate was also higher than found in two retrospective pediatric TBI evaluations without standardized cEEG (EPTS 12.0%) (Chiaretti et al., 2000; Liesemer et al., 2011). The use of cEEG to detect subclinical seizures in the PICU has been published with prevalence rates between 7% and 39% (Jette et al., 2006; Saengpattrachai et al., 2006; Shahwan et al., 2010; Abend et al., 2011; Hahn, 2011; Williams et al., 2011). Most of these studies had few TBI patients, were retrospective, and initiation of the EEG was based on clinical judgment, which may impart bias into the composition of the cohort. This is the first study to prospectively utilize cEEG for all consecutive, unselected, acute TBI patients admitted to the PICU.

This study showed that younger age, AHT mechanism, and presence of intraaxial blood were clinical predictors of subclinical seizures or SE. The presence of SE (clinical or subclinical) was significantly associated with worse outcomes as measured by KOSCHI and hospital length of stay.

Our cohort confirmed past findings that EPTS were more frequent in younger children, specifically <1 year of age (Hendrick & Harris, 1968; Ong et al., 1996; Ratan et al., 1999; Chiaretti et al., 2000; Liesemer et al., 2011). SE was seen most often in children <1.5 years of age. Mechanism of injury has been reported as a risk factor for EPTS (Barlow et al., 2000; Liesemer et al., 2011), and in our cohort EPTS occurred in 77.3% of patients with AHT, more than twice the rate of any other mechanism. One retrospective study of children with AHT found a lower rate (33.0%) of seizures; however, less than half of the children studied had undergone EEG (Goldstein et al., 2010). Our rates were higher likely owing to the systematic incorporation of cEEG

monitoring in all patients, enabling detection of subclinical seizures. Higher TBI severity has been consistently reported to correlate with EPTS risk, (Hahn et al., 1988; Ratan et al., 1999; Chiaretti et al., 2000), but it was not found to be significant in our study. This may be a direct consequence of the regular utilization of cEEG, detecting more subclinical seizures in mild/moderate TBI. Statistical modeling revealed that age at injury and intraaxial hemorrhage (omitting mechanism and severity altogether) were the best fitting predictors of subclinical status epilepticus. Reduced regression analysis further suggested that intraaxial hemorrhage was more important than age at injury for patients with abusive head injury. This could have implications for the evaluation of patients with AHT, which typically occurs <1–2 years old, and suggests that intraaxial hemorrhage is more important to these patients than their age as a risk factor for clinical or subclinical EPTS.

Physiologic changes during subclinical seizures include increases in intracranial pressure and metabolic stress (Vespa et al., 2007b). Subclinical seizures may also cause longitudinal anatomic changes, such as hippocampal atrophy (Vespa et al., 2010). Outcomes in patients with subclinical SE have been poor (Claassen et al., 2006). Therefore, subclinical seizure detection could be important prognostically. Sixteen patients in our study were diagnosed with SE; five showed only clinical seizures, six showed both clinical and subclinical seizures, and five showed only subclinical seizures. Without cEEG monitoring the five subclinical cases would have been missed and some of the cases with both types may not have been detected until much later. Studies have also shown cEEG to be useful to evaluate paroxysmal events that are not seizures, thereby preventing unnecessary therapy (Shahwan et al., 2010).

Intradural/intraaxial blood is known to be a precipitant of PTS, and is used in preclinical animal PTS models (Willmore et al., 1978). In the current study, intraaxial blood was strongly associated with the risk of subclinical seizures, SE, and subclinical SE, but not of any seizures. Fracture on CT scan was associated with SE. This contrasts with results of a recent study (Goldstein et al., 2010) of AHT patients without standardized cEEG use where none of these findings were associated with seizures; however, other findings indicative of more severe injury (cerebral edema, infarction, blurring of the gray–white matter junction, and midline shift) were related to seizures.

Risk–benefit of prophylaxis for pediatric EPTS

Existing evidence suggests that EPTS may reflect the severity of injury as well as contribute to secondary injury, with the potential to worsen long-term outcomes (Barlow et al., 2000; Keenan et al., 2007; Vespa et al., 2007a, 2010) and increase the risk for subsequent development of posttraumatic epilepsy (PTE) (Annegers & Coan, 2000). However, it has been shown that antiepileptic drugs (AEDs) do not prevent late PTE and are not without their own risk, particularly on the developing brain (Temkin et al., 1990; Bittigau et al., 1999; Olney et al., 2004; Young et al., 2004; Kaindl et al., 2006). Therefore, accurate detection of seizures and SE could help direct therapy. The finding of subclinical seizures in one in six pediatric TBI patients admitted to the ICU may be key to altering possible clinical interventions as well as accurately determining the effect of EPTS on global outcomes and late PTE.

Caveats/limitations

To our knowledge, this is the first study to prospectively evaluate EPTS using the gold standard of cEEG in consecutive pediatric TBI patients admitted to the PICU. Differences were noted in the patient populations at two major academic centers. Although patients were of similar age and gender representations, there were significant differences in injury severity and mechanism of injury. These differences in severity and mechanism likely account for center differences in CT findings and rates of seizures detected. However, the overall range of injuries was still consistent with epidemiologic data from pediatric cohorts of moderate-severe TBI, and the variables associated with subclinical seizures were similar at both centers, as well as in the combined analysis. Methodologic and statistical analyses were optimized to minimize potential bias. A potential bias identified is not excluding those with a history of epilepsy, reported by some to be a risk factor for posttraumatic seizures (Ronne-Engstrom & Winkler, 2006).

Electroencephalographer-dependent differences in EEG interpretation represent another potential source of variability. Previous studies of EEG interpretation using multiple readers have shown relatively modest interobserver correlation (Abend et al., 2011). Relying on a single EEG interpreter can reduce variability but may pose limitations on the generalizability of findings. In the validation carried out in this study, EEG parameters were set to simply evaluate the presence or absence of a seizure and the hemisphere of onset to maximize opportunity for interobserver agreement and allow broader interpretation of relevant results. Within these parameters, high concordance (>96% for both) was achieved, although the use of more subtle EEG parameters will require further investigation.

Proposed indications for and value of cEEG use after TBI in children

We propose that cEEG monitoring for subclinical EPTS be strongly considered for all children younger than the age of 2 years admitted to the PICU for acute TBI. In addition, presence of intraaxial blood or demonstration/suspicion of AHT indicates greater risk for subclinical EPTS and thus signifies high-risk groups for cEEG monitoring. This would allow selective intervention with AEDs in patients who have EPTS, without indiscriminately exposing all patients to potential adverse effects. Severity of injury and skull fracture on CT has been shown to be possible risk factors

based on other literature and may be considered as well. Based on the outcome variables used in this study we show that subclinical seizures, SE, and subclinical SE may negatively affect outcome. We interpret this to indicate that rapid detection and treatment of EPTS could be of benefit in the management of pediatric patients with TBI.

We emphasize that the long-term effects of EPTS in pediatric patients on later developmental outcomes and risk of PTE remain an important area for ongoing investigation. Without clear demonstration of long-term risks among pediatric patients with EPTS, the decision to intervene with AEDs for EPTS remains primarily based on related adult data. Those data may not accurately reflect acute or long-term negative effects of AEDs on the developing brain.

Continued follow-up for this cohort will help decipher a major enigma from other PTE studies. Namely, it is known that EPTS is a risk for PTE, and that early prophylaxis can prevent EPTS and associated acute complications, yet has not been shown to diminish the eventual rate of developing late PTE. By accurately identifying pediatric patients with EPTS (clinical or subclinical), a better understanding of the relationship between EPTS and eventual TBI outcome may be achieved.

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