Clinical Approach to Posttraumatic Epilepsy

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Abstract

Traumatic brain injury (TBI) is one of the most common causes of acquired epilepsy, and posttraumatic epilepsy (PTE) results in significant somatic and psychosocial morbidity. The risk of developing PTE relates directly to TBI severity, but the latency to first seizure can be decades after the inciting trauma. Given this "silent period," much work has focused on identification of molecular and radiographic biomarkers for risk stratification and on development of therapies to prevent epileptogenesis. Clinical management requires vigilant neurologic surveillance and recognition of the heterogeneous endophenotypes associated with PTE. Appropriate treatment of patients who have or are at risk for seizures varies as a function of time after TBI, and the clinician's armamentarium includes an ever-expanding diversity of pharmacological and surgical options. Most recently, neuromodulation with implantable devices has emerged as a promising therapeutic strategy for some patients with refractory PTE. Here, we review the epidemiology, diagnostic considerations, and treatment options for PTE and develop a roadmap for providers encountering this challenging clinical entity.

Keywords
- traumatic brain injury
- epilepsy
- posttraumatic epilepsy
- seizure
- neuromodulation

> "…the brain may be injured by contusion, laceration, compression, and it is well known that these insults may result in epilepsy after a silent period of strange ripening. That period lasts for months or years, but these insults produce epilepsy in the case of one individual and not in the case of another." ––W. Penfield (1961)[1]

The association between epilepsy and head injury has been known since antiquity,[2,3] but the societal impact of this connection has never been greater. Traumatic brain injury (TBI) accounts for 2.5 million emergency department (ED) visits, more than 280,000 hospitalizations, and 50,000 deaths in the United States each year.[4] Incidence estimates are staggering—rates of TBI-related ED visits have increased 70% over the past decade,[4] and a TBI now occurs every 21 seconds[5,6]—but these figures are likely conservative because many milder cases go unrecognized, leading to the term "silent epidemic."[7,8] Epilepsy, the enduring tendency for recurrent, unprovoked seizures,[9] is among the most common neurologic disorders[10] and frequently develops in the wake of TBI. Posttraumatic epilepsy (PTE) accounts for 5 to 6% of all epilepsy,[11–13] including up to 20% of acquired forms.[11] Posttraumatic epilepsy is the most common cause of new-onset epilepsy in young adults, and following penetrating brain wounds, the likelihood of developing epilepsy is as high as 53%.[2,14] Indeed, the relative risk of epilepsy after severe TBI is exceeded only by subarachnoid hemorrhage and brain tumor.[15] With the global proliferation in firearms[16] and the identification of military blast exposure as the "signature injury" of recent warfare,[17–19] rates of TBI and PTE will likely continue to increase in the future.

Although often neglected as an outcome measure in TBI studies,[20] PTE is the source of considerable somatic and psychosocial morbidity[21] and will be encountered by general neurologists and primary care physicians alike. Proper management of PTE requires an understanding of the risk factors, natural history, clinical heterogeneity, and treatment options. Here, we review these topics with a focus on clinical approach to PTE. The underlying pathophysiology of PTE and other

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neurologic syndromes related to TBI are reviewed elsewhere in this issue.

Definitions and Risk Factors

A seizure that occurs after head trauma can be described by the time interval between these events. Although definitions vary, many researchers adopt the following[2]: (1) Immediate seizures, which occur less than 24 hours after injury; (2) early seizures, which occur between 24 hours and one week after injury; and (3) late seizures, which occur more than a week after injury. Posttraumatic epilepsy is operationally defined as the occurrence of one or more unprovoked late seizures after TBI.

In both civilian and military populations, the risk of developing PTE depends heavily on the severity of the inciting injury.[19,22–24] The nosology of TBI severity is not universal, but a widely used classification is that of Annegers and colleagues[25]: (1) Mild TBI, which connotes loss of consciousness for less than 30 minutes and no skull fracture; (2) moderate TBI, with loss of consciousness 30 minutes to 24 hours, with or without skull fracture; and (3) severe TBI, involving loss of consciousness greater than 24 hours, with brain contusion, intracranial hematoma, or skull fracture. Compared with the general population, the relative risks of developing epilepsy after mild, moderate, and severe TBI are 1.5, 2.9, and 17, respectively.[24] Consistent with a critical role for injury severity, multivariate analyses indicate that risk factors for PTE include penetrating injuries, multiple contusions, intracranial hemorrhage, and neurosurgical procedures.[24,26–29] A practical implication of these observations is that it is essential to collect as much information as possible about the nature of a patient's prior head trauma for the purposes of risk stratification.

The issue of whether early posttraumatic seizures predict late seizures (i.e., PTE) has been given much attention, but results are conflicting. Risk factors for early and late seizures are similar, and a large, population-based cohort study found that early seizures were not an independent risk factor for late seizures.[24] This suggests that late seizures follow early posttraumatic seizures no more often than they do a first unprovoked seizure in the general population.[30,31] However, other studies have found that early seizures do increase the risk of PTE,[22,26,32–34] and the matter remains controversial. There is more agreement, however, that a first late seizure has a high risk of recurrence, 47% after 1 month and 86% within 2 years in one study.[35] Treatment implications in the context of these data are discussed below.

Other risk factors for PTE have emerged recently, including depression and multiple comorbid medical conditions.[22] Hereditary predisposition to PTE has been long suspected, in line with the "two-hit" hypothesis of other forms of epilepsy,[36,37] and genetic polymorphisms that putatively confer increased susceptibility have been identified.[28,38] A family history of epilepsy was found to increase risk of PTE in children,[39,40] but not in older patients.[14,41]

Natural History

The natural history of PTE can involve a long latency, often several decades, between the inciting trauma and the first late seizure. Although more than 80% of PTE begins within 2 years of TBI, the relative risk of developing PTE remains significantly elevated after >10 years in adults[41] and in children.[40] Thus, vigilant long-term neurologic follow-up is essential. The so-called silent period before the onset of PTE also presents a unique opportunity for prophylaxis against epileptogenesis, and numerous interventions have been explored,[28,42] including antiepileptic drugs (AEDs), inhibitors of intracellular signal transduction, ketogenic diet, therapeutic hypothermia, and exercise, although all remain investigational at present. In addition to monitoring for the onset of PTE, clinicians should be aware that an emerging concept of posttraumatic morbidogenesis frames epilepsy as one of several interconnected endophenotypes,[43,44] which may each require special attention. Prolonged periods of seizure-freedom occur in up to half of patients with PTE,[45,46] somewhat lower than remission rates in the epilepsy population as a whole.[47]

Most early seizures after TBI are of the generalized tonic-clonic type,[48] whereas late seizures are more likely to have focal onset.[49] This pattern may be partially explained by the fact that generalized tonic-clonic seizures are easily recognized, whereas focal dyscognitive seizures (previously called *complex partial seizures*) may initially evade detection. Overall, about two-thirds of patients with PTE have seizures that are focal with secondary generalization,[26,35] but other seizure types, including mesial temporal seizures related to hippocampal sclerosis,[50] epilepsia partialis continua,[51] and interestingly, primary generalized seizures,[49] can result from trauma as well. The frontal and temporal lobes are most commonly affected in TBI, and this is reflected in the distribution of posttraumatic focal epilepsies (temporal > frontal >> occipital/parietal).[44]

Diagnosis

As in any area of neurology, the diagnosis of PTE begins with the collection of a thorough history. Patients often will not volunteer certain incidences of head trauma (e.g., sports-related concussions or physical abuse with blows to the head),[52] and these may only be elicited with focused questioning. Ascertainment bias is inevitable, but should not deter exploration of the circumstances of prior head trauma because the risk of PTE scales with the nature and severity of TBI.[2] Witnesses may be able to provide valuable collateral history, such as the duration of loss of consciousness and occurrence of immediate convulsions. Drug intoxication and withdrawal can be associated with both head injury and seizures,[53] and clinicians should be aware of these confounders. Once the history of head trauma is established, the possibility of seizures can be evaluated. Symptoms to screen for include premonitory aura, episodes of altered awareness or unresponsiveness, déjà vu or jamais vu, involuntary focal motor activity (e.g., clonic movements, hand and oroalimentary automatisms), dysphasia, olfactory or gustatory hallucinations, amnesia or periods of lost time, and unexplained nocturnal injuries or incontinence. In general, the presence of spells that are paroxysmal and

stereotyped should raise high suspicion for seizures.[54] Slow fluctuations in consciousness are often a prominent component of posttraumatic encephalopathy, but are not necessarily epileptic. Similarly, fleeting attentional lapses and cognitive changes that persist over long periods are unlikely to represent seizures. Psychogenic nonepileptic spells (PNES) are common after TBI,[55,56] and are frequently mistaken for epileptic seizures.[57] Gold-standard diagnosis of PNES requires continuous video-electroencephalography (cVEEG) monitoring.[58]

A neurologic exam may reveal deficits referable to cerebral injury, complementing neuroimaging, and in some cases, obviating the need for it.[59] In an acute setting, the exam should include evaluation for signs of skull fracture, level of consciousness, and focal motor or verbal deficits. Exam findings may help prognosticate long-term outcome after TBI,[60] and a variety of clinical scoring systems have been developed in this regard.[61–63]

The EEG findings in TBI are usually nonspecific, and epileptiform activity on EEG does not predict disability outcome[64] or the development of PTE.[65] Notwithstanding recent efforts to develop objective EEG-based criteria for classifying TBI severity,[66–68] EEG traditionally has been regarded as adding little clinical value in patients with TBI.[65] However, there is growing awareness that subclinical seizures, including nonconvulsive status epilepticus (NCSE), are relatively common after TBI[69,70] and can only be detected by cVEEG.[71] In one study of 87 pediatric patients who required intensive care unit (ICU) admission after TBI and were monitored by cVEEG, 42.5% had seizures and over one-third of these patients had subclinical seizures, mostly NCSE.[70] Nonconvulsive seizures have been associated with hippocampal atrophy,[69] so aggressive treatment is warranted. ICU management is often required for patients with moderate–severe TBI, and cVEEG should be considered for at least a subset of these patients to enable early detection and treatment of NCSE. In addition, some information from continuous EEG recordings, such as persistent impairment of α variability, may portend a worse prognosis after TBI.[72]

Cranial imaging by computed tomography (CT) should be obtained urgently after moderate–severe TBI, and repeat CT is indicated for patients who develop seizures after initial imaging. In mild TBI, head CT prompted by posttraumatic seizures is often negative, but when positive, most commonly reveals intracranial hemorrhage,[48] which may be devastating without urgent surgical intervention. Beyond the acute setting, the mainstay of neuroimaging for PTE is magnetic resonance imaging (MRI), which provides the most sensitive means of defining the extent and severity of brain injury. Conventional MRI sequences, including T1-weighted, T2-weighted, gradient-echo, and diffusion-weighted imaging, may identify parenchymal hemorrhages, extra-axial blood products, early ischemia, edema, and gliosis. Advanced MRI techniques, such as susceptibility-weighted imaging and diffusion tensor imaging, are more sensitive to microhemorrhages and white matter injury, respectively,[73] and are being investigated for their potential to improve detection, to identify optimal treatments, and to predict outcomes.[74–76] Other forms of neuroimaging—magnetoencephalography,[77] single photon emission CT,[78] positron emission tomography,[79,80] and EEG coupled with functional MRI[81]—are less prevalent in routine clinical practice, but may one day form the basis for a multimodal imaging-based approach to evaluating patients after TBI.

Management

The neurologic community has come a long way since the days when trephination was the mainstay of treating PTE.[82] There is growing awareness of the clinical heterogeneity of PTE,[49] and optimal treatment can involve pharmacological and surgical options. Medical treatment is usually pursued first, and clinicians must therefore decide when to treat and with which drug. Unnecessary treatment with AEDs may impair neurorehabilitation after TBI,[83] and patients with post-TBI PNES should be treated with antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), and/or cognitive–behavioral therapy (CBT)[84] rather than AEDs. After the diagnosis of PTE is confirmed, the necessity of pharmacotherapy depends on the temporal relationship between onset of seizures and the inciting TBI.

Convulsions are reasonably common in the immediate aftermath of concussive head trauma, and the pathogenesis may relate to brainstem dysfunction secondary to biomechanical forces inducing transient functional decerebration.[85] In a cohort of 22 Australian rugby players, concussive convulsions did not result in development of PTE over a mean follow-up of 3.5 years.[86] The prognosis is therefore thought to be universally excellent, and there is widespread agreement that AED therapy is not indicated.[87]

By contrast, seizure prophylaxis with AEDs is part of standard therapy in the acute phase of moderate–severe TBI. Phenytoin (PHT) treatment significantly reduces the incidence of early posttraumatic seizures (14.2% to 3.6%),[12] and guidelines from the Brain Trauma Foundation and the American Academy of Neurology recommend AED treatment for the first 7 days after severe TBI.[88,89] PHT has the most evidence for use in this setting, but more recently, levetiracetam (LEV) has gained popularity for post-TBI seizure prophylaxis.[90,91] LEV has demonstrated comparable efficacy to PHT[92] and is associated with fewer adverse effects and monitoring considerations.[93] At present, however, there are no prospective, double-blind, randomized controlled trials comparing LEV and PHT after TBI. As discussed above, the prognostic value of early posttraumatic seizures is controversial and early treatment with AEDs does not decrease the risk of PTE.[12,94] Thus, AEDs are effective antiseizure drugs, but are not clearly antiepileptogenic, so AEDs are usually weaned one week after TBI.

Chronic AED treatment is indicated after a first late seizure due to the high risk of recurrence.[35] Principles of AED selection in PTE mirror those for other patients with epilepsy, and standard AEDs should all be effective.[30,95] In many cases, given the paucity of evidence for superior efficacy of one AED over another,[96] AEDs are primarily selected based on consideration of the patient's comorbidities and the drug's spectrum of activity, anticipated side effects, titration rate, dosing

schedule, cost, and potential for drug-drug interactions.[97] There is no doctrine on duration of AED therapy, and much depends on a patient's age, personal preference, and drug tolerability. However, as a rule of thumb, AED withdrawal can be considered after at least 2 years of seizure-freedom, though waiting up to 4 years has been suggested as well.[98]

Despite the development of over 15 third-generation AEDs since the 1980s,[99] 30 to 40% of patients with epilepsy have seizures that are incompletely controlled with medications alone.[100] Medical intractability is predicted after failure of two antiepileptic drugs,[101] and poor prognostic factors include the presence of structural cerebral abnormalities,[47] such as can be seen in PTE. In some medically refractory patients, surgical resection of the epileptogenic tissue is highly effective,[102] and recent evidence supports early consideration of surgical treatment.[103] A patient's candidacy for resective surgery hinges on precise seizure localization by cVEEG and neuroimaging, and the likelihood of seizure-freedom depends on temporal versus extratemporal ictal onset and on the presence or absence of an identifiable lesion.[104] Although epilepsy surgery remains underutilized overall,[105] the frequent presence of focal cerebral pathology in patients with PTE often prompts consideration of surgical options. For example, mesial temporal sclerosis (MTS) is a common pathology in PTE despite the presence of multifocal injury.[50,106] Rates of seizure freedom in selected patients with mesial temporal lobe epilepsy (MTLE) who undergo temporal lobectomy can be as high as 80 to 90%,[107,108] and patients with posttraumatic MTLE may therefore be particularly good candidates for epilepsy surgery.[109] Indeed, surgical outcomes for MTLE are comparable between traumatic and nontraumatic patient populations.[106] Patients with PTE of neocortical origin are less ideal surgical candidates,[50,109] but those with focal encephalomalacia can have good outcomes with electrocorticography-guided resections.[110]

Enthusiasm for surgical resection in patients with medically refractory PTE should be tempered by several considerations: (1) As a group, patients with PTE have seizure foci that are difficult to localize accurately,[109] partly due to technical issues related to prior craniotomies and breach rhythms[111] and because of frequent involvement of the frontal lobes; (2) TBI frequently produces diffuse cerebral injury, which can result in multifocal epilepsy and/or seizure-onset zones that overlap with eloquent brain regions; and (3) scar tissue and adhesions related to the inciting trauma can increase the risk for surgical complications.[110]

For patients with medically refractory PTE who are poor candidates for definitive resection, vagus nerve stimulation (VNS)[112] should be considered for adjunctive treatment. Vagus nerve stimulation involves a device implanted in the neck for open-loop peripheral stimulation of the vagus nerve, which is thought to provide indirect seizure control via retrograde brain inhibition.[113] Although prospective clinical trial data in patients with PTE are lacking, one case-control study found that VNS was associated with greater reduction in seizure frequency in patients with PTE than in patients with non-PTE at 2 years of follow-up (78% vs. 61% of patients with $>$ 50% reduction in seizure frequency).[114]

More recently, a direct form of neuromodulation, called *responsive neurostimulation* (RNS), has emerged as a promising therapy for patients with medically refractory epilepsy.[115,116] Unlike VNS, the RNS system functions in a closed-loop manner, detecting incipient seizure activity with implanted intracranial electrodes and then counterstimulating to terminate seizures via a small, programmable neurostimulator seated in a skull cassette. Optimal candidates for RNS are adults with multifocal seizure onsets and/or seizure foci that are not amenable to surgical resection due to overlap with eloquent brain regions. Over 2 years of follow-up, more than half of patients with RNS experienced at least a 50% reduction in seizure frequency.[117] A related technology, deep brain (anterior thalamic nucleus) stimulation,[118] has been approved in several countries and may soon be available in the United States.[119] Although not without controversy,[120] neurostimulation for epilepsy continues to evolve rapidly, expanding the clinician's armamentarium for treating medically refractory PTE. A strategy for navigating the various diagnostic and treatment options in PTE is outlined in ►**Fig. 1**, which expands upon a previously proposed algorithm.[95]

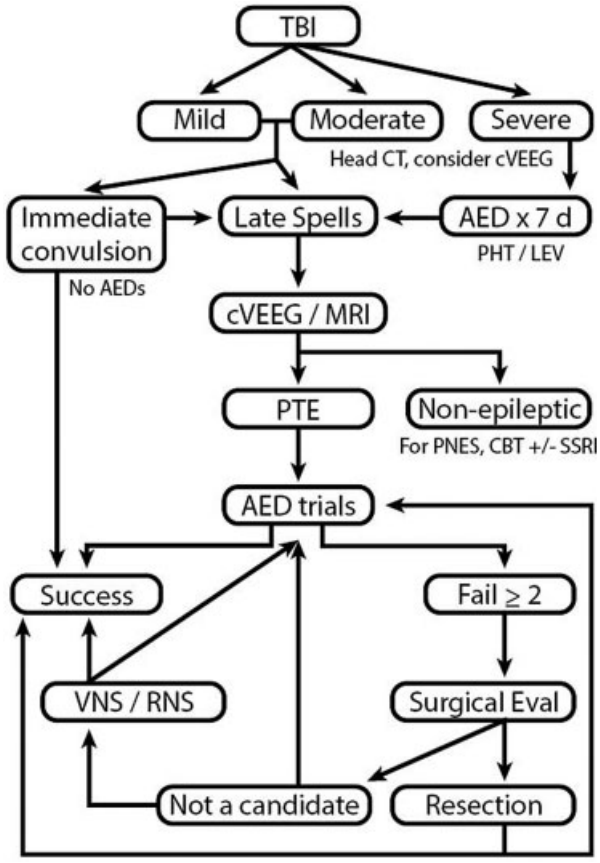

Fig. 1 An algorithm for the management of posttraumatic epilepsy. AED, antiepileptic drug; CBT, cognitive–behavioral therapy; CT, computed tomography; cVEEG, continuous video-electroencephalography; LEV, levetiracetam; MRI, magnetic resonance imaging; PHT, phenytoin; PNES, psychogenic nonepileptic spell; PTE, posttraumatic epilepsy; RNS, responsive neurostimulation; SSRI, selective serotonin reuptake inhibitors; TBI, traumatic brain injury; VNS, vagus nerve stimulation.

Conclusion

Traumatic brain injury is a rapidly growing epidemic and PTE often follows in its wake. Traumatic brain injury offers a unique opportunity for prophylaxis against epileptogenesis, but once developed, PTE is a heterogeneous condition that can be challenging to treat. Clinicians should be aware of the natural history of PTE and the shifting landscape concerning diagnostic and treatment options.

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