

## Epilepsy in head injury

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### Abstract

Posttraumatic epilepsy accounts for about 20% of symptomatic epilepsy in the general population and about 5% patients referred to epilepsy centers. Mechanisms that can provoke posttraumatic seizures are still not well understood. The extent of focal tissue destruction is one of the key determinants of risk of seizures. Early posttraumatic seizures can worsen ischemic injury and increase intracranial pressure. Adverse sequelae of late posttraumatic seizures include a higher mortality and personality disorders. Whilst anticonvulsant prophylaxis of early seizures is recommended, such therapy is yet to be proven to prevent late posttraumatic seizures.

Posttraumatic epilepsy is defined as the occurrence of two or more unprovoked seizures following a brain injury that follows trauma.<sup>1,2</sup> This definition excludes a single post-injury seizure as well as seizures that occur secondary to other epileptogenic mechanisms. Posttraumatic epilepsy accounts for about 20% of symptomatic epilepsy in the general population, and about 5% patients referred to epilepsy centers.<sup>3,4</sup>

Posttraumatic seizures (PTS) has been classified, as immediate (manifesting at <24 hours), early seizures (manifesting <1 week after injury) and late seizures (manifesting >1 week after injury).

### PATHOGENESIS

The mechanisms that can provoke PTS are still not well understood. Immediate seizures may follow disruption of inhibitory cortical, subcortical connections by the immediate effects of injury. Epileptogenic effects of the cascades of neurochemical and metabolic derangements that follow the initial injury (such as elevation of excitatory aminoacids, ionic shifts, changes in extracellular pH), loss of inhibitory neuronal pool due to delayed cell death, may play a role in early seizures. Late seizures may be associated with cortical irritation from a glial scar and/or cortical accumulation of blood breakdown products such as haemosiderin. The combination of a gliotic scar and haemosiderin can significantly increase late PTS risk.<sup>2,4,5</sup>

In diffuse brain injury, the regions with greatest strain effects include basal frontal regions, hippocampus, subiculum, amygdala, entorhinal cortex – all with recognized epileptogenic

potential.<sup>6,7</sup> Focal tissue destruction is the most important factor in the pathogenesis, as seizures are believed to originate injured cortical neurons, explaining the high risk with penetrating injuries, contusions, acute subdural haematoma.<sup>8,9</sup>

### CLINICAL TYPES

Early PTS are mostly focal seizures with secondary generalization. About two-thirds of late PTS are generalized or focal with secondary generalization and at times, both seizure types may coexist.<sup>8</sup> Mesial temporal lobe epilepsy may result from hippocampal sclerosis after traumatic brain injury in young children (age <5 years), an expression of vulnerability of the developing brain to trauma.<sup>10</sup>

### Early posttraumatic seizures

Early studies reported an incidence of 4%–15% for early PTS.<sup>11-13</sup> Currently, with use of seizure prophylaxis, acute clinical seizures have become less common, with a reported incidence of <1% in one large study.<sup>14</sup> However, with continuous EEG monitoring, 22-33 % of patients with moderate and severe head injury demonstrated electrographic seizures, with nearly 50% having non-convulsive seizures.<sup>15</sup> Early posttraumatic seizures can worsen ischemic injury, leading to high lactate levels and acidosis, resulting in increased cerebral blood flow and may cause harmful increases in intracranial pressure.<sup>16</sup> Non-convulsive seizures may have similar deleterious effects.<sup>17</sup> More evidence may be needed to determine if treatment of non-convulsive seizures can result in improved outcomes.<sup>16</sup> Intravenous prophylaxis of early

**Table 1: Risk factors for late posttraumatic seizures** (from references 9, 24-27)

Clinical indicators
<ul style="list-style-type: none"> <li>• Severity of injury (duration of loss of consciousness and posttraumatic amnesia; Glasgow Coma Scale)</li> <li>• Depression, co-morbid conditions at discharge</li> <li>• Older age, family history</li> <li>• Early posttraumatic seizure</li> </ul>
Injury mechanism
<ul style="list-style-type: none"> <li>• Missile injuries, depressed skull fracture with dural penetration</li> </ul>
Type of intracranial lesion
<ul style="list-style-type: none"> <li>• Contusions (especially multiple), acute subdural hemorrhage (especially if operated)</li> <li>• Intracerebral hemorrhage, decompressive craniectomy</li> </ul>

PTS is recommended in severe head injury, with phenytoin being the most commonly used.<sup>18</sup>

#### **Late posttraumatic seizures**

Most late PTS occur within the first 12 months.<sup>9,19</sup> The risk of subsequent seizures increases dramatically after the first seizure, especially in moderate and severe head injury.<sup>20,21</sup> Remission has been reported in 25 to 40 % of those with late PTS and about 13 percent become refractory to AED therapy.<sup>22,23</sup>

#### **Long term risk of Late PTS**

Studies of long term risk of late posttraumatic seizures show considerable heterogeneity with respect to patient populations, outcome end points and risk factors identified. Overall the risk being 5–19% with civilian head injury and 32-50% with military head injury.<sup>9,19,20,24</sup>

In a population based study of children and adults, the 5 year cumulative probability of seizures for mild, moderate and severe head injury was 1.5, 2.9 and 17.2 respectively. Mild head injury did not result in an increased risk after 5 years.<sup>9</sup> The cumulative risk of late posttraumatic seizures within 3 years of discharge in older adolescents and adults hospitalized with traumatic brain injury was 7.6 % for moderate brain injury and 13.6 % for severe brain injury.<sup>25</sup> A recent, large study of children and young adults showed that risk of late posttraumatic seizures remained high for more than 10 years for both mild and severe traumatic brain injury.<sup>25</sup> Penetrating military brain injuries carried persistently high risk of late posttraumatic seizures even after 15 years.<sup>26</sup> The risk factors for late PTS are shown in Table 1.

Adverse sequelae of late PTS include a higher mortality of being nearly three times higher than

normal population; and personality disorders of uninhibited behavior, irritability, and agitated and aggressive behavior.<sup>9,28</sup> These and common co-morbidities of traumatic brain injury such as impaired cognition, depression, decreased self-awareness, fatigue, have a potentially devastating impact on rehabilitation, employability, treatment costs, and burden to caregivers.

#### **Prophylaxis of late posttraumatic seizures**

Prophylaxis should be considered after the first late PTS.<sup>29</sup> In a comprehensive review of anticonvulsant prophylaxis for late PTS, phenytoin, phenobarbitone, valproate, carbamazepine and magnesium did not show prophylactic efficacy. However, these studies suffered from several limitations and only drugs approved before 1980 were tested. More studies with newer anticonvulsants may be needed.<sup>30</sup> The study to understand the mechanisms of epileptogenesis following head injury remains a work in progress. Rational, targeted therapy that can prevent onset of posttraumatic seizures has yet to be devised.<sup>31</sup>

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