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POSTTRAUMATIC EPILEPSY – RISK FACTORS AND ANTIEPILEPTIC PROPHYLAXIS

Abstract: Post-traumatic epilepsy is defined by the development of chronic seizures following head trauma. It comprises five percent of the total cases of epilepsy. The pathophysiology of emergence of posttraumatic attack discusses the role of deposition of iron from the blood to the brain parenchyma, leading to brain tissue being damaged by free radicals as well as the accumulation of glutamate, increasing excitatory activity. Significant risk factors for the development of seizures in the first week after injury include acute intracerebral hematoma (especially subdural hematoma), younger age, increased injury severity, chronic alcoholism, brain contusion, and age >65 years at the time of injury. Type of attacks and severity of trauma play a role in predicting the risk of developing post-traumatic epilepsy. As the mechanisms behind the development of post-traumatic epilepsy are discovered, therapies may be developed that can prevent epilepsy after head trauma has occurred.

INTRODUCTION

Post-traumatic epilepsy (PTE) implies recurrent seizures that occur as a result of brain injury. Brain injury is the most common cause of acquired epilepsy. The risk of developing PTE relates directly to TBI severity, but the latency to first seizure can be decades after the inciting trauma (1). Head trauma accounts for 5% of all epilepsy cases and 20% of cases of symptomatic epilepsy (2). Some studies concluded that the clinically relevant time window for drug delivery is probably extended to 60–120 min after trauma, and that concentrated VPA in a therapeutic range could prevent epileptogenesis (3).

The aim of this review is to actualize the problem of post-traumatic epilepsy, especially in the light of the preventive administration of antiepileptic drugs, and to identify possible risk factors for the development of the PTE.

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DEFINITIONS AND CLASSIFICATIONS

Post-traumatic epilepsy (PTE) is the clinical syndrome of recurrent unprovoked epileptic seizures that occur as a result of stable (non-progressive) lesions of the CNS caused by trauma. Perucca and D'Ambrosio have defined PTE as one or more unprovoked attacks that occur late (> 7 days) after craniocerebral trauma (trauma, which requires some degree of medical care), (4). PTE must be distinguished from post-traumatic attacks (also known as immediate attacks), which are the result of direct injury to the brain, occurring within 24 hours after the injury, while attacks within 7 days called early post-traumatic seizures. If, however, the attack occurs after 7 days, it is classified as late post-traumatic seizure. Approximately 20% of patients with a head injury experience a late post-traumatic attack that does not reoccur later, and should not be classified as the PTE. Moreover, delayed single attack does not require antiepileptic (AE) medication. Late seizures occur after the patient has recovered from the effects of the injury and can occur weeks, months, or even years after the original injury (2).

PATHOPHYSIOLOGY

The mechanism by which brain tissue trauma leads to frequent occurrence of epileptic seizures is unknown. Cortical lesions are apparently important in the development of epileptic activity. Early attacks are probably of various pathogenesis. Post-traumatic attacks are nonspecific response to physical agents. Early attacks can be caused by brain edema, intracranial hemorrhage, as well as brain contusion and laceration.

When tending to patients hospitalized after a head injury, the physician should pay attention to whether there is intracranial bleeding or changes in clinical conditions such as hyponatremia, which can cause seizures in those patients. The pathophysiology of emergence of posttraumatic attack discusses the role of deposition of iron from the blood to the brain parenchyma, leading to brain tissue being damaged by free radicals as well as the accumulation of glutamate, increasing excitatory activity. Animal studies have shown that damage of the blood-brain barrier contributes to the generation of epileptic seizures at PTE (5).

DEFINITION AND CLASSIFICATION OF HEAD INJURIES

In order to understand post-traumatic epilepsy, various forms of head injuries have to be defined. Closed head injuries are injuries that do not penetrate the skull. Such injuries are often manifested in loss of consciousness, even if transient, and may be associated with a large brain damage, depending on the severity of the injury (6).

Open injuries are injuries whith skull penetration present, and patient may not lose consciousness, although brain injury may be serious, or even fatal. Shootings or shrapnel can often inflict such injuries. A concussion is defined as an injury caused

by violent and impact or impulsive forces, and is associated with a transient functional impairments (loss of consciousness, epileptic seizures, amnesia, loss of memory). Contusion represents brain damage that leaves the architecture of the brain intact. There are two sub-types of contusion: cup and contra-cup. Cup injury is brain injury in place under direct impact, while the contra-cup injures the brain far from the place of direct impact. The hippocampus, being high epiletogenic location, is often the subject of contra-cup injuries. With head injuries, two types of intracranial hemorrhage are distingushed – epidural and subdural. Both types of bleeding may occur at the same time.

Patients with brain injury caused by trauma are classified as severe if the GCS (Glasgow Coma Scale) is 8 or less (about 10% of injuries), moderate if the GCS is in 9–12 range (further 10% of injuries), and the rest as mild, with GCS 13–15, (7). The accurate assessment of neurologic injury severity on clinical grounds is often precluded by pre-hospitalization treatment, such as intubation, sedation, pharmacologic paralysis etc (8, 9).

Also, GCS assessment is difficult with specific populations of patients, including infants, young children and patients with pre-existing neurologic impairment. The GCS is also a poor discriminator for less severe TBI, which account for 80–90% of all cases.

EPIDEMIOLOGY

The overall incidence of head injuries in the US is a 200/100 000. Men are more often injured than women, and the peak incidence is between 15 to 24 years (10). The incidence of post-traumatic epilepsy depends on the severity of the injury. Incidence of epilepsy in the general population is ranging from 0.5 to 1%, compared to 2–2.5% incidence of posttraumatic attacks in civilian population with any type of head injury, and 5% in hospitalized patients in neurosurgical departments, (11).

When it comes to severe head trauma, the incidence of PTE is 10–15% among adults and even 30–35% among children. TBI is the cause of 20% of symptomatic epilepsy and 5% of all seizures in general population (12). The incidence of posttraumatic attacks is very high (50%) in a series of war-related injuries involving penetrating head injuries. The incidence of post-traumatic attacks (excluding early seizures) for patients with mild uncomplicated brain trauma is the same in the military and the general population (13, 14). in his overview of studies about PTE, Beghi found that in civilian populations the overall risk to develop PTE estimated at 2–5%, increasing to 7–39% for subgroups with cortical injury and neurologic sequelae (15).

DIAGNOSIS

CT and MRI are now the imaging techniques for detection of acute and subacute brain injury, respectively. Diffusion tensor imaging is being developed to provide more information on structural damage in brain injury. There are several re-

search techniques available for brain injury, particularly relating to cerebral blood flow and metabolism, (16).

Electroencephalography (EEG) is a tool used to diagnose a seizure disorder, but a large portion of people with PTE may not have the abnormal „epileptiform" EEG findings indicative for epilepsy. In individual patients, the EEG does not improve the accuracy of the prediction calculated from clinical data. Patients with persisting or newly developing EEG abnormalities may never have a fit, while 20% of those with late epilepsy had at least one normal record in the first 3 months after injury (16).

RISK FACTORS

Some of the risk factors for the eemergence and development of PTE are: epileptogenic region of the brain affected by injury, type of seizure and severity of trauma (17, 18). The definition of severity of trauma set bay Anegers, who divided head trauma into mild, moderate and severe. Mild injury is defined as injury without fracture of the skull, with the duration of posttraumatic amnesia or loss of consciousness being 30 minutes or less. Moderate injury may be with or without fracture of the skull, and with the period of post-traumatic amnesia or loss of consciousness of 30 minutes to 24 hours. Severe brain injury is characterized by contusion, intracranial hematoma presence, loss of consciousness or post-traumatic amnesia for 24 hours or more.

Important independent risk factors for PTE include acute intracerebral hematoma (especially subdural hematoma), brain contusion, increased injury severity (as reflected by loss of consciousness or posttraumatic amnesia lasting >24 h), occurrence of early posttraumatic seizures, and being older than 65 years at the time of injury.

As high as 86% of patients with one seizure after TBI will have a second in the next 2 years. Longer-term remission rates of 25–40% have been reported. Significant risk factors for the development of seizures in the first week after injury include acute intracerebral hematoma (especially subdural hematoma), younger age, increased injury severity, chronic alcoholism, brain contusion, and age >65 years at the time of injury (19). Type of attacks and severity of trauma play a role in predicting the risk of developing post-traumatic epilepsy. The risk of late attacks (single or repeated) growing at contusion with subdural hematoma, with injuries to the skull fracture, loss of consciousness or amnesia longer than one day (20). Also, the risk for developing PTE are early posttraumatic seizures, neurological clinical features, neurosurgical procedures, personal and family predisposition (21).

PTE CLINICAL PICTURE

Post-traumatic seizures can present as any type of attack. The spectrum ranges from simple and complex partial seizures to secondary generalized seizures. But generalized absence seizures can not be regarded as a consequence of a trauma.

Most of the early attacks are generalized tonic clonic seizures, while late attacks can be of various types (2).

PROPHYLAXIS

Antiepileptic prophylaxis reduces early seizures, but their use beyond 1 week does not prevent the development of post-traumatic epilepsy. Furthermore, prolonged prophylaxis exposes patients to side effects of the drugs and has occupational implications. The American Academy of Neurology recommends that antiepileptic prophylaxis should be started for patients with severe traumatic brain injury and discontinued after 1 week. In same study authors concluded that the use of antiepileptic prophylaxis varies widely and is generally inconsistent with evidence-based guidance. This exposes some patients to a higher risk of early seizures and others to unnecessary use of antiepileptic drugs. Better implementation of prophylaxis is required (22).

Data from the 1970 s show that 60% of neurosurgeons in the US treated TBI patients with antiepileptic drugs for the purpose of prophylaxis of PTE (23), while data from 2000 s show: 36% of neurosurgeons have not applied prophylactic therapy for TBI, 12% have given the therapy to all patients with TBI, and 52% have decided on the basis of specific risk factors (24).

Early prophylaxis with a single antiepileptic drug is recommended for adult patients with severe TBI is following cases: the prolonged loss of consciousness or amnesia, ICH or brain contusions on CT and / or depressed skull fracture. Prophylactic treatment with PHT, started with IV. load, should begin as soon as possible after trauma, in order to reduce the risk of post-traumatic attacks that occur in the first 7 days (Level A). Prophylactic treatment with PHT, CBZ and VPA should not be routinely used 7 days after trauma in order to minimize the risk of attacks that occur after 7 days (Level B), (25). Prolonged AET should be applied only after a diagnosis of epilepsy.

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