Post-traumatic Epilepsy

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Introduction

Epilepsy is a common neurologic complication of traumatic brain injury (TBI) [1–3]. Five percent of all referrals to specialized epilepsy centers are due to confirmed post-traumatic epilepsy (PTE) [4]. Patients with PTE comprise a regular part of the care provided by epilepsy specialists, as well as general neurologists and primary care physicians throughout the world [5]. The objective of this chapter is to provide an overview of post-traumatic seizures and epilepsy by reviewing the definition, epidemiology, and risk factors of epileptic events in TBI. Subsequently, we will discuss the pathophysiology of PTE particularly through animal studies. Finally, the clinical aspects of PTE will be discussed, and we provide a summary of the clinical approach to epileptic events associated with TBI, including diagnostic and therapeutic measures.

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Definition

An epileptic seizure is defined as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" [6]. According to the latest definition proposed by the task force of the International League Against Epilepsy (ILAE), epilepsy is "a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome" [6].

The epileptic events occurring following TBI are classified in one of these categories: [1, 7] immediate post-traumatic seizures (PTSs) occur less than 24 h after TBI, while early PTSs occur within the first week post-injury. Both immediate and early seizures after TBI are considered provoked seizures. They do not meet the definition of epilepsy since they are not necessarily mediated by the pathogenic mechanisms that predispose the patient to manifest spontaneous seizures [6]. Late recurring seizures, or PTE, are unprovoked seizures occurring more than 1 week after TBI.

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Epidemiology

Post-traumatic Seizures

The incidence of immediate seizures is reported to be 1–4% and of early seizures is 4–25% in civilian head injuries [2, 8, 9]. The occurrence of early PTSs depends in part on TBI severity [2, 8]. There are several classification systems for TBI severity. A widely used system is that of Annegers and colleagues (Table 7.1) [1]. Recently, a newer classification, the Mayo Classification System for TBI Severity, has been designed to distinguish between different severities of TBI correlated with the general outcome of the patients after injury (Table 7.2) [10]. Age also plays an important role in the development of PTSs, as children seem to be more likely to develop PTSs compared to adults [1]. In children PTSs are more common than later development of PTE (97% vs 3%) [11]. In addition, other important risk factors have been implicated in the development of PTS, listed in Table 7.3.

Subclinical seizures are seizures which show electrophysiological changes with electroencephalogram (EEG) recordings but display no overt behavioral changes [12]. Subclinical seizures, including nonconvulsive status epilepticus (NCSE), are relatively common after severe TBI in the intensive care unit (ICU) setting [13, 14]. Thirty-three percent of adult TBI patients requiring ICU were reported to have seizures as detected by continuous EEG monitoring [15]. In a pediatric study, the reported incidence of seizures was as high as 42.5%, of whom 7% only had subclinical seizures [14]. Intracranial EEG with electrodes implanted after TBI was able to detect electrographic seizures in 71% of patients that were not apparent on scalp EEG [16], suggesting seizure rates may be even higher than reported. Detection of subclinical seizures is crucial as reports have shown early nonconvulsive PTSs are associated with increased intracranial pressure, metabolic derangements, and long-term hippocampal atrophy [17, 18].

The occurrence of status epilepticus (SE) at onset is high, estimated to be 6.39% in an adult population, comprising 28.57% of the patients with moderate to severe TBI who developed clinical and subclinical PTS [13]. SE rates are even higher in the pediatric population compared to adults. In one study, an average of 18.4% of children with acute TBI developed SE in a pediatric ICU, ranging between 12.5% and 31.3%, depending on the severity of TBI [14]. Seventy

Table 7.1 Annegers' classification of severity of traumatic brain injury

Severity	Description
Mild TBI	Loss of consciousness for less than 30 min and no skull fracture
Moderate TBI	Loss of consciousness 30 min to 24 h, with or without skull fracture
Severe TBI	Loss of consciousness greater than 24 h, with brain contusion, intracranial hematoma, or skull fracture

TBI traumatic brain injury
Data taken from [1]

Table 7.2 Mayo classification system for traumatic brain injury severity

A	B	C
Moderate to severe (definite)	Mild (probable)	Symptomatic (possible)
Meets one or more of the following criteria: 1. Death due to this TBI 2. Loss of consciousness of 30 min or more 3. Post-traumatic anterograde amnesia of 24 h or more 4. Worst Glasgow Coma Scale full score in first 24 h 13 (unless invalidated upon review, e.g., attributable to intoxication, sedation, systemic shock) 5. One or more of the following present: Intracerebral hematoma Subdural hematoma Epidural hematoma Cerebral contusion Hemorrhagic contusion Penetrating TBI (dura penetrated) Subarachnoid hemorrhage Brain stem injury	If none of Criteria A apply, If one or more of the following criteria apply: 1. Loss of consciousness of momentary to less than 30 min 2. Post-traumatic anterograde amnesia of momentary to less than 24 h 3. Depressed, basilar, or linear skull fracture (dura intact)	If none of Criteria A or B apply, If one or more of the following symptoms are present: Blurred vision Confusion (mental state changes) Dazed Dizziness Focal neurologic symptoms Headache Nausea

Malec et al. [10]

Table 7.3 Risk factors of post-traumatic seizures and post-traumatic epilepsy

Post-traumatic seizures	Post-traumatic epilepsy
Acute subdural hematoma	Acute subdural hematoma
Acute intracerebral hematoma	Prolonged post-traumatic amnesia (>24 h)
Younger age	Age older than 65 years
Injury severity	Injury severity
Chronic alcoholism	Midline shift >5 mm
Multiple contusions	Multiple contusions
Depressed skull fractures	Depressed skull fractures
Neurosurgical procedures	Male gender
	Development of an EEG focus 1 month after TBI
	Frontal or temporal lesions on acute computed tomography
	Cortical MRI hyperintense areas
	Comorbid conditions
	Depression

EEG electroencephalography, *MRI* magnetic resonance imaging, *TBI* traumatic brain injury

percent of these children showed subclinical SE [14]. Younger age, abusive head trauma, and intracranial hemorrhage were the risk factors of developing SE in this study.

Post-traumatic Epilepsy

PTE accounts for 5–6% of all epilepsies [19]. The frequency rate of PTE varies in different studies between 1.9% and 53% [1, 2, 8, 9, 20, 21], depending on injury severity and mechanism. Patients with TBI have increased risk of developing epilepsy compared to the general population, and the relative risks of developing epilepsy after mild, moderate, and severe TBI are 1.5, 2.9, and 17, respectively [2]. Furthermore, the mechanism of injury in penetrating head trauma and closed-head injuries is different, and the former is more likely associated with PTE (50% in penetrating injuries versus up to 23.6% for the closed-head injuries) [2, 3, 9]. The bone and iron-containing metal fragments in the wounds of war survivors are potentially more epileptogenic than lead fragments from bullets. Hence, civilian injuries with bone fragments alone do not significantly increase the risk for PTE [9, 21, 22]. Furthermore, the duration of epilepsy, seizure frequency, and response to antiepileptic drug (AED) therapy is correlated with severity of TBI [2, 23]. In 27% of patients with penetrating war injuries, epilepsy persisted up to 15-year post-injury as compared with the risk in the general population [9]. Whether early PTS is a risk factor for PTE is a matter of controversy. While some studies found that PTSs were not an independent risk factor for PTE [2], other studies have demonstrated the presence of early PTSs as a precursor [21, 24], or even the most consistently significant risk factor for PTE in adults [7, 24], but this is certainly not true for children [7].

Family History/Genetic Associations Hereditary predisposition to PTE and related genetic polymorphisms has been long debated [25–27]. Although some studies have linked certain genes to PTE, many of them need to be duplicated.

While Schaumann and colleagues showed that family history of epilepsy could precipitate individuals into early PTSs and PTE [28], others found that family history of epilepsy increases the risk of PTE in children [29, 30] but not in older patients [9, 31].

Genetic association studies propose that there might be a genetic element to the development of PTE. A study showed that TBI patients with an apolipoprotein Eε4 (APOEε4) allele, a gene encoding a cholesterol transporter into neurons, experienced a higher risk of PTS [32]. In a review made by Cotter and colleagues, the most promising candidates were the pro-inflammatory gene Interleukin-1beta (IL-1b) SNP (rs1143634) and A1 adenosine receptor (A1AR) SNP (rs10920573) by which the individuals with heterozygous genotype seemed to be at higher risk for developing PTE. However, other genes such as glutamic acid decarboxylase 1 (GAD1) and methylenetetrahydrofolate reductase (MTHFR) C677T have been associated with early PTSs [33].

More recently, a genetic variation in solute carrier family 1 member 1 (SLC1A1), a gene encoding the neuronal glutamate transporters, was associated with reduced time to first seizure and increased seizure risk up to 3-year post-injury. When individuals were homozygous (GG) for the SLC1A1 SNP rs10974620 minor allele, the risk of seizure over this period increased significantly. Likewise, in individuals who were homozygous (TT) for the SLC1A1 SNP rs7858819 minor allele, the risk of PTE was higher when follow-up began on day 2 post-injury [34].

Mechanistic target of rapamycin (mTOR) complex 1 (mTORC1) is a protein involved in the regulation of cell proliferation and cell metabolism that widely has been associated with tumors including tuberous sclerosis. In a review recently published by Myers and colleagues, mTORC1 activation was considered as a contributing factor causing mossy fiber sprouting and neurogenesis, predisposing the patients to develop epilepsy after TBI although the significance of it has not been confirmed yet [35].

Pathophysiology

Human studies and animal models have attempted to discover the pathophysiological mechanisms for PTE, and various mechanisms have been proposed. A number of animal models have been employed at different developmental stages and with injuries of varying severity and location. One of the most well-studied models is fluid percussion injury (FPI), a model of closed-head TBI [36]. In this model, injury is delivered through a craniotomy by rapid fluid injection. The fluid pulse first strikes the intact dura and then moves into the epidural space [37]. Craniotomies can be applied to the midline to produce more diffuse injuries or laterally to produce mixed focal and diffuse injury [37]. Early electrophysiological changes [38] as well as PTE have been described [36, 39, 40]. Controlled cortical impact (CCI) injury is another widely used experimental model of closed-head injury that was recently identified as a model of injury-induced epilepsy [41]. This model often utilizes an electronically controlled pneumatic impactor to apply a focal contusion injury to the brain surface through a craniotomy [42].

Experimental models have described potential biological changes after TBI in three distinct temporal phases. The first phase ranges from a few seconds to minutes [43], consisting of immediate release of excitatory neurotransmitters including glutamate, followed by ion channel activation and cal-

cium influx [44]. Hyperexcitation results in energy depletion and cell death [44]. One of the underlying ionic changes identified early after the injury is potassium accumulation that is caused by failure of the ionic ATP pump [45] leading to altered resting membrane potential and neuronal excitability, with a loss of inhibitory postsynaptic potentials [46]. In addition, an increase in extracellular potassium converts spikers to a burster state in the CA3 region of the hippocampus [47]. Also, hyperexcitability in the CA1 subregion of the hippocampus has been reported by in vitro studies [48, 49].

Secondary injury is characterized by altered local cerebral blood flow regulation, breakdown in the blood brain barrier (BBB), and initiation of inflammatory and neuronal death, occurring within hours to days after TBI. During the inflammatory response, cytokines are released [50] which inhibit the uptake of glutamate by astrocytes [51] and modulate excitatory neurotransmission in the brain through glutamate receptors [52, 53]. For instance, IL-1β modulates neuronal hyperexcitability through Ca^{2+}, glutamatergic, and GABAergic pathways [54]. Glial glutamate transporter protein (GLT) which regulates the extracellular glutamate level also decreases after TBI, particularly in the neocortical and hippocampal regions leading to increased level of glutamate and hyperexcitability [55, 56]. Patients with PTE are more likely to show BBB disruption compared to non-epileptic patients after TBI, and slow waves are identified in EEG in 70% of cases [57].Tomkins and colleagues also showed that the size of lesion with BBB disruption was significantly larger in PTE patients [57].

The third phase is the latent period between the injury and the first successive seizure and is when epileptogenesis takes places [58]. It is characterized by morphological changes including mossy fiber sprouting, dendritic modifications, interneuron loss, rewiring of synaptic circuits, glial cell activation, ectopic cell proliferation, and gliosis [41, 59–62]. During this phase, excitability is increased both in CA1 [63] and dentate gyrus [64]. Loss of GABAergic interneurons decreases the inhibition on pyramidal cells [65–67]. Moreover, not only mossy fiber sprouting and loss of inhibition but also the increased connections on the dentate granule cells together enhance the excitability of hippocampus [47, 68–72]. This could also explain how injury at the neocortex progresses to mesial temporal seizures at a later time. Some groups have shown that seizures are originally neocortical at onset, but over time, the mesial temporal region transforms to an epileptogenic zone [73]. In fact, in approximately 61% of patients with PTE, seizures emanate from the temporal lobe [74], and magnetic resonance imaging (MRI) has shown that about 35% of these patients have mesial temporal lobe sclerosis (MTS). It is unclear, however, if MTS could be a secondary phenomenon [74]. Furthermore, prolonged seizures at the acute post-TBI phase have been implicated in hippocampal atrophy at the later phase of injury [18]. It is, however, worth mentioning that it is not uncommon that TBI results in multifocal pathology [74]. In conclusion, neuronal loss, chronic neuroinflammation, and network reorganization in the overlaying cortical regions are implicated in epileptogenesis.

Clinical or Natural History

Forty-seven percent of late PTSs recur after 1 month, while an 86% recurrence rate is observed within 2 years after injury [75]. In general, the relative risk of developing PTE after severe TBI remains significantly high even after 10 years both in adults [2] and in children [30], whereas patients with mild TBI exhibit a normalization of the risk after the first 5 years [2]. Christensen and colleagues believe that the absolute risk of PTE decreases significantly, and the yearly absolute risk remains below 1% for all types of brain injury including severe TBI by 5 years of follow-up [76]. One study showed that the mean latency to seizure was 3.5 years [77], ranging from 2.1 years for MTS to 5.1 years for all lesional neocortical cases. Age may be a determining factor in the latency period of seizures after trauma. There was a latency period of about 3 years in the patients who were over 15 years at time of injury versus a 13-year latency period in those who were 2 years or younger at the time of injury [78].

Seizure onset location can be very variable after TBI. In a study of 60 patients with moderate to severe TBI and PTE, 52% developed generalized seizures, 34% had focal seizures, and 15% showed focal seizures with secondary generalization; however, this was based on seizure semiology and not electrophysiology [75]. By contrast, in a 10-year retrospective study based on EEG recordings from the epilepsy monitoring unit, 93% had localization-related epilepsy arising most commonly from temporal or frontal lobes [77], and 4.8% displayed generalized epilepsy. Of temporal lobe epilepsy cases, just under half had MTS, and about one-third were nonlesional. In humans, owing to the shape of the skull, the frontal and temporal cortices are susceptible to contusion, accounting for the greater prevalence of post-traumatic contusion [79–81]. Likewise, in most animal studies, frontal neocortical or limbic epilepsy are more common than parietal/occipital seizures regardless of FPI location [82]. The other explanation for the predilection of the frontal lobe to epileptogenesis, although not well established, could be higher intrinsic susceptibility to tissue damage or the known tendency of prefrontal neurons to burst discharges and hypersynchronization [82]. In experimental models, frontal neocortical foci develop within 1 month following FPI, while it takes several months for limbic regions to transform to an epileptogenic zone [73]. Whether frontal neocortical seizures are capable to kindle the hippocampus through propagation [73] is a proposed

explanation. Direct hippocampal injury could also cause limbic epileptogenesis although more slowly [82]. In two studies, 24% to 35% of patients had mesial TLE (MTLE), while neocortical foci were identified in 12–48% of patients [74, 83]. TBI can induce MTLE in children younger than 5 years, while neocortical epilepsy tends to occur later in life [74]. However, recently, Gupta and colleagues reported that 83% of patients with MTS following TBI had their injury after the age of 5 years. Englander and colleagues believe that although TBI has a propensity toward frontal and temporal lobes, parietal lobe involvement may also reduce the overall seizure threshold [21].

The remission rates of seizures vary between 25% and 40% once PTE is diagnosed (and treated), and up to half of patients with PTE show prolonged periods of seizure freedom [84].This is slightly lower than remission rates in other epilepsy populations [85]. Patients with high frequencies of seizures during the first year following injury are less likely to achieve remission [86].

Investigations

Following a seizure associated with acute head injury, investigation should involve assessment of the biochemical parameters, such as hyponatremia, along with exploring for possible intracranial hemorrhage. Hyponatremia induced by head trauma may lower the seizure threshold [86]. Acute brain edema, perioperative events including cerebral interventions or stress from general anesthesia, and metabolic disturbances account for a high proportion of seizures which develop during the first month after brain injury [21]. In patients developing PTS after moderate to severe TBI, CT scan should be performed urgently. If the seizures occur after initial imaging, a repeat CT is indicated.

Patients with PTE should be approached similarly to patients with a first non-traumatic epileptic seizure. All patients with epilepsy should be asked specifically about head trauma, since patients do not usually volunteer certain incidences of head trauma such as sports-related concussions [87]. In addition, psychogenic non-epileptic seizures (PNES) are common after TBI [88, 89] and are frequently mistaken for epileptic seizures [90]. They should be ruled out with appropriate investigations, including video-EEG monitoring if necessary.

Magnetic resonance imaging (MRI) is the most sensitive means in identifying the extent and severity of brain injury and is the recommended neuroimaging modality in patients with PTE. Conventional MRI sequences, including T1-weighted, T2-weighted, gradient echo, and diffusion-weighted imaging, may discover parenchymal hemorrhages, extra-axial blood products (hemosiderin deposits), early ischemia, edema, and gliosis [91]. While the epileptogenic role of hemosiderin deposits has been established [20], precocious formation of a gliotic scar around a hemosiderin deposit reduces the risk of PTE [92]. Advanced MRI modalities including diffusion tensor imaging (DTI) and functional MRI (fMRI) identify early and late changes that might correlate with epileptogenic foci [93]. Susceptibility-weighted imaging and DTI are more sensitive to microhemorrhages and white matter injury, respectively [94].

The EEG findings in TBI are usually nonspecific, and the presence of epileptiform activity does not predict the development of PTE [95] or disability outcome [96]. As described earlier, continuous EEG monitoring is worthwhile to rule out subclinical seizures, particularly NCSE in the ICU setting. The scalp EEG is negative in more than 20% of patients with PTE during the first 3 months after TBI [95]. However, it remains useful for localization of the epileptogenic zone as well as measurements of the extent of damage and in predicting relapse before AED is withdrawn [97]. Intracranial recordings also have demonstrated interictal spikes and fast ripples early during the epileptogenic process in patients with established PTE, representing a more sensitive method than routine scalp recordings in identifying the epileptic activity in these patients [16].

Management

The decision to initiate pharmacotherapy depends on the temporal relationship between the inciting brain injury and onset of seizures. In immediate seizures which occur immediately following head trauma, antiepileptic therapy is not indicated. Indeed, the pathophysiological mechanism of immediate seizures might be related to transient functional decerebration with loss of cortical inhibition and is characterized by initial tonic phase within 2 s of impact, followed by a clonic or myoclonic phase, which may last for several minutes. Immediate seizures do not lead to development of PTE [98].

In contrast, since early seizures increase cerebral perfusion pressure and intracranial pressure, seizure prophylaxis is the recommended therapy during the first 7 days of moderate to severe TBI based on the latest guideline (2016) of the Brain Trauma Foundation. Phenytoin treatment significantly reduces the incidence of early PTSs (3.6–14.2%) [99]. While phenytoin has been widely used to prevent early PTS, levetiracetam recently has gained attention for seizure prophylaxis in TBI [100]. However, a high-quality, head-to-head randomized clinical trial (RCT) between phenytoin and levetiracetam is lacking. Levetiracetam has demonstrated comparable efficacy to phenytoin in non-controlled studies [101–103] and is associated with fewer adverse effects, monitoring considerations [104], and better long-term outcomes [103]. An observational study on severe TBI revealed that epileptiform EEG abnormalities are more likely to persist in

patients treated with levetiracetam compared to phenytoin [105]. Compared to placebo, carbamazepine has been documented to be effective in the prevention of early PTSs only in one true RCT [106]. Although similar results have been reported for valproate [107], this drug has lesser capacity to prevent early PTSs compared with phenytoin.

Compared to the established efficacy of early PTS, there is no evidence for pharmacological prophylaxis of the development of PTE [86, 99, 108]. Nevertheless, patients with early PTS, dural-penetrating injuries, multiple contusions, and/or SDH requiring evacuation may benefit from antiepileptic therapy beyond the first week post-injury [21, 107, 109, 110]. Principles of AED selection in PTE are identical to other patients with epilepsy, and no specific AED has been recommended for PTE [111, 112]. Neuropsychological consideration is required to be taken prior to starting AEDs [22]. Inappropriate treatment with AEDs may impair neurorehabilitation after TBI [113], and patients with post-TBI PNES could benefit from antidepressants, such as selective serotonin reuptake inhibitors and/or cognitive–behavioral therapy [114] rather than AEDs. 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 [115].

Experimental Interventions

One of the main goals of PTE studies is to develop a therapeutic strategy which could be delivered during the latent period after TBI in order to prevent epileptogenesis and the development of PTE. Investigators have focused on various mechanistic pathways as potential therapeutic targets. Many studies have attempted to find antioxidant and neuroprotective drugs which prevent the lipid peroxidation of neuronal membranes. Based on the knowledge that magnesium blocks glutamate transmission at NMDA receptors, continuous infusion of magnesium sulfate was carried out within 8 h after moderate or severe TBI. However, this double-blinded RCT did not appear to prevent PTE [23]. The effect of magnesium on PTS could not be assessed because of concomitant use of phenytoin. In a ferrous chloride animal model, tochopherol (vitamin E) use was associated with a delay in the onset of electrical seizures on EEG [116]. The use of adenosine and its derivatives in post-traumatic animal models showed suppression of epileptic discharges through scavenging free radicals such as OH [117]. Subsequently, Malhotra et al. demonstrated that adenosine and its analogues protect against seizures induced by chemical agents through their action on A1 receptors [118].

Although the efficacy of corticosteroids has been established in spinal cord injury, the administration of these agents is controversial in TBI. Previously, Hoeppner had shown that prednisone prevents epileptogenesis in a metallic aluminum-injected animal model [119]. However, in a randomized placebo-controlled trial, the risk of death within 2 weeks after brain injury was higher in the group that received corticosteroids compared with placebo. The prevalence of seizure did not differ significantly between the two groups during this period [120]. In a retrospective study, corticosteroids treatment within the first day of head trauma resulted in increased seizure activity and was not associated with any decrease in PTE [121].

As discussed earlier, TBI initiates a cascade of neuroinflammation in the brain, which may induce epileptogenesis and contribute to development of PTE. As such, recent investigations have attempted to focus on neuroinflammatory agents as the novel therapeutic targets in the post-traumatic phase. Diamond and colleagues demonstrated that patients who developed PTE had a higher ratio of cerebrospinal fluid (CSF)/serum IL-1β and lower levels of serum IL-1β, whereas the difference between CSF IL-1β levels was not significant [122]. Dextromethorphan derivative is an experimental treatment which reduces both neuroinflammation and nonconvulsive seizures in a penetrating ballistic-like brain injury (PBBI) model [123]. Minozac prevents experimental seizure susceptibility by suppression of cytokine upregulation in the hippocampus in a "two-hit" injury model [124]. Most recently, perampanel, an antiepileptic drug, has been shown to have neuroprotective effects through reduced neuronal apoptosis, inhibition of lipid peroxidation, and suppression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IL-1β, as well as increase in the levels of anti-inflammatory cytokines IL-10 and transforming growth factor-β (TGF-β 1) [125] although its prophylactic effect on PTS or PTE has not been studied. Recently, cooling has gained attention as a prophylactic treatment in PTE, possibly via anti-inflammatory mechanisms. Focal mild cooling prevented the onset of epileptic seizures in a rostral parasagittal PFI model both during and after the treatment. Rare remaining seizures were shorter than in controls [126].

Studies have demonstrated that the mTOR signaling pathway is abnormally activated in TBI, and rapamycin, an mTOR inhibitor, suppresses epileptogenesis of dentate gyrus granule cells in the ipsilateral temporal lobe in CCI models [127, 128]. Inhibition of mTOR also showed antiepileptogenic and neuroprotective effect in an organotypic hippocampal culture model of PTE [129]. While exogenous insulin-like growth factor-1 (IGF-1) has neuroprotective effect early after TBI, in long term, it contributes to epileptogenesis through activation of mTOR cascade [130]. In animal epilepsy models, activation of cannabinoid type-1 (CB1)

receptor prevents the seizure [131]. Cannabinoid receptors downregulate after TBI, leading to hyperexcitability. This is followed by upregulation in 4 weeks. Despite the protective role of the CB1receptor agonists [131], Echegoyen et al. showed that a single use of a CB1receptor antagonist immediately after TBI could disrupt the epileptogenic process and prevent PTE occurrence [132]. In contrast, Nissinen J and colleagues showed that either immediate single dosage or long-term treatment with SR141716 (a CB1 receptor antagonist) initiated 30 min after injury did not have antiepileptic effect in a lateral FPI model [133]. This difference was attributed to later timepoint assessment, different types of assessment of seizure susceptibility, and the number of included animals.

Surgical Intervention

The presence of focal cerebral pathology in patients with PTE prompts the consideration of surgical options in medically refractory patients [91]. Indeed, the success rate of surgical resection appears to be comparable to that in the non-traumatic population [77, 134]. Therefore, PTE patients should be worked up similarly to non-traumatic patients with epilepsy in terms of determining surgical candidacy. In an optimal treatment plan, both pharmacological and surgical options should be considered when appropriate, since early surgery prevents progressive secondary injury from recurrent seizures [77]. The likelihood of seizure freedom depends on the ictal onset zone as well as the presence of an identifiable lesion [135]. Rates of seizure freedom in PTE patients with MTLE who undergo temporal lobectomy can be as high as 69–90% [77, 136, 137], compared with 33% in patients with frontal lobe epilepsy, similar to what is seen in the non-traumatic population [77]. While neocortical seizures are less ideal surgical candidates [74, 83], the presence of focal encephalomalacia predicts a good outcome with electrocorticography-guided resections [138].

Nevertheless, in the surgical approach in patients with medically refractory PTE, several challenges might be encountered. Firstly, diffuse cerebral injury induced by TBI can result in multifocal epilepsy which may not be surgically amenable. Secondly, owing to prior craniotomies and breach rhythms, seizure foci might be difficult to localize precisely [139]. In addition, orbitofrontal cortex is commonly involved, impacting accurate localization of the epileptogenic zone [83].

Neuromodulation is a palliative treatment which is reserved for medically refractory patients who are not suitable candidates for conventional resective surgery, either because the seizure onset zone cannot be adequately localized or because it involves eloquent cortex which is not safe to remove. Neuromodulation is believed to provide high-frequency stimulation which desynchronizes the cerebral cortex and prevents seizure. Neuromodulation modalities which are used currently in the treatment of patients with medically refractory epilepsy are deep brain stimulation (DBS), vagal nerve stimulation (VNS), and responsive neurostimulation (RNS).

VNS in post-traumatic patients is thought to be comparable to the non-traumatic population. However, one case-control study indicated that VNS was associated with more than 50% reduction in seizure frequency in 78% of patients with PTE as opposed to 61% in patients with non-traumatic epilepsy at 2-year follow-up, suggesting it may have greater efficacy in this group [140]. Similarly, DBS of the anterior nucleus of the thalamus (ATN) showed a seizure frequency reduction by 40.4% in refractory PTE patients [141]. However, the seizure reduction effect was only significant if the seizures originated from one or both temporal lobes compared with seizures arising from frontal, parietal, and occipital regions or multifocal/diffuse seizures. In addition, the number of responders during the blinded evaluation period was not significantly different between the groups. However, the seizure frequency reduction and responder rates increased significantly in long-term nonblinded follow-up by 56% and 54%, respectively.

Unlike the other two modalities, RNS is a closed-loop system that prevents seizures by detecting epileptiform activities and stimulating the seizure onset zone. Two studies showed a significant difference in seizure frequency reduction (37.9–41.5%) between active and control groups [142, 143]. However, the percentage of the responder was not significant. Similar to DBS, improved efficacy was observed in long-term stimulation. However, there have been no reports of RNS specifically in patients with PTE, and therefore, it is not clear whether efficacy is similar in this population.

Conclusion

PTE is a serious common complication of TBI, comprising 5% of all epilepsies. Several risk factors have been identified, anticipating the likelihood of developing PTS and PTE. Severe TBI is correlated with an increased risk of developing PTS and PTE. Whether PTS increases the risk of PTE is controversial. Recently, genetic association studies have identified a number of genetic variants predisposing patients with TBI to PTS or PTE. Numerous experimental studies have attempted to identify the nature of hyperexcitability after TBI. The post-traumatic animal models have recently highlighted the putative role of inflammation as one of the underlying pathophysiology of neuronal hyperexcitability. Localization-related epilepsy represents the most

common epilepsy occurring after TBI, and there is a high predilection for temporal and frontal lobe epilepsy in this regard. High percentage of recurrence is observed within the first 2 years after injury. Although the role of AEDs in prophylactic treatment of PTS has been well established, they are not able to prevent PTE. Phenytoin is a highly recommended prophylactic therapy within the first week after TBI although levetiracetam has shown comparable effect to phenytoin. No neuroprotective agent has been proved to prevent PTE or PTS in human. Clinical approach and principles of AED selection in PTE are identical to other epilepsy syndromes, and surgery may be indicated in patients who do not respond properly to AEDs.

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