

# Post-traumatic Epilepsy: An Overview

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## 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. Use of seat belts and helmets also make this a preventable cause of epilepsy. Multiple theories have been postulated to explain the mechanisms behind the development of post-traumatic epilepsy, including free radical damage caused by blood in the brain parenchyma, increases in excitatory activity, and changes in the inhibitory functions of the brain. 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 is the development of chronic recurring seizures following head trauma. The head injury, through mechanisms that are still being investigated, is believed to be the initiating event in a cascade of processes that result in epileptogenesis. Individuals sustaining head injury have a threefold higher risk of developing epilepsy than the general population (Langendorf and Pedley, 1997). Overall, five percent of all cases of epilepsy are attributable to head injury (Langendorf and Pedley, 1997). Even though head injury contributes to a small percent of the total cases of epilepsy, it is a significant preventable cause of epilepsy. This article will explore various aspects of post-traumatic epilepsy, including pertinent terminology, epidemiology of the disorder, mechanisms of epileptogenesis, as well as some clinical considerations.

## DEFINITIONS AND CLASSIFICATIONS

In order to understand post-traumatic epilepsy, various forms of head injury have been defined (Adams et al., 1997). Closed head injuries are injuries in which nothing penetrates the skull. Such injuries often result in loss of consciousness, at least transiently, and can be associated with gross damage of the brain depending on the severity of the injury. An open head injury is one where the skull is penetrated by an object, as seen in a gunshot or shrapnel wound. In this type of injury, the patient may not experience loss of consciousness although severe or even fatal injury may result. A concussion is defined as an injury resulting from a violent shaking or jarring of the brain with an associated transient functional impairment (i.e., loss of consciousness, seizure, amnesia, or loss of

mentation). A contusion is a bruising of cerebral tissue with preservation of its original architecture. There are two subtypes of contusions: coup and contra-coup. Coup injury refers to injury to the brain directly under the site of impact. In contra-coup injuries, the injury takes place distal to the site of impact. The hippocampus, a highly epileptogenic site, is often subject to contra-coup injury.

The two types of intracranial hemorrhages that are important for discussing head injuries are epidural and subdural hematomas. These two types of hemorrhage, which can occur simultaneously, differ in where they occur. Epidural hematomas are hemorrhages occurring above the dural layer and are frequently associated with temporal or parietal skull fracture and laceration of the middle meningeal artery or vein. The patient remains lucid after the original injury but suffers a gradual increase in neurologic symptoms and loss of consciousness over the following hours or days. This condition may progress to death if left untreated. Subdural hematomas are hemorrhages occurring under the dural layer. Blood tends to accumulate rapidly in epidural hematomas due to the typical rupture of an artery, whereas subdural hematomas can progress slower due to rupture of a vein. Because of this, careful observation after head injury must be instituted to prevent the patient from developing a neurological crisis after an apparent "full recovery." The clinical manifestations of these two injuries can overlap and identifying which type of injury is present may not be possible until either surgery or a CT scan is performed.

Following head injury, there are two broad categories of seizures that may occur – early or late. Early seizures are acute seizures that occur as a result of the physical effects of the trauma (i.e., within one to two weeks after injury). 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. They can be a single or recurrent event. Recurrent late seizures are considered post-traumatic epilepsy (Langendorf and Pedley, 1997).

## EPIDEMIOLOGY

Each year, in the United States there are 500,000 head injuries serious enough to produce skull fractures, neurological symptoms, and/or require admission to a hospital. The overall incidence of head injury in the United States is 200/100,000. Men are more commonly affected than women, and the incidence peaks between the ages of 15 and 24. (Langendorf and Pedley, 1997).

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Among this group of people, measuring the incidence of post-traumatic seizures has been difficult taking into account the incidence of epilepsy in the general population, the presence of other risk factors, failure to exclude all acute symptomatic seizures after the injury, loss to follow-up, and confusion with single late seizures after the initial injury (Langendorf and Pedley, 1997). Studies have cited incidences from 53% after war injuries to between 1.8% and 5.0% in civilian populations (Annegers et al., 1998).

Early seizures occur in two to five percent of patients suffering head injury, with seizures occurring more frequently in children than in adults. If only severe head injuries are accounted for, the incidence jumps to between 10% and 15% for adults and between 30% and 35% for children (Langendorf and Pedley, 1997). In adults, late seizures follow early seizures 25% to 35% of the time. Early seizures are not as predictive in children as they are in adults (Langendorf and Pedley, 1997). One study of the Olmsted County, Minnesota population, found that incidence ratio of late seizures (single or multiple) was 1.5 after mild injuries, 2.9 after moderate injuries, and 17.0 after severe injuries (Annegers et al., 1998). In the Vietnam Head Injury Study, 53% of veterans who suffered a missile injury eventually had at least one seizure with many experiencing multiple seizures. Half of the patients experienced a seizure within the first year after the injury. Fifteen percent, however, did not experience a seizure until five or more years later (Salazar et al., 1985).

The type and severity of head injury also play a role in determining the of risk of developing epilepsy afterwards. In the Olmsted County, Minnesota study, risk factors for late seizures (single or multiple) were a brain contusion with subdural hematoma, skull fracture, loss of consciousness, or amnesia for more than one day (Annegers et al., 1998). The Vietnam Head Injury Study also found that there was an increased risk of seizures if metal fragments were retained in the brain, there was an intracranial hematoma, or the patient experienced persistent neurologic deficits following injury. The degree of loss of brain tissue as a result of the injury was also positively correlated with the likelihood of developing seizures (Salazar et al., 1985).

With non-penetrating head injuries, the first late seizure occurs within the first year in 60% of individuals. Depressed skull fractures and intracranial hematomas are also associated with increased risk of late seizures (Langendorf and Pedley, 1997). The increased risk after intracranial hematomas is noteworthy, since the presence of blood in the parenchyma of the brain is one of the elements being investigated in the development of post-traumatic epilepsy. The possibility that some individuals have genetic susceptibility in developing post-traumatic epilepsy is another theory that is actively being studied, although there is little

supporting evidence.

### MECHANISMS OF EPILEPTOGENESIS

There are multiple theories that have been developed to explain the mechanisms behind what causes chronic seizures after a head injury. Among these are the formation of damaging free radicals by blood in the parenchyma of the brain, increases in excitatory activity following injury, and changes in the inhibitory functions of the brain. Several animal models have also been developed to explore the possibilities of different types of head injury from concussions to penetrating head injury.

Since parenchymal blood is associated with an increased risk in developing epilepsy, possible mechanisms involving this type of insult have been explored. Hemoglobin was studied as an agent involved in epileptogenesis. Once there is a bleed into brain tissue, red blood cells are lysed with a subsequent release in hemoglobin that is broken down into heme and iron. Both breakdown products have been shown to have physiological effects on synaptic transmission that may lead to epileptogenesis (Yip and Sastry, 2000). Indeed, there is an animal model where epilepsy is induced by injecting ferrous or ferric chloride into the brains of rats. The epileptogenic effect of iron is thought to be related to the formation of free radicals that cause direct injury to neuronal membranes and cell death. If antiperoxidant compounds are given, seizure development can be blocked (Langendorf and Pedley, 1997). Iron injected into the brain has also been found to effect the release and metabolism of the excitatory neurotransmitter glutamate. One study found a decrease in glutamate transporter protein (a protein expressed by astrocytes that is involved with glutamate reuptake) after iron injection (Samuelsson et al., 2000). Another study using chemiluminescence found that iron injections affected both the levels of free radicals and excitatory amino acids (Kucukkaya et al., 1998).

Another avenue in the exploration of epileptogenesis is the role of excitatory amino acids. Studies have found increased levels of glutamate and aspartate in the brains of rats suffering from seizures after brain injury (Nilsson et al., 1994). Similar results have been found in humans (Ronne-Engstrom et al., 1992). Glutamate is widespread in brain as well as in the extracellular fluid. It is involved in many metabolic functions. Glutamate is thought to exert an excitotoxic effect on the brain in large amounts (Evans, 1962). At the same time, however, it serves as a precursor for the inhibitory neurotransmitter GABA ( $\gamma$ -aminobutyric acid), so its effects on the pathogenesis of epilepsy may be more complicated.

Calcium is thought to be the main ion involved in excitotoxicity. Excitatory glutamate receptors are important in the influx of calcium into the cell. There are three subtypes of glutamate receptors – NMDA (N-methyl-D-aspartate),

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metabotropic, and AMPA ( $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionate). The NMDA glutamate receptor subtype contains magnesium, which maintains the channel in an inactive state until other excitatory events (e.g., via AMPA and metabotropic receptors) cause the magnesium to dissociate from the receptor, leading to an influx of calcium. Calcium, once within the cell, is able to stimulate a cascade of events, which may even result in cell death. Drugs blocking the NMDA receptor have been found to have unacceptable side effects, limiting their clinical use. The metabotropic receptor, acts indirectly on ion channels through second messengers. Drugs affecting various subtypes of these channels have been found to have convulsive or anticonvulsive properties depending on which channel subtype was being affected (Porter and Meldrum, 1998). The AMPA receptor, on the other hand, is relatively impermeable to calcium. It has been found that if the GluR2 subunit of this channel is down-regulated. This may lead to the formation of channels that cause an increased influx of calcium into the cell and eventually cell death (Kandel and Siegelbaum, 2000). Through these three types of receptors (and their interactions) a significant influx of calcium can take place that may have permanent consequences for the cell.

Following brain injury, there is a large calcium-dependent increase in extracellular potassium, which may be due to the increased amounts of excitatory amino acids present (Katayama et al., 1990). Potassium itself increases neuronal excitability and, therefore, the likelihood of seizures and cell death (Langendorf and Pedley, 1997). Thus, a physical insult to the brain may initiate a cascade of excitatory events that can result in neurotoxicity and seizure activity.

Another area being investigated is the role inhibition plays in the process of epileptogenesis and how injury may perturb the system towards developing seizure activity. One theory is that changes in the brain following injury result in the loss of the normal background inhibition necessary to prevent seizure activity (Langendorf and Pedley, 1997). GABA is an important amino acid neurotransmitter that has inhibitory (i.e., hyperpolarizing) effects due to its stimulation of chloride channels. GABAergic activity is thought to play a major inhibitory role in normal brain function, and it is this activity that may be affected by brain injury. Medications that mimic or stimulate GABAergic activity have been found to have antiepileptic qualities, lending credence to the idea that changes in inhibition play a role in epileptogenesis (Porter and Meldrum, 1998).

Studies have found that an increase in inhibitory activity may also cause seizure activity. One such study used isolated rat cortical islands as a model. Pieces of cortex were partially isolated in rats and allowed to remain in vivo for two to three weeks before the animal was sacrificed and brain slices were shown to have epileptiform activity. In this study, it was found that these epileptiform slices had

increased inhibitory activity (Prince et al., 1997). The authors postulated that following injury the sprouting of inhibitory axons may make increased synapses with pyramidal cells, leading to increased inhibition and synchronization of neuronal firing.

Animal models have also been used to examine the consequences of head injury on epileptic activity. A popular model that is widely used is the fluid percussion injury model, where saline is rapidly injected into a closed cranial cavity, resulting in increased intracranial pressure and a brief displacement of neural tissue. This type of injury is believed to be similar to the closed-head injuries often seen in humans, such as what happens with a concussion. This animal model has been used to demonstrate that damage to the hippocampus, an area of the brain often damaged in temporal lobe epilepsy, can result even after mild head trauma (Hicks et al., 1993). Another method of modeling human injury in animals is the creation of freeze lesions, which may simulate a more penetrating injury that causes direct damage to brain tissue.

The reactions of the brain to injury seem to be varied and quite complicated, and the use of experimental models in piecing together mechanisms of epileptogenesis will inevitably be only partially applicable to humans because of the sheer variety of multiple insults that can arise from a head injury. Most likely, a combination of factors underlies the genesis of seizure activity. One interesting (although highly controversial) study published recently found that preventing seizures using phenobarbital actually delayed functional recovery after a brain insult in rats (Montañez et al., 2000). This implies that the seizures themselves may be a way that the brain copes with injury and recovers. Thus, preventing seizures immediately after brain injury (i.e., prophylaxis) may prove more harmful than beneficial.

**CLINICAL CONSIDERATIONS**

Post-traumatic seizures may present anywhere in the spectrum of simple and complex seizures, including secondary and secondarily generalized seizures. However, general absence seizures are not thought to be caused by head injury (Langendorf and Pedley, 1997). Most early seizures are found to be of the generalized tonic-clonic type, whereas in late post-traumatic seizures the seizure types are more varied (Langendorf and Pedley, 1997).

Patients that arrive with moderate or severe head injury should be imaged with a CT scan immediately, and the study should be repeated if the condition of the patient does not improve. Imaging should also be repeated in cases of mild head injury complicated with a seizure or unexpected event (e.g., such as an acute change in mental status) during the course of patient recovery. EEG (electroencephalogram) has only a limited role in evalu-

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ating patients with early post-traumatic seizures who are experiencing intermittent behavioral changes. It is not useful in predicting the development of post-traumatic epilepsy (Langendorf and Pedley, 1997).

In patients with severe head injury, standard treatment involves the use of phenytoin prophylactically against seizures that might complicate the acute management of the patient. If seizures do not occur, it is recommended to cease treatment after one or two weeks (Langendorf and Pedley, 1997). With recent results showing that initial prevention of seizures after injury results in delayed recovery, this standard of treatment may come under closer scrutiny in the coming years. Early treatment with phenytoin has not been shown to reduce the incidence of late seizures, indicating that this drug does not seem to have an effect on the epileptogenesis of post-traumatic seizures (Temkin et al., 1990). Because of these findings, the current practice is to provide early treatment for a few weeks in those with moderate to severe head injury to prevent early post-traumatic seizures that may complicate the management of an acutely sick patient but not to use long term prophylaxis.

In individuals with a single unprovoked seizure, the decision whether or not to begin antiepileptic drug treatment depends on the risk of the individual for developing further seizures. While a first early seizure is not correlated with later recurrent seizures, a singular late seizure has a 65% to 90% chance of progressing to recurrent seizures (Langendorf and Pedley, 1997). Because of this risk, long-term treatment is indicated in individuals suffering a single late seizure. Phenytoin is the drug of choice in treating and preventing early and late seizures while carbamazepine and valproate have also been found useful in the treatment of late seizures (Langendorf and Pedley, 1997). Newer epileptic medications are currently being tested but their effectiveness has yet to be determined. If phenytoin is used, it is important to monitor both total and free phenytoin levels in the bloodstream, since this medication is present in both free and protein-bound forms in the serum. At very low levels, phenytoin metabolism is proportionate to the rate at which it the drug is presented to the liver (i.e., first-order metabolism). At therapeutic levels, however, the maximum capacity of the liver to metabolize the drug is reached and small increases in the amount of medication may produce large increases in plasma levels, resulting in toxicity (i.e., zero-order metabolism). The side effects of these drugs should also be monitored, since cognitive impairment may result.

Prognosis after the development of post-traumatic epilepsy is unclear. About one half of patients with late seizures experience prolonged remissions (Langendorf and Pedley, 1997). The chance of extended remission seems to be reduced if intracranial hemorrhage, partial seizures, and frequent seizures during the first year after the injury are observed (Langendorf and Pedley, 1997).

**CONCLUSION**

Post-traumatic epilepsy is a relatively common condition, comprising five percent of the total cases of epilepsy. It is also a preventable disorder as many head injuries can be prevented with proper seat belt or helmet use. Why certain people develop seizures after only a mild insult, yet others sustaining more severe traumatic injury do not remains a mystery. Even though the mechanisms are not completely understood, the fact that there is a demonstrable event leading to epileptogenesis allows this type of epilepsy to be studied in animal models and clinical studies. As the underlying mechanisms of this disorder are elucidated, new treatments may be discovered with the aim of developing preventative therapies after head trauma has occurred.

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