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Epilepsy After Brain Injury – Understanding the Link and Managing the Condition

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ABSTRACT

Post-Traumatic Epilepsy (PTE) is a neurological disorder characterized by recurrent seizures that occur as a result of traumatic brain injury (TBI). It represents a significant medical challenge due to its complex pathophysiology, diverse clinical manifestations, and the long latency period between the initial injury and the onset of epilepsy. It typically manifests weeks, months, or even years after the initial trauma, complicating the prognosis and management of head injury patients. The incidence of PTE varies widely, influenced by the severity and nature of the brain trauma, with higher risks associated with penetrating injuries, severe brain contusions, and hemorrhagic lesions. Pathogenetic mechanisms involve a cascade of molecular and cellular events, including neuroinflammation, blood-brain barrier disruption, and neuronal hyperexcitability, which contribute to the formation of epileptic networks. Diagnosis relies on a detailed patient history, neuroimaging, and electroencephalography (EEG) to confirm seizure activity and exclude other causes. It is often delayed and complicates early intervention strategies. Current management primarily focuses on seizure control through antiepileptic drugs (AEDs), but response rates are variable, and many patients suffer from drug-resistant epilepsy. Advances in neuroimaging and biomarker research hold promise for earlier detection and targeted therapies. This review synthesizes recent findings on the epidemiology, pathophysiology, diagnosis, and management of PTE,

highlighting the need for a multidisciplinary approach to improve outcomes for individuals affected by this condition.

Key words: epilepsy, post-traumatic epilepsy, seizures, traumatic brain injury, psychogenic non-epileptic seizures, dissociative seizures, prophylaxis, antileptic drugs

1. Introduction

Epilepsy is a neurological disorder characterized by a long term propensity to produce unprovoked seizures and by the associated comorbidities including neurological, cognitive, psychiatric, and impairment the quality of life [1]. It is defined as a brain disorder characterized by unprovoked seizures occurring at least 24 hours apart or a single seizure with a high risk of recurrence [2]. While most cases of epilepsy can be well controlled, a significant minority of patients experience intractable or medically refractory epilepsy, which requires substantial resources for care.[3]

Traumatic brain injury (TBI) is a condition characterized by damage to the brain resulting from an external force applied to the head, which can disrupt the normal function of the brain. [4] It has been emerging as a significant concern recently due to the rising number of cases leading to long-term disability, impacting the healthcare system.[5] The effects of TBI can persist long after the initial injury, causing motor and cognitive deficits due to neuroinflammation and other pathological processes.[6]

Post-traumatic epilepsy (PTE) is a significant concern following traumatic brain injury (TBI), with various studies highlighting the association between brain injury and the development of epilepsy [7]. Acquired epilepsy can result from different brain insults such as TBI, stroke, or central nervous system infections, leading to recurrent seizures [8]. The occurrence of seizures after head injury is a recognized complication of TBI and has been demonstrated to worsen functional outcome significantly[9]. The risk of epilepsy following TBI varies depending on the severity of the injury, with a higher relative risk observed in severe cases.[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.[10]

2. Classification of Post-traumatic epilepsy

Post-traumatic epilepsy (PTE) have been classified based on the time of onset after injury. The ones occurring within 24 hours are called "immediate." Early seizures" appear between 24 hours and one week. Those after one week are "late seizures". [11] In some cases, repeated unprovoked seizures one week after trauma traditionally referred to as "PTE" might occur. These are different from acute episodes (< 1 week), which are mostly triggered. The PTE can lead to a detrimental effect on the quality of life.[12]

3. Epidemiology

Traumatic brain injury (TBI) is an important contributor to morbidity and mortality, and results in reduced quality of life and lifespan. [13] An estimated 1.7 million traumatic brain injuries occur annually in the United States; 1.2 million traumatic brain injuries occur annually in the European Union (including Iceland, Norway, and Switzerland). [13] The development of posttraumatic epilepsy can vary, with some cases occurring soon after the injury while others may manifest months to years later.[14] Research suggests that early post-traumatic seizures

within the first week following TBI are associated with a higher likelihood of developing epilepsy later on. [15] Additionally, epileptiform abnormalities in the electroencephalogram (EEG) shortly after TBI can independently predict the onset of PTE within the first year.[16]

The incidence of early seizures (usually within 1 week of injury) ranges from 2.1 to 16.9% and, in general, is correlated with the distribution of head-injury severity within the specific group being studied. Of the patients in one series, 10% were in status epilepticus, a presentation more common in children. [17]

Depending on the series, the incidence of late seizures ranges from 1.9% to >30%. [17] Like the incidence of early PTSs, the variability in this finding is likely due to variability within the patient populations being studied, especially with respect to injury severity. [18] In general, most late PTSs occur during the first year after injury, although they can also occur for many years afterward.[18]

4. Mechanism

The pathogenesis of PTE involves a complex interplay of various mechanisms initiated by the brain insult, leading to an epileptogenic process culminating in unprovoked seizures over time. [19] Animal models have been crucial in studying PTE, highlighting it as a severe complication associated with traumatic brain injury (TBI).[20]

Immediate post-traumatic seizures likely occur because the impact from the injury stimulates brain tissue that has a low threshold for seizures when stimulated. [21] Early post-traumatic seizures can be the result of the secondary effects of the head trauma such as cerebral edema, intracranial hemorrhage, cerebral contusion or laceration, alterations in the blood–brain barrier, changes in extracellular ions, excessive release of excitatory neurotransmitters such as glutamate, damage to tissues caused by free radicals, and changes in the way cells produce energy.[22]

One critical aspect in the development of PTE is the disruption of the blood-brain barrier (BBB), which plays a significant role in the pathogenesis of epilepsy post-TBI. [23] The blood-brain barrier (BBB) guards the neurons against the toxins in the blood and allows very selective molecules to pass through while preventing others. [24] Patients who developed PTE had a greater BBB disruption area than those who recovered without any seizure attacks. [24] Mechanisms underlying PTE include also neuroinflammation-induced processes such as oxidative stress and mitochondrial dysfunction, contributing to the onset and progression of epilepsy post-TBI. [25] Furthermore, the decrease in inhibitory controls, potentially linked to axon collateral rupture, has been proposed as a mechanism in the pathophysiology of PTE.[26]

Late seizures are thought to indicate permanent changes in the brain's structure that are thought to result from neuronal and synaptic loss, aberrant sprouting, and rewiring.[27]

Understanding these multifaceted mechanisms is crucial for developing effective treatments and interventions to manage and prevent PTE in individuals who have experienced traumatic brain injuries.

5. Risk Factors

Risk factors for the development of epilepsy after brain injury have been extensively studied. Several key factors have been identified that increase the likelihood of developing post-traumatic epilepsy (PTE).[28]

These risk factors include the severity of the brain injury, with more severe injuries correlating with a higher risk of developing both early and late post-traumatic seizures. [29] Additionally, specific types of injuries such as penetrating brain injuries and depressed skull

fractures have been associated with an increased risk of epilepsy following trauma. [30] The presence of acute symptomatic seizures shortly after the injury has also been identified as a significant risk factor for the development of epilepsy post-brain injury. [31] Other risk factors include the occurrence of seizures within the first week after the traumatic brain injury, acute intracerebral hematoma (especially subdural hematoma), brain contusion, and increased injury severity. [32] Age is also a factor, with individuals over 65 years old at the time of injury being at a higher risk of developing epilepsy post-trauma.[33] Furthermore, factors such as intracranial hemorrhage, cortical contusion, and the level of post-injury consciousness impairment have been implicated as potential risk factors for PTE. [31] Moreover, encephalomalacia after traumatic brain injury has been identified as a factor that can lead to epilepsy.[34] The presence of retained foreign materials such as bullet fragments in penetrating brain injuries has been associated with a greater risk of inducing post-traumatic epilepsy. [35] Additionally, the emergence of pathologic high-frequency oscillations (pHFO) has been linked to injury severity and the progression to spontaneous seizures, suggesting pHFO as a potential EEG biomarker for epilepsy development after brain injury. [36] As well as the nature of the injury, additional risk factors for the development of PTE have been identified including a prior history of alcohol abuse. [37] The brunt of cerebral trauma is well known to be carried by the frontal and anterior temporal lobes, related to bony structures of the skull but lesion location has been inconsistently associated with seizure risk, with studies pointing to different parts of the brain as carrying the highest risk.[38,39]

6. Diagnosing Post-Traumatic Epilepsy

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), and these may only be elicited with focused questioning [40] . The concept of early and late seizures and PSE is straightforward to apply in clinical practice in most cases. If a patient has a seizure within a week of stroke, it is an early seizure and considered acute symptomatic. [41] Although such a seizure carries a risk of subsequent epilepsy, this risk does not warrant the diagnosis of PSE. In contrast, a seizure occurring more than one week after stroke is considered an unprovoked late seizure. [41] This infers a >60% risk of seizure recurrence and the patient meets the diagnostic criteria for epilepsy.[41] Clinicians may be tempted to assume that seizures occurring following head injury are epileptic. However, TBI is also associated with dissociative seizures (previously called psychogenic non-epileptic seizures).[42]

First of all a neurologic exam may reveal deficits referable to cerebral injury, complementing neuroimaging, and in some cases, obviating the need for it. In an acute setting, the exam should include evaluation for signs of skull fracture, level of consciousness, and focal motor or verbal deficits. [40] After the neurologic examination there has been significant focus on computed tomography, EEG and MRI after TBI to evaluate risk of PTE.

6.1. Computed Tomography

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, which may be devastating without urgent surgical intervention.[43]

6.2. EEG

The EEG findings in TBI are usually nonspecific, and epileptiform activity on EEG does not predict disability outcome or the development of PTE. [44] In individual patients the EEG does not improve the accuracy of the

prediction calculated from clinical data**.** [44] However, 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. [45] Another In electroencephalograms (EEGs) during the acute phase following TBI, as these abnormalities can independently predict the development of PTE within the first year post-injury. In another finding results shows that in electroencephalograms (EEGs) during the acute phase following TBI, as these abnormalities can independently predict the development of PTE within the first year post-injury.[15]

6.3. MRI

Magnetic resonance imaging (MRI) 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, extraaxial blood products, early ischemia, edema, and gliosis. [46] We have now neuroimaging tools that are sufficiently sensitive to discern both more gross indicators of pathology, as well as microstructural changes in white matter, and micro-hemorrhages using newer imaging technologies.[47]

It is recommended to obtain neuroimaging and an EEG after PTS.[48] In some studies, the presence of interictal abnormalities or hematomas increase the likelihood of PTE; however, no definite predictors have been clearly identified.[2]

7. Traumatic brain injury and psychogenic nonepileptic seizures

Psychogenic nonepileptic seizures (PNESs), also known as pseudoseizures, are diagnosed when disruptive changes in behaviour, thinking, or emotion resemble epileptic seizures (ES), but no paroxysmal discharges are seen on electroencephalogram (EEG) and do not originate from another medical illness**.** [49] These seizures are psychological in origin and are not associated with neurobiological factors typical of epileptic seizures. [50] PNES superficially resemble epileptic seizures, and 1 in 5 patients referred to epilepsy clinics with a prior diagnosis of refractory PTE actually have psychogenic nonepileptic seizures.[51] Most reports point to onset of nearly all dissociative seizures (81–89%) within a year of TBI, whereas epilepsy risk declines more gradually in the years following trauma.[52]

What is interesting, significantly more women than men (3:1) are affected by psychogenic nonepileptic seizures, compared to a male preponderance for epileptic seizures. This may be due to greater female vulnerability to any number of predisposing factors.[53]

Diagnosing PNES can be challenging, as they can mimic epileptic seizures, leading to the need for a staged approach and specific criteria for diagnosis. [54] Clinical manifestations of PNES can include a range of motor, sensory, and mental symptoms, representing an involuntary response to psychological triggers. [55] Diagnosis of PNES is suspected by anamnesis, physical examination, ictal semiology, and personal and psychiatric history, but the gold standard for diagnosis is video electroencephalogram (Video-EEG). This technique results in a definitive diagnosis in almost 90% of patients.[56] To meet criteria for *documented PNES*, the clinical history should favor PNES and habitual events must be recorded on vEEG demonstrating the absence of epileptiform activity.[57]

Given their psychological basis, the treatment approach for PNES involves psychological interventions aimed at addressing the underlying psychological factors triggering the seizures. [58] Psychological treatments such as psychotherapy, cognitive-behavioral therapy

(CBT), and stress management techniques have shown promise in managing PNES.[59] These therapies focus on identifying and addressing the psychological stressors or traumas that may be contributing to the onset of PNES episodes.[60] Collaborative care involving a multidisciplinary team comprising neurologists, psychiatrists, psychologists, and social workers is often recommended for the comprehensive management of PNES.[61] This team-based approach ensures that patients receive holistic care addressing both the psychological and physical aspects of their condition.[62]

Increased awareness of the distinguishing features of post-traumatic dissociative seizures may help to tease these cases apart from their epileptic counterparts enabling appropriate management for the best chance of seizure reduction and improved quality of life.[42]

8. Prophylatic treatment

The current management of PTE typically involves the prophylactic administration of antiepileptic drugs such as phenytoin or levetiracetam within the first seven days following the initial injury.[2] However, studies have shown limited evidence for the effectiveness of pharmacological therapies in preventing or treating symptomatic seizures in PTE.[2] There is one randomised trial of phenytoin v placebo in the treatment of early seizures in association with TBI.[63] This demonstrated a reduction in early seizures but in the continuation phase, no reduction in the later development of epilepsy. Levetiracetam has no benefit compared to phenytoin.[63] Prophylactic treatment with antiepileptic drugs (AEDs) also does not improve functional outcome from TBI.[64] There is also the suspicion that prophylactic use of AEDs over a long period is associated with an increased risk for seizures.[64] For these reasons, AEDs are commonly used for a short time after head trauma to prevent immediate and early, but not late, seizures.[64]

9. Treatment of symptomatic seizures

No randomized controlled studies of AEDs have compared the different AEDs for the symptomatic treatment of seizures in PTE.[65] 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.[66] Recent research has explored alternative treatments for PTE, such as the neuroprotective effects of naltrexone in preventing TBI-associated neuroinflammation and epileptogenesis.[67] During the test in a mouse model naltrexone ameliorated neuroinflammation and neurodegeneration, reduced interictal events and prevented epilepsy, illustrating that naltrexone is a promising drug to prevent TBI-associated neuroinflammation and epileptogenesis in post-traumatic epilepsy.[67]

Approximately one-third of epilepsy will prove refractory to medication and it is not clear if there is any systematic difference in post-traumatic cases compared to other causes. In this group epilepsy surgery may be considered.[42] Modern studies confirm that it may be successful in those appropriately selected, where the injury is either unifocal, or if multifocal, that investigation confirms that only one region is epileptogenic and where the patient is able to cope with the neuropsychological consequences of resection.[68] For patients with certain types of epilepsy, resective epilepsy surgery may result in seizure freedom.[69]

However enthusiasm for surgical resection in patients with medically refractory PTE should be tempered by several considerations:

- As a group, patients with PTE have seizure foci that are difficult to localize accurately, partly due to technical issues related to prior craniotomies and breach rhythms and because of frequent involvement of the frontal lobes[70]

- TBI frequently produces dffuse cerebral injury, which can result in multifocal epilepsy and/or seizure-onset zones that overlap with eloquent brain regions; and
- scar tissue and adhesions related to the inciting trauma can increase the risk for surgical complications [71]

For patients with medically refractory PTE who are poor candidates for definitive resection, vagus nerve stimulation (VNS) should be considered for adjunctive treatment. [72] With two to four years of VNS therapy, about 8% of patients will reach seizure freedom, and about 50 – 60% will have at least 50% reduction in seizure frequency.[73] VNS has been used for more than twenty years in clinical practice and serves a vital role for patients with epilepsy who are poor surgical candidates, such as those with generalized or nonlocalizable epilepsy, and individuals who have failed resection.[73]

More recently, a direct form of neuromodulation, called responsive neurostimulation (RNS), has emerged as a promising therapy for patients with medically refractory epilepsy. [74] The RNS System continuously monitors neural electroencephalography (EEG) activity at the possible seizure onset zone, where electrodes are placed and responds with electrical stimulation when a predefined epileptic activity is detected. [75] The controlled clinical trials in the United States have demonstrated longterm utility and safety of the RNS System. Seizure reduction rates have continued to improve over time, reaching 75% over 9 years of treatment.[75]

Conclusion

In conclusion, post-traumatic epilepsy remains a significant and challenging consequence of traumatic brain injury, underscoring the need for early and accurate diagnosis to optimize patient outcomes. Advances in neuroimaging and biomarker research are improving our ability to predict and manage PTE, but gaps in our understanding of its pathophysiology persist. Enhanced awareness among healthcare providers and early intervention strategies are crucial in mitigating the long-term impact of PTE on patients' quality of life. Future research should focus on refining diagnostic criteria and exploring novel therapeutic approaches to prevent and treat post-traumatic epilepsy effectively.

Author's contribution

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