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Post-traumatic epilepsy: an overview

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Abstract

Post-traumatic seizures (PTS) and post-traumatic epilepsy (PTE) are complications from traumatic brain injury (TBI). PTE refers to recurrent and unprovoked PTS that occur at least 1 week after TBI. Seizures during the first week after TBI are considered provoked, an acute complication from head injury, while seizures occurring 1 week after TBI are considered a manifestation of PTE and if only a single seizure occurs it is known as late PTS. EEG and neuroimaging help in the diagnosis of PTE. Predictors for PTE include TBI severity, presence of intracranial bleeding and early PTS. Several clinical trials have demonstrated that antiepileptic drugs are effective in reducing the frequency of acute PTS, but do not appear to alter the natural history of late PTS or PTE.

Keywords

antiepileptic drugs; head injury; post-traumatic epilepsy; prophylaxis; seizures; traumatic brain injury

Definitions & classification

As proposed by the International League Against Epilepsy and the International Bureau for Epilepsy in 2005, epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological and social consequences of this condition [1]. Epilepsy is further defined as recurrent unprovoked seizures occuring at least 24 h apart [2]. Post-traumatic epilepsy (PTE) is a life-long complication of traumatic brain injury (TBI) [3]. PTE and post-traumatic seizures (PTS) have both been used to describe seizures occurring after head trauma that are believed to be causally related to the trauma itself [3]. PTS are seizures occurring in the first week after TBI, and are considered to be provoked by head injury. PTE is defined as one or more unprovoked seizures that occur at least a week after TBI [4]. These are not universally

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accepted definitions, as some studies have allowed up to 4 weeks after head injury for early PTS [3].

The occurrence of seizures after head injury is a recognized complication of TBI and has been demonstrated to worsen functional outcome significantly [5]. Bruns and Hauser performed an epidemiologic review of TBI and determined that the incidence of TBI is between 180 and 250 per 100,000 per year [6]. Other studies, using data from the CDC, report a higher incidence of TBI based on emergency room visits, hospitalizations and deaths [7]. The percentage of TBI patients who develop PTE is not known. It is estimated that TBI is an etiological factor in up to 20% of symptomatic epilepsies in the general population [8].

In approximately half of PTE cases, seizures begin within the first year and in 80%, within the first 2 years. One population-based study estimated that 86% of patients with one seizure, occurring at least 1 week after TBI, had a second seizure within 2 years [9]. A second population-based study reported the cumulative incidence of PTE as 9.1 per 100 persons in the first 3 years after TBI [10]. Variations in the estimation of the incidence of PTE are caused by differing definitions used for both TBI and PTE [3] and varying lengths of follow-up in studies. Most studies of TBI and PTE are not population based and may only include more severely injured individuals [10].

The incidence of PTE in the civilian and military populations correlates with the severity of the inciting injury. This correlation between the incidence of PTE and severity of TBI explains most of the variability in the overall incidence of PTE, which ranges from 4 to 53% [3,11,12]. For example, in TBI with penetrating head injury, as with ballistic penetration, incidence of PTE was reported to be as high as 53% [3,11]. In 1980, Annegers *et al.* developed a three-tier classification for TBI severity: mild, moderate and severe (see Table 1) [13]. A universally accepted classification for TBI severity has not yet been developed [3].

Predictors of PTE

The frequency of seizures in patients with PTE is not associated with any identifiable variables and often varies widely, even within generally homogeneous populations [3]. Several case studies and review articles have attempted to identify risk factors for PTE (Table 2). Upon reviewing the literature, Ferguson *et al.* [10] determined that there is an overall agreement that increased severity of TBI appears to lead to an increased risk of PTE [9,14–18]. The most consistent risk factor for PTS is the presence of intracerebral blood, which can result in up to a 30% increase in the risk of PTS [3,19]. The most consistently significant risk factor for PTE is the occurrence of early PTS (i.e., within 1 week after head injury) [3,20,21]. The presence of subdural hematoma, brain contusion and multiple risk factors of severe TBI also increased the overall rate of PTE [21]. Increasing severity of PTE also correlated with higher seizure frequency, as well as epilepsy that is refractory to antiepileptic drug (AED) therapy [20]. Recently published data from the Vietnam Head Injury Study 35-year follow-up report suggested that patients with penetrating head injuries

carry a high risk of developing PTE decades after their injury [22]. The same report also concluded lesion location, lesion size and lesion type were predictors of PTE.

Although not identified as an independent risk factor, depression is recognized as a common comorbidity with epilepsy [10,23–26]. One case series documented that individuals identified as having depression at hospital discharge were almost twice as likely to develop PTE [10]. In addition, the presence of comorbid conditions, especially three or more, was linked with increased likelihood of developing PTE [10].

Diagnosis & evaluation of PTS & PTE

There has been significant focus on computed tomography, EEG and MRI after TBI to evaluate risk of PTE. Angeleri *et al.* performed a 12-month prospective study evaluating clinical progress, EEG and computed tomography at four scheduled intervals [27]. Some patients in this study also underwent MRI. Results showed correlation of PTE with early seizures, frontal or temporal lesions on acute computed tomography, development of an EEG focus 1 month after TBI, and cortical MRI hyperintense areas, including hemosiderin [27]. In subsequent work, serial MRI studies of TBI patients enrolled in the Angeleri *et al.* study were evaluated from 1994 to 2000 [28]. Increased risk for PTE was found after surgical treatment for subdural hematomas or contusions, as well as for a subgroup with hemorrhagic contusions on acute imaging and resulting hemosiderin dregs incompletely surrounded by gliosis on follow-up MRI [28]. In addition to identifying risk factors for PTE, several studies have demonstrated that the risk for PTE after TBI is initially high and decreases over time [15,21,29].

It is recommended to obtain neuroimaging and an EEG after PTS [30]. In some studies, the presence of interictal abnormalities or hematomas increase the likelihood of PTE; however, no definite predictors have been clearly identified. In 1975, Jennett did not find EEGs to be significantly useful in predicting development of PTE after TBI [31]. The 2003 American Academy of Neurology practice parameter for the use of AED prophylaxis in severe TBI also references the need for further research into the utility of EEG in differentiating which patients are at increased risk of developing PTE [32].

Treatment of PTS & PTE

Randomized clinical studies of PTS and PTE are limited despite the fact that the onset of PTE is delayed and most survivors of cases of severe TBI accessed the healthcare system early after their TBI. The discrete nature of TBI allows for an opportunity for preventive intervention for PTE. However, only a few randomized studies examining the prevention of PTE (class I or II studies) have been published [33,34]. There are trends in these and other studies suggesting that several AEDs, such as phenytoin, phenobarbital, carbamazepine and valproic acid, are effective for the prevention of early PTS, but not late PTS or PTE. A meta-analysis review, using Cochrane-pooled data methodology from several randomized controlled clinical trials, confirmed that prophylactic treatment with phenytoin or carbamazepine were effective in reducing the risk of early, but not late, PTS [33,34]. These studies have led to the recommendation of prophylactic AED therapy during the first week after TBI, but not continuing AED therapy beyond then unless late PTS develop [30].

Formisano *et al.* evaluated patients with severe TBI. In their study, patients who did not receive prophylactic therapy did not develop PTE in the 2-year follow-up period [35]. In another clinical trial, 5 days of continuous infusion of magnesium – a glutamate antagonist – at the NMDA receptor, given within 8 h after moderate or severe TBI, was demonstrated not to be neuroprotective and might, in fact, have a negative effect in the treatment of significant head injury [36].

No randomized controlled studies of AEDs have compared the different AEDs for the symptomatic treatment of seizures in PTE. The presence of other comorbidities, including psychiatric symptoms such as depression, might often dictate the selection of AED treatment, such as long-term therapy using lamotrigine [25,37]. In clinical practice, patients with intractable PTE are treated with a variety of anticonvulsants, devices such as vagus-nerve stimulation and resective surgery of limited lesions. Patients who received anticonvulsants as prophylactic treatment or who only had early PTS undergo downward titration of anticonvulsants over a few weeks. No randomized studies are available owing to different timing or rates of anticonvulsant discontinuation for this particular group.

Conclusion

Post-traumatic epilepsy is a common etiological factor among the epilepsies. Severity of TBI and presence of intracranial bleeding are predictors for PTS. Seizures within the first week after TBI appear to be a provoked reaction to the head injury. Preventing these early seizures with AED therapy is possible, but it does not alter the susceptibility to late seizures or the development of PTE. Further research is needed to better understand the neurobiology underlying this complex medical condition.

Future perspective

In 2007, the NIH held a conference on curing epilepsy. One of the workshops identified several potential areas for the discovery of mechanisms and novel targets to prevent epileptogenesis in several situations, including TBI. The areas targeted as promising biomarkers were [38–40]:

- Genomic
- Biochemical
- Electrophysiological
- Neurobehavioral
- Imaging

Using these biomarkers, it might be possible to conduct more targeted clinical trials, focused on TBI patients who have the highest probability to develop PTE. The other important advance has been the development of several animal models that more accurately represent the spectrum of neurobiological responses after TBI, opening the possibility for new experimental targets of truly antiepileptogenic therapies [41,42].

There are multiple medical and social issues related to epilepsy that have been well documented. As summarized in a review article by Bushnik *et al.*, these issues include anxiety, depression, poor self-esteem, cognitive impairment, social isolation, decreased employment and driving ramifications [43]. Further research is underway to assess these issues in patients with TBI and those with PTE.

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Executive summary

Definitions & classification

- Post-traumatic epilepsy (PTE) refers to recurrent and unprovoked post-traumatic seizures (PTS) that occur at least 1 week after traumatic brain injury (TBI).
- Seizures during the first week after TBI are considered to be provoked by the head injury and known as early PTS.
- Seizures occurring 1 week after TBI are considered as a manifestation of PTE and are called late PTS.

Predictors of PTE

- Predictors for PTE include TBI severity, presence of intracranial bleeding and early PTS.

Diagnosis & evaluation of PTS & PTE

- It is recommended to obtain neuroimaging and EEG after PTS.

Treatment of PTS & PTE

- Several clinical trials have demonstrated that antiepileptic drugs are effective in reducing the frequency of acute PTS, but do not appear to alter the natural history of PTE.

Table 1

Classification of severity of traumatic brain injury.

Severity	Description
Mild TBI	No skull fracture found, and ≤30 min post-traumatic amnesia or LOC
Moderate TBI	Skull fracture or other injuries, post-traumatic amnesia or LOC lasting between 30 min and 24 h, and not meeting criteria for severe TBI
Severe TBI	Documented brain contusion, intracerebral hematoma, or >24 h post-traumatic amnesia or LOC

LOC: Loss of consciousness; TBI: Traumatic brain injury.

Data taken from [13].

Table 2

Independent risk factors for post-traumatic seizures and post-traumatic epilepsy.

Risk factors for PTS	Risk factors for PTE
Acute intracerebral hematoma	PTS
Acute subdural hematoma	Acute intracerebral hematoma
Younger age	Acute subdural hematoma
Increased injury severity	Brain contusion
Chronic alcoholism	Increased injury severity
	Age older than 65 years at time of injury

PTE: Post-traumatic epilepsy; PTS: Post-traumatic seizures.

Modified with permission from [3].