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Review

Post-traumatic epilepsy: An overview

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Abstract

Post-traumatic epilepsy (PTE) is a recurrent seizure disorder secondary to brain injury following head trauma. PTE is not a homogeneous condition and can appear several years after the head injury. The mechanism by which trauma to the brain tissue leads to recurrent seizures is unknown. Cortical lesions seem important in the genesis of the epileptic activity, and early seizures are likely to have a different pathogenesis than late seizures. Anti-epileptic drugs available for treatment are phenytoin, sodium valproate, and carbamazepine. Newer anti-epileptics are helpful, particularly in patients with associated post-traumatic stress disorders; however, no randomized controlled studies are available to prove that one of these drugs is better than the other. Current evidence is that the treatment of early post-traumatic seizures does not influence the incidence of post-traumatic epilepsy. Routine preventive anticonvulsants are not indicated for patients with head injuries, and treatment in the acute phase does not reduce death or disability rates.

Keywords: Head injury; Trauma; Seizures; Post-traumatic seizures; Post-traumatic epilepsy

Contents

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1. Introduction

Post-traumatic epilepsy (PTE) is defined as a recurrent seizure disorder due to injury to the brain following trauma [1]. The disorder is classified as immediate seizures (<24 h after injury), early seizures (<1 week after injury) and late seizures (>8 days after injury) [2]. In this article, we review the salient features of post-traumatic epilepsy, its pathophysiology, and its management.

1.1. Epidemiology

Post-traumatic epilepsy is an established consequence of head injury, and the incidence of PTE is highest among young adults as they are more prone to head injury [3,4]. PTE accounts for 20% of symptomatic epilepsy in the general population and 5% of all epilepsy patients referred to specialized epilepsy centers [4–6]. In military series, the incidence of PTE is much higher (up to 50%), as these studies also include many patients with penetrating head injuries [7]. The incidence of immediate seizures is 1–4%, early seizures 4–25%, and late post-traumatic seizures 9–42% in civilian head injuries [3,7–9]. Approximately, 80% of individuals with PTE experience their first seizure within the first 12 months post-injury and more than 90% by the end of the second year [10]. In penetrating brain injuries, the risk of PTE is approximately 50% (patients followed up for 15 years) [3]. The incidence of subclinical seizure activity is much higher than that of overt seizures and is even higher in penetrating injuries than in non-penetrating injuries [11]. In one series, the reported incidence of combined non-convulsive seizures and overt seizures was 22%; of these, the incidence of non-convulsive seizures was as high as 52% [12].

1.2. Clinical types

In up to two-thirds of patients, late post-traumatic seizures are generalized or focal, with secondary generalization, and often both seizure types may coexist [13,14]. Although uncommon, mesial temporal lobe epilepsy may result from traumatic brain injury and occurs mainly in young children (age < 5 years), while neocortical epilepsy occurs later in life [15]. This may be because of the vulnerability of the developing brain to trauma, resulting in hippocampal sclerosis [16].

1.3. Risk factors

Much less is known about the characteristics of traumatic brain injury (TBI), which is associated with an increased risk of seizures; the magnitude and duration of the increase is also unclear [3,4]. However, certain risk factors have been consistently identified, placing TBI patients at significant risk of developing post-traumatic epilepsy. These risk factors include duration of loss of consciousness, missile injuries, intracerebral hemorrhage, diffuse cerebral contusions, prolonged (3 days) post-traumatic amnesia, acute subdural hematoma (SDH) with surgical evacuation, early post-traumatic seizure, and depressed skull fracture [2,8,14,17,18]. Brain contusions and subdural hematomas are the strongest risk factors for late seizures, and this increased risk persists for up to 20 years [3].

1.4. Contusions

The amount of focal tissue destruction is the most important factor in predicting the development of early and late post-traumatic seizure [14,19]. Injured neurons in the cerebral cortex are believed to be the origin of seizure activity. This can be explained by the fact that individuals with multiple or bilateral contusions have more injured cortical neurons, increasing the number of potential foci of seizure activity. Also, the presence of multiple contusions or a large midline shift indicates that neurons between the grossly contused areas are injured, and thus, more likely to originate or propagate a seizure. Although TBI has a predilection for the frontal and temporal lobes, parietal lobe involvement, detected by CT scan, may be another indicator of additional pathology that lowers the overall seizure threshold [14].

1.5. Non-contusional hematomas

While there is an association of peritraumatic hemorrhage (i.e., contusion, acute SDH) with delayed PTE, many lesions, such as subarachnoid or intraventricular hemorrhages, extradural hematomas (EDHs) not requiring evacuation and punctate hemorrhages do not seem to put individuals at much greater risk for late PTE than individuals without these lesions. This provides some assurance that the risk with these injuries is relatively low, even if greater than in the general population without TBI [14,20].

1.6. Time to development of late post-traumatic seizure

A high proportion of seizures occurring during the first month after TBI are due to acute brain swelling, perioperative events both from cerebral manipulation or stress from general anesthesia, and metabolic factors [14]. The occurrence of the vast majority (80%) of cases of late PTE is

in the first year post-injury and over 90% by 18 months post-injury, provides evidence that this is the period of highest risk. Up to 15–20% of patients may have their first seizure after 2 years post-injury [7,10,14,21]. Although a seizure during the first week after injury (early post-traumatic epilepsy) is associated with a higher incidence of late PTE (after the first week post-injury), a late post-traumatic seizure is correlated with an even higher rate of recurrence [3,13,21].

1.7. Severity of injury

Although early seizures and possibly a low Glasgow Coma Scale (GCS) score on admission (<8) may be associated with an increased risk of developing late epilepsy, injury severity, as measured by initial GCS score alone, is not sufficient to predict late post-traumatic seizure risk, i.e., those individuals with the most severe injuries, as evaluated by GCS scores, may not survive, and those with GCS scores of 3–8 who do survive have no more cortical injury leading to seizure activity than individuals with GCS scores of 9–12 [14,21]. The relative risk of seizures is 1.5 after mild injuries (loss of consciousness or amnesia less than 30 min), but with no increase after 5 years; 2.9 after moderate injuries (loss of consciousness from 30 min to 1 day or a skull fracture); 17.2 after severe injuries (loss of consciousness of more than 1 day, SDH, or brain contusion) [3,4].

1.8. Civilian injuries versus war injuries

The estimated relative risk of seizures after penetrating war injuries is very high (up to 53%), and 27% of patients may have persistent epilepsy up to 15 years post-injury as compared with the risk in the general population [3,7]. The lower rates of PTE in civilians who suffered missile wounds may relate to differences in fragment caliber and velocity and to the shorter evacuation time to neurosurgical centers [7,22]. Wounds of survivors of war injuries may contain bone and iron-containing metal fragments, thought to be more epileptogenic than lead fragments from bullets. Civilian injuries with bone fragments alone do not greatly increase the risk for late post-traumatic seizure [7,14,22].

1.9. Neurosurgical intervention

Although individuals with SDHs alone do not have higher seizure risk, those undergoing surgery for such have very high rates of late post-traumatic seizure. Patients with multiple intracranial surgeries also have very high rates of late PTE. This can be explained by the fact that, although clinical deterioration is always the most pressing indication for surgical intervention, the strongest radiographic indication is a significant intracranial shift. A high degree of shift may be caused by a very large hematoma or additional cortical and subcortical tissue swelling from sudden deceleration forces. This sudden negative pressure caused by rapid deceleration results in both tearing of cortical bridging veins and parenchymal injury, adding to the degree of shift. Surgical treatment in these patients often involves a large craniectomy and enlargement of the size of the intradural compartment with a patch graft, both of which allow the brain to swell outside of the cranium. The obvious conclusion is that these individuals have quantitatively more brain injury, either multifocal or larger individual foci, which may become epileptogenic over time. The tissue damage seen in individuals surviving EDH is routinely less than in acute SDH, potentially explaining the relatively lower risk for late PTE with extradural hematoma [14].

1.10. Pathophysiology

Traumatic brain injury results in potentially epileptogenic brain damage through several mechanisms, which often coexist within a single patient [19]. Immediate and early seizures are likely to have a different pathogenesis than late seizures, and are considered to be direct reactions to brain damage [6,23]. Late seizures are thought to be due to damage to the cortex by free radicals, generated following iron deposition from extravasated blood, and increased excitotoxicity due to accumulation of glutamate [24].

Pathophysiology also varies according to the type of injury, as closed head injuries produce diffuse axonal injury with shearing of axons, diffuse edema, and ischemia leading to the release of excitatory amino acids, cytokines, bioactive lipids, and other toxic mediators causing secondary cellular damage [25]. Penetrating brain injury produces a cicatrix in the cortex and is associated with an increased risk of PTE of approximately 50% [7]. Non-penetrating head injuries, including focal contusions and intracranial hemorrhages, are associated with a risk of PTE of up to 30%. In this setting, the mechanism of epileptogenesis may be partly related to the toxic effects of hemoglobin breakdown products on neuronal function [26].

Following head injury or hemorrhagic cortical infarction, there is deposition of ferrous compounds into neural tissue. This is followed by a Haber–Weiss iron-catalyzed reaction that results in the hyperproduction of hydroxyl radicals, triggering subsequent formation of peroxidative agents, peroxidation of phospholipid membranes, and disruption of the cell wall leading to cell death [27]. The induction of an epileptic focus by iron deposition is also related to decreased nitric oxide synthase activity [28]. These possible pathophysiological mechanisms of PTE have been studied using an animal model of PTE, originally developed by Willmore et al. in which epileptic seizures in the rat brain were induced by iron injection [20,29]. Iron liberated from hemoglobin, and hemoglobin itself, are associated with the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), both of which have been demonstrated to be involved in the mechanism of seizures induced by iron ions in the rat brain [20,29]. Excessive activation of excitatory amino acid neurotransmitter receptors during seizures is known to generate NO and ROS, including $O_2^{\bullet -}$, H_2O_2, and $^{\bullet}OH$,

followed by accelerated production of neurotoxic guanidino compounds, causing a vicious circle of reactions [30,31]. ROS, especially •OH, are responsible for the induction of peroxidation of unsaturated fatty acids that are components of neuronal membranes. Such reactions may be followed by excitatory and inhibitory neurotransmitter changes, especially the increased release of excitatory amino acids, such as aspartic acid, and the decreased release of inhibitory amino acids, such as γ-aminobutyric acid [32–35]. This accelerated release of excitatory amino acids can trigger excitotoxicity at the NMDA receptors in acute seizures and may be followed by the formation of a chronic epileptogenic focus [32,33].

1.11. Investigations

Investigation of a seizure in a patient after a recent head injury should focus on assessing whether the seizure was caused by a change in a biochemical parameter, such as development of hyponatremia or an intracranial bleed. In a clinically stable patient whose serum electrolytes are within the normal range and whose neurologic examination is the same as before the seizure, further lab studies are not needed. In a patient presenting some time after injury, the usual investigations that are applicable for the first epileptic seizure should be performed. Admission may be needed for status epilepticus or to carry out videotelemetry to assist in the diagnosis. The opinion of a neurologist will be helpful to establish/confirm the diagnosis. Neuropsychological assessment is necessary to document the patient's baseline functioning before starting anti-epileptic medication, and it will be a part of the workup if the patient is considered for surgery.

1.12. Serum prolactin

Frequently increased levels of serum prolactin (SPRL) are observed immediately after generalized and complex partial seizures. Presumably, hormone release is caused by the propagation of epileptic activity, usually from the temporal lobe to the hypothalamic pituitary axis. Numerous reports have demonstrated that measurement of the post-ictal SPRL level can differentiate between pseudoseizures and seizures [36,37]. However, others have reported that estimation of SPRL is not a useful method for the differentiation of psychogenic non-epileptic from true epileptic seizures [38,39]. Nonetheless, this is still more of a subject of research rather than a well-recognized standard test [39,40].

1.13. Electroencephalogram (EEG)

EEG is useful for focus localizations and prognostication of severity, but not for predicting the likelihood of PTE developing in a given patient [41]. An additional complicating factor may be the difficulty in successfully recording and interpreting EEGs in patients who may be agitated and confused following their injury [21]. However, EEG may be helpful in predicting relapse before anticonvulsant medication is withdrawn [42].

1.14. Role of imaging

Magnetic resonance imaging (MRI) of the brain is the study of choice and many clinicians choose to perform it in all patients with PTE. When MRI is not available and also in emergency situations, CT scan of the head will allow visualization of underlying pathology that may need urgent intervention (for example, an intracranial hematoma or depressed fracture). It has been demonstrated that the presence of focal hemorrhagic brain damage on CT scan is one of the most powerful factors predicting early and late epilepsy [19]. MRI is superior to CT scan in patients with late PTE, and the possible epileptogenic role of hemosiderin has been evaluated by brain MRI [43]. Demonstration of hemosiderin deposits on T_2^*-weighted imaging, with formation of the gliotic scar around the hemosiderin, is a significant predictive factor for seizure occurrence [44]. MRI is also more sensitive for the detection of traumatic white-matter abnormalities, including diffuse axonal injury, when compared with CT [45].

1.15. Management

Seizure activity in the early post-traumatic period after head injury may cause secondary brain damage as a result of increased metabolic demands, raised intracranial pressure, and excess neurotransmitter release. It is recommended that early PTE be treated promptly, as seizure activity will further damage the already compromised brain [46]. Although concern about the adverse effects of early seizure activity has been the primary therapeutic rationale for the prophylactic use of anti-epileptic drugs in the management of acute traumatic head injury, recent pathophysiological studies have shown that some anti-epileptic drugs may also have neuroprotective effects. Animal models have indicated that phenytoin reduces neuronal damage in hypoxia, and that carbamazepine and valproate may also have neuroprotective effects [47,48]. The neuroprotective effect of phenytoin may be mediated by a voltage-dependent blockade of sodium channels [49,50]. Anti-epileptic drugs, by contrast, have unusually narrow therapeutic margins and well-documented toxicity, even in neurologically stable patients [49,50].

1.16. Non-prophylactic treatment

Anti-epileptic drugs available for treatment are phenytoin, sodium valproate, carbamazepine, and phenobarbital. In most cases, administering the medication via the intravenous (IV) route is desirable, as the patient is still in the recovery stage from the head injury. Intravenous phenytoin and sodium valproate are drugs of choice and are usually effective in stopping seizures [46,51,52]. However, no randomized controlled studies are available to prove that one

of these drugs is better than the other [46,51,52]. New compounds, such as free radical scavengers and antiperoxidents, show encouraging results, but their use is still experimental and clinical application is limited. Newer anti-epileptics (topiramate, gabapentin, and lamotrigine) have been used successfully, particularly for patients with PTE associated with post-traumatic stress disorders [2,53–55].

1.17. Prophylactic anticonvulsant

In 1973, 60% of clinicians in the USA treated TBI patients prophylactically with anticonvulsants [56]. A recent survey of clinicians in 127 neurosurgical departments showed that 36% do not prophylactically treat head-injured patients, 12% prescribe prophylactic anticonvulsants for all head injury patients, and the remaining 52% decide based on the patient's particular risk factors [2]. Phenytoin and carbamazepine have been effective in preventing early PTE in high-risk patients following head injury; however, prophylactic use of phenytoin, carbamazepine, or phenobarbital is not recommended for preventing late post-traumatic seizures [8,51,52]. Phenytoin has the most evidence to support its use to reduce early post-traumatic seizures, but it should only be used for treating immediate and repeated tonic–clonic seizures occurring within the first 24–48 h. If treatment is given for only 1 week, the risk of acute idiosyncratic reactions will be small [49,50,57,58]. After the first week, routine use of seizure prophylaxis following head injury is not recommended, particularly for those individuals who have isolated lesions and whose cumulative risk is relatively low. However, patients with early PTE, dural-penetrating injuries, multiple contusions, and/or SDH requiring evacuation may need continuation of anticonvulsant medication beyond the first week post-injury [14,46,57,58]. Although anti-epileptics appear to decrease the rate of early seizures, there is no evidence that the prevention of early seizures affects mortality, morbidity, or the development of late PTE [49,50,57,58].

1.18. Side effects

It must be remembered that anti-epileptics are not benign drugs; for example, a high rate of side effects has been demonstrated in patients treated with phenytoin for 1 week post-injury. Potentially fatal reactions to this drug include intravenous site reactions [59], exfoliative dermatitis, [60] granulocytopenia, [61] transient hemiparesis, [12,62] permanent B-cell immunodeficiency [63], and fatal phenytoin hypersensitivity syndrome [49]. There have also been some Class II data to suggest that both phenytoin and carbamazepine have negative effects on cognition, particularly involving tasks with significant motor and speed components [64]. There is experimental evidence from animal research to suggest that patients treated with diazepam do not recover somatosensory evoked potentials [12].

1.19. Surgical considerations

Most of the time, TBI results in bilateral and multifocal injury leading to poorly localized, multifocal, and nonlesional extratemporal epilepsy that is less likely to benefit from surgery [15,65]. However, surgery is a very effective treatment for intractable frontal-lobe epilepsy secondary to encephalomalacias [66]. Patients are more likely to become seizure-free if they have a focal ictal beta discharge on their scalp EEG. Complete resection of the encephalomalacia and adjacent electrophysiologically abnormal tissues should be attempted for favorable outcome [66]. Compared to neocortical epilepsy, the surgical results are much better in post-traumatic mesial temporal sclerosis with focal lesion on extensive scalp and intracranial ictal EEG recordings, neuroimaging, and neuropsychologic evaluations [15,66]. Incomplete identification of the gliotic region is responsible for the more frequent failure of surgery in neocortical PTE than in temporal lobe epilepsy [65].

1.20. Neuropsychological consequences

In a prospective study of 210 patients, no significant difference in neuropsychological outcomes at 1 year was found between those head-injured patients who had PTE and those who did not [67]. However, at 5 years post-injury, recurrent seizures play a large role in the causes for readmission, along with psychiatric difficulties and general health maintenance [9]. In a prospective study of 490 patients having seizures, established epilepsy appeared to reduce functional and social outcome but had no effect on rehabilitation goals and reemployment [68]. Apart from the head injury, anti-epileptics may also impair performance on neuropsychological tests. The adverse effects of anti-epileptics include neurobehavioral effects and cognitive impairments. There is also some preliminary evidence to suggest that anticonvulsants may inhibit learning and brain plasticity, particularly in children, which may or may not be reversible [68–70]. These side effects become more prominent if treatment with anticonvulsants is extended beyond 1 week. However, there is little evidence available on pediatric head injuries and anticonvulsant management, as the available data suggest that their seizure profile and response to anticonvulsants is different than in adults [11].

2. Conclusion

A large percentage of PTE is preventable in the sense that the causative injuries are themselves preventable. Preventive strategies, such as the use of child seats and helmets when cycling are mandatory in developed countries, whereas in developing countries further awareness and education are needed. Patients with PTE need regular follow-up for review of medications, monitoring of drug side effects, examination of neurological status, and neuropsychological assessment

for any cognitive dysfunction. Early PTE should be treated promptly. After the first week, routine use of seizure prophylaxis following head injury is not recommended, particularly in patients with isolated lesions and in whom cumulative risk is relatively low. Patients with occurrence of early post-traumatic seizure, dural-penetrating injuries, multiple contusions, and/or SDH requiring evacuation may need continuation of anticonvulsant medication beyond the first week post-injury.

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