

Post-Traumatic Epilepsy: Review

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Abstract

Post traumatic epilepsy is defined by recurrent seizures secondary to brain injury following head trauma and represent the most frequent cause of epilepsy in young adults. Most post traumatic epilepsies start within two years from trauma, but in some cases may present several years after the brain injury. Severe traumatic brain injuries tend to correlate with an increased risk of developing early and late post-traumatic seizures. A cranial trauma creates a potentially epileptogenic brain damage through a number of different mechanisms. Several structural, physiological and biochemical modifications occur in a brain after a head injury that promote oxidative stress mechanisms and excitotoxic mechanisms. Current evidence shows that prophylactic use of antiepileptic drugs prevent the occurrence of early post-traumatic seizure but does not influence the incidence of post-traumatic epilepsy. Some authors propose treatment with antioxidant drugs in acute phase of severe traumatic brain injuries in order to prevent early tissue changes established in the traumatized tissue.

Keywords: Post-traumatic epilepsy; Post-traumatic seizures; Traumatic brain injuries; Head trauma

Introduction

Post-traumatic epilepsy (PTE) is a form of symptomatic epilepsy defined by the presence of recurrent seizures secondary to traumatic brain injury [1]. It is presumed that there is a mechanism induced by a head trauma that leads the brain tissue to develop a chronic predisposition to the development of seizures. We distinguish from immediate post-traumatic seizures (PTSs) which occur within 24 hours after injury, early seizures which occur within a week after injury and finally late seizures which occur after one week after injury. Immediate and early seizures belong to the group of provoked seizures and they do not define epilepsy since they are not underlying a pathogenic mechanism that chronically predisposes the patient to manifest epileptic seizures [2]. Post-traumatic epilepsy is determined by the presence of late seizures and therefore unprovoked.

Epidemiology

Post-traumatic epilepsy (PTE) is the most frequent cause of epilepsy in young adults as they are more at risk of the exposure to head injury [3,4]. Traumatic head injury (TBI) represent one of the most important epilepsy risk factors in children, with increased epilepsy risk 7.02-fold (for severe TBI) in univariate analysis [5]. Estimated proportion of presumed causes of incident epilepsy related to TBI range between 2% and 16% in European Countries [6]. The study of PTE epidemiology stems from the analysis of military records at the beginning of the twentieth century, with reference to the American Civil War, to the First World War, to the Second World War and other more recent studies have been carried out on traumatized soldiers from the Korean War and the War in Vietnam [7-11]. PTE epidemiology mainly uses frequency rates of epilepsy in traumatized patients and rates of "incidence ratio" between population with head injury and general population. Severe traumatic brain injuries tend to correlate with an increased risk of developing early and late post-traumatic seizures compared to mild and moderate TBIs [12]. Obtaining reliable epidemiological data on the frequency of epilepsy in patients with TBI requires prospective studies with long periods of follow-up (at least 10 years). Although, at a distance of 10-15 years, it is difficult to establish, with certainty, a direct cause-effect correlation between head trauma and incident epilepsy. In industrialized countries the proportion of epilepsy attributed to brain injuries is higher in past studies than in

recent ones [4,13]. TBIs and other risk factors have actually modified their frequency over time; the reasons are attributable to modification in socio-economic status and amelioration in emergency health care. However, improved survivorship of severe traumatized patients could increase proportion of PTE in future epidemiological investigations.

Early and immediate PTSs

Early PTSs occur in various series of cases with a variable frequency comprised between 2.6% and 16.9%, depending on the severity of TBI [14,15]. In the infant population early epileptic seizures are much more frequent compared to late seizures and they very often tend to occur as immediate seizures (within 24h) [16]. In general, severe TBIs are associated with a high frequency of early crises, with rates that in adults are 20-30 times higher in comparison with mild and moderate TBIs [17].

Late PTSs

Frequency rates of late PTSs are variable in different studies with values comprised between 1.9% and 30%; such differences are correlated to the different entity of TBIs in the various series of cases. Annegers et al. have published a prospective study with a follow-up of over 10 years, reporting an average PTE frequency of 2.1% in TBI patients; the percentage was significantly higher (12%) if considering only subjects with severe TBI [14]. PTE frequency and incidence studies in military populations inevitably show higher rates compared to studies carried out in the general population, with regard to a higher risk of severe TBIs. In fact, military series of cases show frequency rates varying from 34% [10] to 53% [11]. Most patients with PTE tend to have the first unprovoked seizures (PTSs) within the first year from trauma (approximately 80%) and in almost all of them they occur within the

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second year. Annegers calculated that a patient with TBI has a risk of unprovoked seizures during the first year ("incidence ratio") eleven times higher than the general population, 3.5 times in the following 4 years, 2.39 times after 5 years and 1.56 times 10 years after injury. A patient with mild TBI shows a normalization of the risk (incidence ratio 1.1) after the first 5 years, while a patient with severe TBI shows high values even after 10 years (incidence ratio 4.0) [14].

Risk Factors

Epidemiological studies have generally revealed a higher risk of early and late seizures in relation to the severity of the head injury [18]. The characteristics of the trauma and the presence of any associated lesions represent risk factors for a successive development of early and immediate PTs or late PTs. A recent study [19] that retrospectively compared a population of subjects without head injury (non TBI group) and subjects with moderate and severe TBI with skull fracture revealed, on behalf of the latter, a relative risk of 10.6 % (HRs) to develop epilepsy. In the past, Jennet [20] showed that the presence of compound depressed skull fractures was associated to a higher general risk of early and late PTs. The studies found the following risk factors for early epileptic seizures: acute subdural hemorrhage, acute intraparenchymal hemorrhage, need of surgery, infant age and amnesia lasting more than 30 minutes, history of chronic alcoholism. Risk factors for late PTs are acute subdural hematomas, acute subdural hemorrhage, multiple brain contusions, age over 35, transient amnesia which lasts more than 24 hours and male gender [19]. Some studies have considered the presence of early PTs as a risk factor for late PTs in adults [20,21], but this is certainly not true for the infant population [20] and according to Annegers [14], it is not even a risk factor for the adult population. Acute subdural hematoma is the intracranial lesion which has highest risks of developing both early and late PTs. The role of genetic susceptibility that regulate response to cerebral injury is not clear; most of epidemiological studies did not find that family history of epilepsy could represent a significant risk factor for early and late PTs [22].

Clinical Presentation

Patients with PTE in most cases have focal epilepsy or focal epilepsy with a secondary generalization. The clinical characteristics of the seizures depend on the location of the lesion and the precocity of the secondary generalization. In patients with a history of trauma in childhood (less than five years) can manifest mesial temporal lobe epilepsies, as a trauma in the temporal region at an early age can induce the appearance of mesial temporal sclerosis [23,24]. Status epilepticus (SE) at onset is not uncommon; Jennett calculated a frequency of 10% in patients with PTs [20]. The infant population undoubtedly has a higher probability of SE compared to the adult one.

Course (Natural History)

Most PTEs start within two years from trauma (about 90%) [25], the first 18 months after injury is the period at a higher risk to develop late PTs. Once PTE is diagnosed, the remission rates of seizures vary between 25-40%. Patients with high frequencies of PTs during the first year after injury have a low probability of remission.

Pathogenesis

There are several structural, physiological and biochemical modifications occurring in a brain after a head injury. A cranial trauma creates a potentially epileptogenic brain damage through a number of different mechanisms, which are not yet fully elucidated. In fact,

different pathogeneses recognize early seizures and late seizures. The studies in this regard made use of animal and in vitro models with PTE. In 1978, Willmore [26] used an animal model where iron (ferric chloride) was injected into the cortex of rats, with an evidence of epileptiform anomalies in EcoG recordings after convulsive epileptic seizures. Direct inoculations of hemoglobin into brain cortex were used in other animal models [27] recently; some authors studied a PTE model induced by lateral fluid percussion of the rat cortex, with the detection of an increased susceptibility to seizures at a distance of 30 days [28]. In vitro models, thin layers of hippocampus are used in order to evaluate the response of the micro cortexes correlated to mechanic injuries or any changes in the concentrations of neurotransmitters. Immediate and early seizures are considered direct reactions of a brain damage and they are correlated to an altered vessel regulation of the local cerebral blood flow, to an alteration of the hematic-encephalic barrier and to an increase of the intracranial pressure with focal or diffused presence of ischemic, hemorrhagic, inflammatory or necrotic damage [29]. The results of studies conducted on animal models of chronic epilepsy have suggested that late seizures are caused by two main pathogenic pathways: oxidative stress mechanisms, excitotoxic mechanisms - neuronal hyper excitability. The mechanism of oxidative stress implies a trauma accompanied by a leakage of red blood cells, with a consequent formation of free radicals mediated by the iron contained in hemoglobin; these free radicals react with the methylene groups in the double lipid layer of neuronal membranes with subsequent lipid peroxidation of the neuronal membranes and mitochondria and the alteration of the function of the sodium/ potassium pump ATPase activity. The result of this sequence of events is a reduction of the chronic convulsive threshold of a group of neuronal cells. The excitotoxic mechanism is explained by the extra cellular increase of excitatory amino acids immediately after injury, with increased levels of glutamate and aspartic acid [30]. These traumatized cells tend to assume excitatory aminoacids more readily than controls and present increased expression of the sodium-coupled neutral amino acid transporters subtypes 1 (SNAT1) and subtypes 2 (SNAT 2) [31]. Traumatized in vitro cells tend to form axonal sprouting with a higher immunoreactivity to GAP 43 (Grown Associated Protein); these cells show an altered excitability, evidenced by the presence of synaptic potentials with prolonged post-synaptic components [32]. According to some authors [33], the impaired neuronal plasticity in injured brain areas can promote the appearance of focal dysplasia if TBI occurs soon after birth when the process of neuronal migration is not yet fully completed.

Diagnosis

In patients with seizures at a short distance from cranial trauma it is necessary to exclude other potential causes of provoked seizures. A trauma patient often presents conditions of metabolic and circulatory instability, with high probability of alteration in the biochemical parameters, such as hyponatremia, which may lower the epileptogenic threshold.

Electroencephalogram (EEG)

EEG in a patient with TBI is useful for the localization of the lesion focus and for the measurements of the extent of damage, but it is not able to define the probability to develop epilepsy; more than 20% of patients with PTE have a negative EEG during the first three months after injury [34]. Anomalies may be present, ranging from a simple slowdown in the base activity of slow lesional waves in a localized focus. In patients with immediate seizures, sequences of spikes inscribed on

slow focal activity can be noted, prevalently in the temporal regions (most exposed to contusive lesions). In later stages EEGs can be useful in predicting a possible recurrence of seizures before the prophylactic therapy is suspended [35].

Neuroimaging

In emergency “settings”, the frontline examination is a CT scan of the head, a quick investigation and possible in any condition of the patient. The CT immediately shows the presence or absence of intra- or extra-parenchyma hemorrhagic foci, which can lead to a possible choice of neurosurgical treatment. Brain MRI represents the study of choice in patients with late seizures since it is an investigation that allows a better anatomy definition of the brain and gives the exact outcome of any post-traumatic lesion. T2-weighted images and gradient echo sequences may well highlight the presence of hemosiderin deposits that have a potential epileptogenic role. Messori et al. [36], through the analysis of T2 images from more than 130 patients, showed how a precocious formation of a gliotic scar around a hemosiderin deposit reduces the risk of PTE.

Prophylaxis

The use of anticonvulsants in acute phase of injury is quite common in clinical practice. The manifestation of immediate or early seizures can affect the patient’s prognosis since it may increase the cerebral perfusion pressure and the intracranial pressure. The prophylactic therapy of PTE is mainly intended to block or delay epileptogenic mechanisms established after TBI. In the studies of epilepsy, “kindled” animal models are used in the testing of antiepileptic drugs; the choice of animal and “in vitro” models specific for PTE allows the study of, not only anticonvulsive properties of drugs, but also potential antiperoxidant effects which contrast the pathogenic mechanism underlying PTE. Some authors proposed to apply the experience derived from new approaches to the treatment of acute stroke, where the concept “time is brain” is the most important thing; the possibility of preventing early tissue changes established in the traumatized tissue may be the basis for the actual prophylactic treatment of PTE.

Antiepileptic drugs

The use of antiepileptic drugs (AEDs) at an early stage in order to prevent PTE is rather controversial. Several AEDs have been tested in observation studies and randomized clinical trials (RCTs) as a prophylactic therapy for PTE. The results of RCTs seem to show a moderate effect only on early PTEs, not on the late ones. Phenytoin (PHT) has been the most studied drug in patients with TBE since 1940 [37]. Temkin demonstrated that an early administration of PHT prevented early PTSs in an excellent way, while it did not prevent the complete onset of late PTSs both during the first year of therapy and in the following years without therapy [38]. A meta-analysis of all the trials conducted on PHT showed similar results [39]. The administration of PHT with Phenobarbital (PB) had been studied in several series of studies, starting from 1979, without providing any univocal and significant data of effectiveness. There is not much literature about Carbamazepine (CBZ); only one true randomized clinical trial is reported [40] and this showed a good efficacy in the prevention of early PTSs, but not in the late ones. Similar results have been reported for VPA [41], however with less capacity to prevent early PTSs compared with PHT. As for more recent drugs, data are still poor, since it is necessary to perform long term prospective studies. Among these, a particular attention has been paid to Levetiracetam (LEV), a drug that, unlike other AEDs, shows an efficacy both in

kindling animal models and in PTE animal models. An observational study on severe head injuries revealed a good capacity of LEV to prevent early PTEs, comparable to PHT, but with a greater tendency to persistence of epileptiform EEG abnormalities [42]. At present, a “safety” RCT is going on, which is mainly considering the tolerability of LEV in PTE. Preliminary data show a low rate of adverse events and suspension of the drug, and a good efficacy with a temporary 53% reduction of PTE risk, although the percentage is likely to decrease during the prolongation of the follow-up [43]. Zonisamide is an antiepileptic drug which has showed antioxidant efficacy through the detoxification of NO and OH⁻ ions (by scavenging NO and OH⁻ ions) with a consequent stabilization of the neuronal membrane [44]. In general, the recommendations for drug prophylaxis of early PTSs provide Phenytoin as frontline drug, Levetiracetam and Carbamazepine as second choice drugs; Phenobarbital and Valproate are not considered indicated for PTS prophylaxis. Drug prophylaxis of late PTSs is not recommended because of its absolute lack of evidence in observational clinical trials and RCT.

Natural antioxidants

The study of pathogenic mechanisms of PTE has been focusing on the use of antioxidant drugs in order to prevent the lipid peroxidation of neuronal membranes. In animal models, Tocopherol (vitamin E) has shown a reduction of electrical crises on EEGs, induced by the administration of FeCl₂ (reduced onset of EEG seizures induced by intracerebral FeCl₂) [45]. The combination of vitamin E, ascorbic acid and vitamin C showed to have antiepileptic effects on the same animal models [46].

Miscellaneous agents

Magnesium sulfate was tested in the acute phase of injury for its neuroprotective capacity shown in studies in vitro; some observational studies and a RCT [47] were carried out and they revealed a reduction of early epileptic seizures, while late PTSs were unchanged. The statistical analysis of the trial results showed, however, very large confidence intervals, so large as not to consider the benefit statistically relevant on early PTSs. Adenosine showed anticonvulsant activity in several animal models of epilepsy through its action on A1 receptors [48]. The use of adenosine in animal models of PTE detected a detoxification capacity (scavenging) from free radicals released by the administration of FeCl₂ [49]. Anticonvulsant properties of melatonin have been known for a long time; pinealectomy induces convulsive seizures in experimental animals [50]. Studies in vitro and above all on animal models have shown an ability of inhibition of the lipid peroxidation mechanism [51]. The pathogenic hypothesis of an excitotoxic mechanism in PTE focuses on medicines which can restrict the entry of intracellular calcium and antagonize NMDA receptors [52]. Calcium antagonists as Nimodipine have been used for several years in vasospasm prophylaxis in subarachnoid hemorrhage following a trauma or not, presenting a potential antiepileptogenic mechanism. Glutamate antagonists have been used in patients with ischemic stroke and TBI in several clinical trials, but without any significant results [53].

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