Pediatric Neurology 52 (2015) 174–181

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Post-Traumatic Epilepsy in Children—Experience From a Tertiary Referral Center

Jun T. Park MD [a,b,*], **Harry T. Chugani MD** [b]

[a] *Division of Pediatric Epilepsy, Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University School of Medicine, Cleveland, Ohio*
[b] *Divison of Pediatric Neurology, Department of Pediatrics, Children's Hospital of Michigan, Wayne State University School of Medicine, Detroit, Michigan*

ABSTRACT

BACKGROUND: Post-traumatic epilepsy after a traumatic brain injury occurs in 10%-20% of children. Unfortunately, a biomarker that could provide prognostic information about both post-traumatic epilepsy and cognitive development is lacking. In this first of a series of studies, we have reviewed and analyzed clinical variables in children following traumatic brain injury to understand the epidemiologic and clinical characteristics of post-traumatic epilepsy in our urban population. **METHODS:** We performed a retrospective electronic chart review of patients who had suffered traumatic brain injury and subsequently evaluated at Children's Hospital of Michigan from 2002 to 2012. Various epidemiologic and clinical variables were analyzed. **RESULTS:** Patients who had severe traumatic brain injury and post-traumatic epilepsy had an abnormal acute head computed tomography. These patients had increased number of different seizure types, increased risk of intractability of epilepsy, and were on multiple antiepileptic drugs. Hypomotor seizure was the most common seizure type in these patients. There was a high prevalence of patients who suffered nonaccidental trauma, all of whom had severe traumatic brain injury. **CONCLUSIONS:** This study demonstrates a need for biomarkers in children following traumatic brain injury to reliably evaluate the risk of post-traumatic epilepsy.

Keywords: post-traumatic epilepsy (PTE), nonaccidental trauma (NAT), seizure semiology, hypomotor seizures, epileptic spasms, traumatic brain injury (TBI), brain injury and seizures

Pediatr Neurol 2015; 52: 174-181

Introduction

Post-traumatic epilepsy (PTE) is a common cause of morbidity in children after a traumatic brain injury (TBI), occurring in 10%-20 % of children following severe TBI.[1-5] A diagnosis of PTE is reserved for patients who have had two or more unprovoked seizures following TBI.[6] Unfortunately, the pathogenesis of PTE remains poorly understood, and there are no biomarkers at this time to help predict reliably the risk of epilepsy and, thus, prevent PTE[7,8] and its comorbidities.

At the Children's Hospital of Michigan (Detroit), a level I pediatric trauma center, we have been applying advanced neuroimaging techniques to elucidate the mechanisms associated with PTE to identify an accurate biomarker that could provide prognostic information regarding both PTE and cognitive development following TBI. In this first of a series of studies, we have reviewed and analyzed clinical variables in children who had suffered TBI to understand the epidemiologic and clinical characteristics of PTE in our urban population.

Study design and methods

A retrospective electronic chart review was performed on patients who had suffered TBI and subsequently referred

Article History:
Received September 18, 2014; Accepted in final form September 20, 2014

* Communications should be addressed to: Dr. Park; Division of Pediatric Epilepsy; Department of Pediatrics; Rainbow Babies & Children's Hospital; Case Western Reserve University School of Medicine; Cleveland, Ohio.
E-mail address: jun.park@uhhospitals.org

0887-8994/$ - see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2014.09.013

to a child neurologist (any one of the seven neurologists in both inpatient and outpatient) at Children's Hospital of Michigan from 2002 to 2012. These patients were identified after interrogating a large database of all new patients maintained in the Division of Pediatric Neurology. A separate database was then constructed on patients who had received various diagnoses that included PTE, focal neurological deficit(s), postconcussive syndrome, and persistent headaches. A total of 321 patients' charts were reviewed and, of these, 47 patients were diagnosed with PTE. These 47 subjects form the basis of the current report.

Multiple clinical variables in these 47 subjects were reviewed: age at TBI, sex, perinatal complications, type of trauma, that is, accidental (AT) and nonaccidental (NAT), imaging and neurophysiologic data, degree of TBI (mild, moderate, severe), surgical interventions, time of first seizure, seizure types and semiology based on descriptions and/or neurophysiologic data, antiepileptic medications, treatment response, follow-up duration, and outcome. Seizure onset time was classified as immediate (<24 hours after injury), early (<1 week after injury), or late (>8 days after injury), as in previous studies.[9] Severity of injury was classified as mild, moderate, or severe. Mild injury was defined as loss of consciousness or amnesia lasting <30 minutes. Moderate injury was defined as loss of consciousness from 30 minutes to 1 day or a skull fracture. Severe injury was defined as loss consciousness for >1 day, presence of subdural hematoma, or brain contusion.[10,11]

Seizures were categorized using the semiological classification based on the history and, when available, review of the seizures on video electroencephalography (VEEG; Table 1). Using this approach, instead of the International League Against Epilepsy classification, allowed us to study the seizures based exclusively on ictal clinical semiology.[12,13] When classifying the seizures, we chose to be as precise as possible depending on the availability of the seizure descriptions. For instance, hypomotor seizure category was used if the salient feature was immobility or a reduction in movements, as in infants and young children where consciousness cannot be assessed.[14] In this age group hypomotor seizures are likely a bland form of "complex partial" seizures with no or minimal automatisms.[15] Tonic-clonic seizure category was used if there was a report of "body stiffening followed by jerking" without any indication to a specific body part.

Methodology of subject identification

The database includes both outpatient and inpatient evaluations. Patients who were referred to the outpatient neurology clinic were either previously hospitalized and seen by a neurologist or were referred by a physician for an initial evaluation of concussion and/or TBI and related comorbidities. The on-call inpatient neurologist evaluated patients after a head injury if the hospitalist, neurosurgeon, physiatrist, or intensivist saw a specific indication, which typically included a prehospital spell or a seizure. If there was mention of a seizure or any other type of seizure-like event immediately after the TBI and before hospital admission, these patients would be seen, as requested by the treating physician. Therefore not all patients who had suffered a "head injury" were necessarily observed by a child neurologist. All patients with diagnosis of a head injury with or without associated comorbidities seen in the outpatient neurology clinics (which includes outlying satellite clinics) were reviewed and followed by the neurologist. We excluded patients who only had one seizure in the acute/subacute stages of recovery, but did not have additional unprovoked seizures before the cutoff time period. All pediatric neurologists in our division had approximately equal participation in evaluating the previously mentioned patients.

It is possible that there were patients who suffered TBI and may have had subclinical seizures in the pediatric intensive care unit. These patients may have had hypoxia and/or asymptomatic stroke during the recovery phase in the intensive care unit. However, unless they were referred to one of our child neurologists for evaluation, these patients were not monitored for development of PTE. Also, those children who had a concussion but were not referred to our pediatric neurology division were not included in our database, as we would not have had knowledge of such patients. Our study only looked at patients who were initially referred to our center for evaluation of clinical seizures (and subsequently electrographically confirmed) after a head injury. Those who were initially referred for a clinical seizure, but confirmed to have nonepileptic events were not included in this study. Lastly, neonates with

TABLE 1.
Semiological Seizure Classification*

Epileptic Seizure
Aura
Somatosensory aura†
Auditory aura†
Olfactory aura
Abdominal aura
Visual aura†
Gustatory aura
Autonomic aura†
Psychic aura
Autonomic seizure†
Dialeptic seizure‡
Typical dialeptic seizure‡
Motor seizure†
Simple motor seizure†
Myoclonic seizure†
Epileptic spasm†
Tonic-clonic seizure
Tonic seizure†
Clonic seizure†
Versive seizure†
Complex motor seizure‡
Hypermotor seizure‡
Automotor seizure‡
Gelastic seizure
Special seizure
Atonic seizure†
Hypomotor seizure‡
Negative myoclonic seizure†
Astatic seizure
Akinetic seizure†
Aphasic seizure‡
Paroxysmal event

* Semiological classification as published by Lüders et al.[12]
† Left/right/axial/generalized/bilateral asymmetric.
‡ Left hemisphere/right hemisphere.

TABLE 2.
Cohort Sex

Sex	Mild TBI	Moderate TBI	Severe TBI	Total
Male	7	0	24	31
Female	1	0	15	16

Abbreviation:
TBI = Traumatic brain injury

hypoxic-ischemic injury at birth were excluded, as were patients with previous history of seizure, provoked or unprovoked.

Accuracy of diagnosis

All seizure histories were obtained through detailed face-to-face interviews with the immediate family members and/or patients if able during the neurology clinic visit or during inpatient consultation. Those patients who were diagnosed with PTE all had concussion and/or TBI and had more than one seizure beyond the acute stage. Seizure history both in the acute phase and months after the injury were well documented in the clinic and/or inpatient consultation note by the neurologist. There were many patients who had only one seizure in the acute phase and no subsequent seizure(s); these patients were not included in the present analysis. Because all patients who were initially screened were seen by a child neurologist at our institution, in addition to having subsequent follow-up evaluations for seizures, including electroencephalography (EEG) studies, we believe that the diagnosis of PTE in our cohort is reliable. After a head injury, a caretaker may have missed a subtle clinical seizure; however, we think this is minimal at best as patients with PTE in our cohort had multiple seizures.

Imaging findings in patients who had TBI as a result of nonaccidental trauma (NAT) were not detailed in this study as they commonly showed severe, multiple findings. These imaging findings included combinations of multilobar intraparenchymal hemorrhages, subdural hemorrhages, skull and/or facial bone fractures, infarction, hemorrhagic/nonhemorrhagic contusions of parenchyma, subcortical regions, and brainstem, and later, multilobar, multicystic encephalomalacia, porencephaly, and/or subdural hygromas.

The semiological classification of the seizures was based on detailed history and/or VEEG results when available, as described by Lüders et al.[12] Not every patient had a VEEG and, on many occasions, only interictal epileptiform discharges and no seizures were recorded. We want to stress

TABLE 3.
Imaging Results in Relation to Severity of TBI

	Mild TBI	Moderate TBI	Severe TBI
NML HCT on day 1*	7	-	0
NML brain MRI 1 mo later†	-	-	0
No imaging	1	-	0

Abbreviations:
HCT = Head computed tomography
MRI = Magnetic resonance imaging
NML = Normal
TBI = Traumatic brain injury
* Day 1: day of TBI
† 1 month after TBI

TABLE 4.
NAT versus AT in Relation to Severity of TBI

	Mild TBI	Moderate TBI	Severe TBI
NAT	0	0	21
AT	8	0	18

Abbreviations:
AT = Accidental trauma
NAT = Nonaccidental trauma
TBI = Traumatic brain injury

that the semiological classification used in our study is based solely on the clinical description of the seizures and/or ictal VEEG data, when available. It was not our intention to correlate clinical seizure type (semiological classification) with EEG or VEEG. The classification used allowed clear identification of ictal semiological features independent of any other test results. In addition, this system allowed categorization of seizures according to the degree of detail available about the seizures (Table 1). For example, if the only description of the seizure by the mother was "whole body shaking," this was classified as "clonic seizure" after confirming the epileptic nature of the events. If the clinical description was "jerking and stiffening," then the classification of "simple motor seizure" was used (Lüders et al.). Unless a sequence of seizure semiology describing a tonic seizure was immediately followed by clonic seizure, no assumption was made to classify "jerkings and stiffening" as a generalized tonic-clonic seizure. Likewise, the presence of hypomotor seizures (manifesting as behavioral arrest) was supported electrographically to differentiate from nonepileptic behavioral arrest. In the semiological classification of seizures, the evolution of seizure symptoms is indicated by considering each symptom as one component of a seizure. A seizure type consists of one or more of these components, which are listed in order of appearance and are linked by arrows; for example, abdominal aura → bilateral asymmetric tonic seizure (Lüders et al.). To have more than one seizure type, a patient has to have the second and third seizure types completely different from the first and from each other.

Results

Characteristics of the cohort

Of the 321 children with TBI in our database, PTE was diagnosed in 47 (15%). There were 31 (66%) male and 16 (34%) female patients, and their ages ranged from 1 day to 15 years. Among the 47 patients with PTE, eight (17%) had mild and 39 (83%) had severe TBI. Interestingly, no patient in the moderate TBI group had an identified seizure by the family or clinician between Day 1 and Week 1 of injury in

TABLE 5.
Time of First Seizure After TBI

Onset	Mild TBI	Moderate TBI	Severe TBI
<24 hr	4	0	9
1 day-1 wk*	0	0	3
>8 days	4	0	15

Abbreviation:
TBI = Traumatic brain injury
* Seizure occurrence between 1 day and 1 week after TBI.

TABLE 6.
Seizure Semiology-Known versus Unknown

Seizure Semiology	Mild TBI (Total 8)	Severe TBI (Total 39)
Known	8	31
Unknown	-	8

Abbreviation:
TBI = Traumatic brain injury

our limited number of cohort. It is possible that seizures may not have been recognized either because of subtle or atypical presentation. Of the 8 children with mild TBI, 7 were male, whereas among the 39 patients who had severe TBI, 24 (62%) were men and 15 (38%) were women (Table 2).

No patients with mild TBI had neurosurgical intervention or were placed on any empiric therapy for seizures within 24 hours of injury.

Acute imaging

Seven patients who had mild TBI had normal head computed tomography (CT) on the day of TBI, and one patient did not have any imaging (Table 3). None of the patients with severe TBI had normal head CT. A total of three patients with severe TBI had penetrating brain injury by a bullet. Magnetic resonance imaging revealed bullet fragments in parenchyma in two patients and in skull bone at the site of trauma in one patient. The seizure semiology of the latter patient could not be ascertained. There was no mention in the neuroradiology reports about parenchymal bony fragments in any of the patients with severe TBI.

NAT and AT

Twenty-one (54%) of the 39 patients with severe TBI had NAT, whereas all the eight patients with mild TBI had AT (Table 4). Eighteen (46%) of the 39 patients with severe TBI had AT. Age at the time of NAT ranged from Day of life 19-15 years of age.

Post-traumatic seizures

First seizure after a TBI occurred within 24 hours in 13 patients (28%), all of which were from the mild and severe TBI groups; 3 (6%) patients who suffered severe TBI had seizures between 24 hours and 1 week after injury, and 19 (40%) patients from the mild and severe TBI groups had seizures after 8 days (Table 5).

In the mild TBI group, 4 (50%) of the 8 patients had the first seizure in less than 24 hours after TBI, and the remaining 4 (50%) patients had the first seizure 8 days after the TBI.

By comparison, in the severe TBI group, nine (23%) of the 39 patients had the first seizure within 24 hours after TBI, three (8%) patients had the first seizure between 1 day and 1 week of TBI, and 15 (38%) had a first seizure > 8 days after the injury. Twelve patients (30%) had seizures of unknown onset.

Seizure semiology

Of the 39 patients with severe TBI, seizure semiology was unknown in eight, whereas all of the eight patients who suffered mild TBI had known seizure semiology (Table 6). Five (62%) of the eight patients with mild TBI had one seizure type, whereas three (37%) patients had two seizure types (Table 7). No patient with mild TBI had more than two seizure types. Of the 39 patients with severe TBI, 31 (80%) patients had known seizure semiology (Table 8). Seizure semiology of the eight (18%) patients could not be ascertained, either because of paucity of records and/or due to non-working phone numbers (Table 9). These patients consisted of 2 patient who had bullet injuries; five patients who suffered NATs, one of whom was subsequently diagnosed postoperatively with meningitis and subdural empyema needing an evaluation and ventriculostomy, and the last patient who suffered an AT needing an EVD and an ICP monitoring device Shunt.

Twenty (61%) of the 31 patients with severe TBI had one seizure type, 8 (29%) patients had two seizure types, and 3

TABLE 7.
Mild TBI Seizure Semiology*

Patient	Sex	Age at Injury	Type of Injury	Head CT	Current AED(s)	Seizure Semiology
One seizure type						
1	M	8 yr	AT	normal	LEV	Tonic-clonic
2	M	6 yr	AT	not done	LEV	Right versive →dialeptic
3	M	9 yr	AT	normal	LEV	Automotor →simple motor
4	M	3 yr	AT	normal	none	Right leg clonic
5	M	11 yr	AT	normal	VPA	Automotor
Two seizure types						
6	M	8 yr	AT	normal	VPA	Hypomotor, tonic-clonic
7	M	4 yr	AT	normal	PHB	Right face and leg clonic, myoclonic
8	F	23 mo	AT	normal	LEV	Left versive, tonic-clonic

Abbreviations:
AED = Antiepileptic drug
AT = Accidental trauma
F = Female
LEV = Levetiracetam
M = Male
PHB = Phenobarbital
TBI = Traumatic brain injury
VPA = Valproate
* Semiological classification, Lüders et al.[12]

(10%) patients had three seizures types (Tables 8). Six (19%) patients had infantile spasms and one of the three patients with epileptic spasms developed Lennox-Gastaut Syndrome. Epileptic spasms were not seen in the patients who had mild TBI (Table 7).

Antiepileptic drugs in relation to severity of TBI

Seven (88%) of eight patients who had mild TBI were on one antiepileptic drug (AED), and none of the patients were on more than one (Table 7). One patient in this group was

TABLE 8.
Severe TBI Seizure Semiology*

Patient	Sex/Age at Injury	Type of Injury/ Skull Fracture	Bullet Injury	Neurosurgical Procedure	Current AED	Follow-Up Duration	Seizure Semiology
One seizure type							
1	M/4 mo	NAT/no		Craniectomy, EVD/ICP/ shunt	PHB, LEV	16 days	Right arm tonic-clonic
2	F/7 mo	NAT/yes		-	weaned off	1 yr	Tonic-clonic
3	F/5 wk	AT/yes		-	LEV	5 mo	Generalized tonic→oral automotor
4	F/3 mo	NAT/no		-	LEV	4 mo	Left limb tonic→clonic
5	M/8 yr	AT/yes			OXC	10 yr	Tonic-clonic
6	M/15 yr	AT/yes	yes	EVD/ICP	unknown	7 yr	Tonic-clonic
7	F/3 mo	AT/yes		-	OXC, LMG	2 yr	Clonic
8	M/12 yr	AT/yes		-	TMX	5 mo	Dialeptic
9	F/19 days	NAT/no		-	OFF	7 mo	Generalized tonic
10	M/infant†	NAT/no		-	OXC	2 yr	Hypomotor
11	M/4 yr	AT/no		EVD/VP shunt	OXC	3 yr 8 mo	Hypomotor
12	M/3 yr	AT/yes			OXC	17 mo	Hypomotor
13	M/16 yr	AT/yes	yes	Shunt	OXC	4 yr 3 mo	Clonic
14	M/2 mo	NAT/no		EVD, VP shunt	LEV	6 yr 1 mo	Tonic-clonic
15	M/2 mo	NAT/no		VP shunt, subdural shunt	PHB, TMX	18 mo	Infantile spasms
16	M/13 days	AT/yes		Craniectomy, VP shunt	PHT, CBZ, LMG	15 yr	Hypomotor→right limb clonic
17	M/4 mo	AT/yes		-	OXC, TMX, VPA, CLZ	8 yr	Automotor→left limb clonic→GTC*
18	M/6 mo	NAT/no		Hematoma evacuation	LEV, OXC, CLB	2 yr 8 mo	Generalized tonic→gelastic
19	F/infant	AT/yes		-	LEV, VGN	9 mo	Epileptic spasms
20	M/4 mo	AT/no		VP shunt	LEV	1 yr 2 mo	Hypomotor seizure
Two seizure types							
21	F/infant†	NAT/no		-	TMX	10 yr	Tonic-clonic, hypomotor
22	F/8 yr	AT/no		-	LCS, CLB, LEV, ZNS, OXC	3 yr 3 mo	Hypomotor, generalized tonic→epileptic spasms
23	M/2 mo	NAT/no		-	VGN, OXC	8 yr 5 mo	Epileptic spasms, right versive
24	F/17 mo	AT/yes		-	OXC	2 yr	Left limb clonic, right limb clonic
25	F/2 mo	AT/yes		-	VPA, RFN, ZNS, OXC, LEV	3 yr	Epileptic spasms, hypomotor→right versive→bilateral arm tonic
26	F/8 yr	NAT/no		-	PHB, TMX, VGN	3 yr 3 mo	Hypomotor, hypermotor→bilateral arm tonic
27	F/birth	AT/yes		-	PHB, PHT, VPA	4 yr 4 mo	Limb clonic, epileptic spasms
28	M/5 mo	AT/yes		-	PHB, PHT, VPA	9 yr	Right leg clonic, right versive→generalized motor
Three seizure types							
29	M/15 yr	AT/yes		b/l craniectomy, R temporal/L frontal lobectomy	LMG, LEV	2 yr 7 mo	Left limb tonic, hypomotor, GTC

(*continued on next page*)

Table 8 (*continued*)

Patient	Sex/Age at Injury	Type of Injury/ Skull Fracture	Bullet Injury	Neurosurgical Procedure	Current AED	Follow-Up Duration	Seizure Semiology
30	M/1 mo	NAT/no		Shunt	OXC, VPA, TMX, RFN, CLB, KD	7 yr	Hypomotor, automotor, generalized tonic
31	F/39 yr	NAT/no		-	LEV, LMG, TMX, CLZ	1 yr	Myoclonic, left eye tonic→hypomotor, left limb clonic

Abbreviations:
AED = Antiepileptic drug
AT = Accidental trauma
b/l = Bilateral
CBZ = Carbamazepine
CLB = Clobazam
CLZ = Clonazepam
EVD = Extraventricular drainage
F = Female
GTC = Generalized tonic-clonic seizure
ICP = Intracranial pressure
KD = Ketogenic diet
L = Left
LCS = Lacosamide
LEV = Levetiracetam
LMG = Lamotrigine
M = Male
NAT = Nonaccidental trauma
OXC = Oxcarbazepine
PHB = Phenobarbital
PHT = phenytoin
R = Right
RFN = Rufinamide
TBI = Traumatic brain injury
TMX = Topiramate
VGN = Vigabatrin
VP = Ventriculoperitoneal
VPA = Valproate
ZNS = Zonisamide
* Semiological classification, Lüders et al.[12]
† Infants with unknown age at injury.

seizure free and off of AED. One patient who had an adverse reaction to valproate (i.e., pancytopenia) was switched to phenobarbital. Another patient was not on any AED after two reported seizures and subsequently had a normal 20 minute EEG and 1-day VEEG. This same patient as mentioned previously did not undergo imaging.

Fifteen (38%) of 39 patients who had severe TBI were on one AED, 19 (49%) were on two or more AEDs, and 3 (7%) were seizure free on no AED (Table 10). There were five patients, with one seizure type, who were acutely placed on empiric seizure medicine(s) and subacutely stopped. Phenobarbital and/or phenytoin were the only documented AEDs that were used for a duration of 1-2 weeks.

Discussion

The prevalence of PTE in children ranges from 0.2% to 9.8%.[3,6,10,11,16,17] A population-based study showed that >15% of people with severe TBI developed epilepsy.[10] However, this prevalence increases to >20% in patients with penetrating injury, a depressed skull fracture, or a subdural hematoma.[18] In our pediatric cohort, 15% of patients who had TBI developed PTE, which is within the reported range of previous studies. This finding in our cohort may be an underestimate as many more patients who had only one seizure at the time of chart review were excluded. Some of these may later have developed (or will develop) unprovoked seizures, thereby satisfying criteria for PTE. Furthermore, there may be patients not accounted for who had moved away or who are being treated by a neurologist outside of our hospital. Moreover, there may be patients who had concussion but did not yet develop a seizure, because it has been demonstrated that the risk of a first seizure continues to be elevated for >10 years after a severe head injury.[10] Finally, it should be pointed out that not every child with TBI, particularly in the absence of seizures, is referred to a pediatric neurologist even in our own hospital; indeed, some are followed by physiatrists as they undergo rehabilitation.

Post-traumatic seizures are more frequent in children after inflicted versus noninflicted TBI.[19-21] The reported rates after inflicted TBI are 48%-65% vs 15%-17% after non-inflicted TBI.[19,21] NAT as the cause of severe TBI was significant in our series, reaching 53% of patients with severe TBI and PTE and 45% of all patients who had PTE. We believe that the sampling bias because of the location of our urban hospital may explain why more than half of the patients who had severe TBI suffered NAT. In our cohort, all the patients who suffered NAT had severe TBI with recurring pathologic findings, such as skull fractures, subdural hematoma, and retinal hemorrhages. Subdural hematoma occurs more likely after a NAT than after AT.[19,21] Indeed, the development of a subdural hematoma has been identified as an independent risk factor for PTE after TBI in both children and adults.[3,4,11]

TABLE 9.
Severe TBI Unknown Seizure Semiology*

Patient	Sex/Age at Injury	Type of Injury/Skull Fracture	Bullet Injury	Neurosurgical Procedure	Current AED	Follow-Up Duration
32	M/15 yr	AT/yes	Yes	-	CBZ	3 yr
33	F/7 mo	NAT/no		-	PHT	>2 yr
34	F/6 mo	NAT/yes		ventriculostomy, burr hole-subdural empyema evacuation	OXC	8 mo
35	M/5 mo	NAT/no		-	PHT, PHB	2 yr
36	M/3 yr	AT/yes	yes	-	weaned off	4 yr
37	F/7 mo	AT/yes		EVD/ICP	PHB	4 yr 3 mo
38	M/8 mo	NAT/yes		-	OXC, LMG	1 yr 4 mo
39	M/3 mo	NAT/no		VP shunt	weaned off	4 mo

Abbreviations:
AED = Antiepileptic drug
AT = Accidental trauma
CBZ = Carbamazepine
EVD = Extraventricular drainage
F = Female
ICP = Intracranial pressure
LMG = Lamotrigine
M = Male
NAT = Nonaccidental trauma
OXC = Oxcarbazepine
PHB = Phenobarbital
PHT = Phenytoin
TBI = Traumatic brain injury
VP = Ventriculoperitoneal
* Infants with unknown age at injury.

Many researchers have reported that early onset of seizures is the strongest predictor of PTE.[6,10,22] This effect is not independent of the severity of injury[23] and, indeed, we found that 83% of the patients with severe TBI developed PTE. In addition, all the patients with severe TBI had an abnormal head CT within 24 hours of injury. This supports the notion that the more severe the injury, the higher the risk for PTE.[11] However, we could not make an association between immediate seizures, occurring within 24 hours of TBI and increased risk of later PTE. This may be because of the limited number of patients in our sample. Both experimental animal models and human studies have shown that PTE often starts later even in absence of acute seizures at the time of insult.[24] In fact, the seizure latency may be up to several years.[24]

Two randomized controlled trials >20-30 years ago to evaluate the risk of early (within 7 days after injury) seizure rate between AED prophylaxis, started within 24 hours after injury versus no prophylaxis (Temkin et al.[25] and Young et al.[26]) showed conflicting results. The latter study showed no significant difference in the early seizure rate between the two groups (no prophylaxis versus prophylaxis, 2.3% vs 4.0%; $P = 1$). In addition, the clinical trials have shown that treatment with AEDs after TBI did not protect against development of late epilepsy.[27] Moreover, the practice of using AED prophylaxis varied among neurosurgeons and neurologists at our center. It was unclear if an AED was begun in the immediate or early stage after the brain injury or the prophylactic AEDs were discontinued after the early stage. Consequently, we were unable to reliably conclude whether AED prophylaxis versus no prophylaxis influenced the diagnosis of PTE.

TABLE 10.
Response to AED in Relation to Severity of TBI

Patients	Mild TBI	Moderate TBI	Severe TBI
One AED	7 (88%)	-	15 (38%)
Two or more AEDs	0	-	19 (49%)
SZ free, off AED	1 (12%)	-	3 (7%)
Lost to follow-up	0	-	1 (3%)
Unknown	-	-	1 (3%)

Abbreviations:
AED = Antiepileptic drug
SZ = Seizure
TBI = Traumatic brain injury

The correlation between severity of head injury and increased risk for PTE is confirmed in the present study on a pediatric population. However, we found that these patients also had increased number of seizure types, increased risk of developing epileptic spasms, and increased risk of being on two or more AEDs to control the seizures, indicating the intractability of some PTE. The epileptic spasms tended to be refractory in spite of treatment with adrenocorticotropin hormone and/or vigabatrin. Four of the six patients with epileptic spasms had other seizure types. The commonest seizure type previously reported in an adult cohort in a prospective study was generalized tonic-clonic seizures, followed by complex partial seizures.[28] In our study of pediatric patients, the commonest seizure type in patients who had severe TBI was hypomotor seizures, which in the International League Against Epilepsy classification would be classified as complex partial seizures.[29] An explanation for the increased prevalence of hypomotor seizures in this group could be partly attributed to the increased prevalence of NAT in our cohort, of which 76% was less than 1 year of age.

Conclusion

Individuals with severe TBI and PTE all had an abnormal acute head CT. These patients had increased number of different seizure types, including epileptic spasms and

hypomotor seizures. Hypomotor seizure was the most common seizure type in these patients. Having had a severe TBI increased the risk for being on more than one AED and intractability of epilepsy. Epileptic spasms were not seen in patients with mild TBI and PTE. There was a high prevalence of patients who suffered NAT, who all had severe TBI. Sampling bias because of the urban location of our hospital may explain this finding. A limitation of our study is the small sample size and the fact that we could not include the patients who moved away or those patients whose caretakers were noncompliant with clinic visits, a problem not infrequently encountered in our hospital. Finally, it is clear from the present study that there is a need for biomarkers in children following TBI to reliably assess the risk of PTE.

References

1. Appleton RE, Demellweek C. Post-traumatic epilepsy in children requiring inpatient rehabilitation following head injury. *J Neurol Neurosurg Psychiatry*. 2002;72:669-672.
2. Barlow KM, Sposwart JJ, Minns RA. Early posttraumatic seizures in non-accidental had injury: relation to outcome. *Dev Med Child Neurol*. 2000;42:591-594.
3. Hahn Ys, Fuchs S, Flannery AM, Bartehl MJ, McLone DG. Factors influencing posttraumatic seizures in children. *Neurosurgery*. 1988; 22:864-867.
4. Ong LC, Dhillon MK, Selladurai BM, Maimunah A, Lye MS. Early posttraumatic seizures in children: clinical and radiological aspects of injury. *J Pediatr Child Health*. 1996;32:173-176.
5. Ratan SK, Kulshreshtha R, Padey RM. Predictors of posttraumatic convulsions in head injured children. *Pediatr Neurosurg*. 1999;30:127-131.
6. Annegers JF, Grabow JD, Groover RV, Laws Jr ER, Elveback LR, Kurland LT. Seizures after head trauma: a population study. *Neurology*. 1980;30(7 pt 1):683-689.
7. Adelson PD, Bratton SL, Carney NA, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 19. The role of anti-seizure prophylaxis following severe pediatric traumatic brain injury. *Pediatr Crit Care Med*. 2003;4:S72-S75.
8. Temkini NR. Antiepileptogenesis and seizures prevention trials with antiepileptic drugs: meta-analysis of controlled trials. *Epilepsia*. 2001;42:515-524.
9. Iudice A, Murri L. Pharmacological prophylaxis of posttraumatic epilepsy. *Drugs*. 2000;59:1091-1099.
10. Annegers JF, Hauser WA, Coan SP, et al. A population-based study of seizures after traumatic brain injuries. *N Engl J Med*. 1998;338: 20-24.
11. Annegers JF, Coan SP. The risks of epilepsy after traumatic brain injury. *Seizure*. 2000;09:453-457.
12. Lüders HO, Acharya J, Baumgartner C, et al. Semiological seizure classification. *Epilepsia*. 1998;39:1006-1013.
13. Lüders HO, Burgess R, Noachtar S. Expanding the international classification of seizures to provide localization information. *Neurology*. 1993;43:1650-1655.
14. Benbadis SR Text book of epilepsy surgery. Special seizures: localizing and lateralizing value. 53 a. Pages 488–490.
15. Kallen K, Wyllie E, Lüders HO, et al. Hypomotor seizures in infants and children. *Epilepsia*. 2002;43:882-888.
16. Frey LC. The epidemiology of posttraumatic epilepsy: a critical review. *Epilepsia*. 2003;44:11-17.
17. Hauser WA, Annegers JF, Rocca WA. Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. *Mayo Clin Proc*. 1996;71:576-586.
18. Temkin NR. Risk factors for posttraumatic seizures in adults. *Epilepsia*. 2003;44(Suppl. 10):18-20.
19. Kenan HT, Runyan DK, Marshall SW, Nocera MA, Merten DF: A population-based comparison of clinical and outcome characteristics of young children with serious inflicted and noninflicted traumatic brain injury. Pediatrics 2004;114:633–639.
20. Vinchon M, Defoort-Dhellemmes S, Desurmont M, Dhellemmes P. Accidental and non-accidental head injuries in infants: a prospective study. *J Neurosurg*. 2005;102:380-384.
21. Ewing-Cobbs L, Kramer L, Prasad M, et al. Neuroimaging, physical, and developmental findings after inflicted and noninflicted traumatic brain injury in young children. *Pediatrics*. 1998;102: 300-307.
22. Temkin NR, Haglund MM, Winn HR. Post-traumatic seizures. In: Yuomans JR, ed. *Neurlogical surgery*. 4th ed. Philadelphia: WB Saunders; 1996:1834-1839.
23. Herman ST. Epilepsy after brain insult, targeting epileptogenesis. *Neurology*. 2002;59(Supple 5):S21-S26.
24. Lowenstein DH. Epilepsy after head injury: an overview. *Epilepsia*. 2009;50(Suppl. 2):4-9.
25. Temkin NR, Dikmen SS, Wilensky AJ, et al. A randomized, double-blinded study of phenytoin for the prevention of post-traumatic seizures. *N Engl J Med*. 1990;323:497-502.
26. Young B, Rapp RP, Norton JA, et al. Failure of prophylactically administered phenytoin to prevent late posttraumatic seizures. *J Neurosurg*. 1983;58:236-241.
27. Temkin NR. Epilepsy after head injury: an overview. *Epilepsia*. 2009; 50(Suppl. 2):4-9.
28. Thap A, Chandra SP, Sinha S, Sreenivas V, Sharma BS, Tripathi M. Post-traumatic seizures-a prospective study from a tertiary level trauma center in a developing country. *Seizure*. 2010;19:211-216.
29. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia*. 1981;22:489-501.