Exploring the Relationship Between Traumatic Brain Injury and Post-Traumatic Epilepsy: A Review

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INTRODUCTION

According to the Centers for Disease Control and Prevention (2020), traumatic brain injury (TBI) is considered a major public health problem in the United States. Each year, 2.53 million Americans, including 812,000 children, document a TBI-related emergency room visit (1). TBI is a disruption in the brain's normal function, caused by a bump or blow to the head or by penetrating head injury (1). These injuries range in severity and can cause damage to one area of the brain, as in focal injuries, or multiple areas of the brain, as in diffuse injury (2).

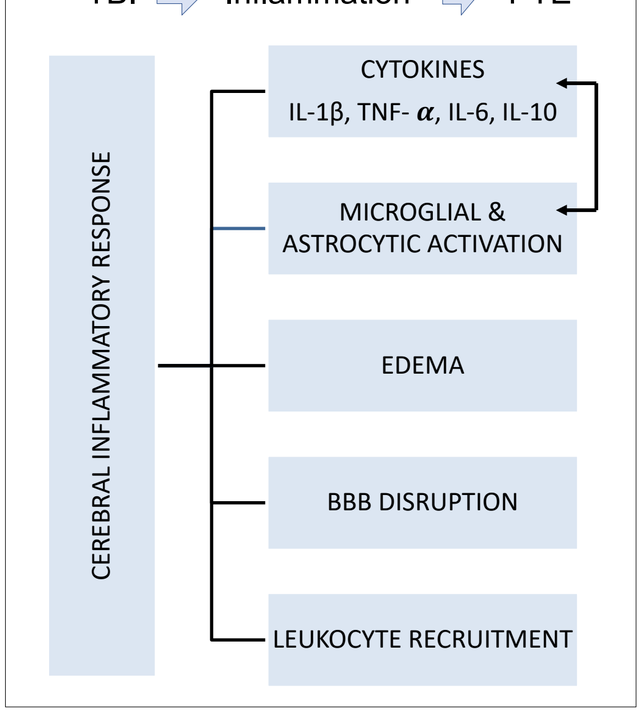
Secondary processes related to TBI can result in both temporary and long-term neurological disabilities, including post-traumatic epilepsy (PTE), a recurrent seizure disorder secondary to trauma to the brain (6, 7). While the exact relationship between TBI and PTE has not been identified, various pathophysiological processes have been suggested. Furthermore, there are currently no definitive tests to evaluate TBI patients to determine the neurological conditions that may arise. Research suggests the utilization of biomarkers associated with neurological damage as a means of diagnosing patients presenting with head trauma. It is also suggested that these biomarkers may give insight into the physiological processes occurring after injury (9).

METHODS

The search engine PubMed was used. Search criteria included terms such as traumatic brain injury, epidemiology, post-traumatic epilepsy, mild TBI, diffuse TBI, sport-related concussion, neuroinflammation, astrocytes, gliosis, and biomarkers. Information from the Centers for Disease Control and Prevention and the American Association of Neurological Surgeons was also examined. Results were narrowed down to include literature from the years 2015-2021 and relevant literature from peer-reviewed journals was evaluated.

RESULTS & DISCUSSION

Mechanisms of PTE (7,13)



Biomarkers (3,9,14)

Protein Biomarker Levels - TBI	
S100B	↑
GFAP	↑
UCH-L1	↑
Tau	↑

Protein Biomarker Levels - PTE	
S100B	↑
GFAP	↑
UCH-L1	↑
Tau	↑

Genetic Biomarkers & Risk of PTE

Variant Gene	Function	Risk of PTE
GAD1	GABA synthesis	↑
SLC1A1	Glutamate transporter	↑
SLC1A3	Glutamate transport	↑
IL-1	Encodes IL-1β	↑

Often resistant to anti-epileptic drugs, it is vital to identify mechanisms associated with PTE and ways to prevent and treat its development (7). Future studies should also take the pediatric population into consideration, as the structural differences of the pediatric brain may alter the processes involved (10).

Consideration should also be given to the interaction of TBI, epilepsy, and COVID-19. Early studies have connected the SARS-CoV-2 virus, neuroinflammation, and epilepsy (11,12). Further information is needed regarding the mechanisms of SARS-CoV-2-induced epilepsy, especially in patients presenting with TBI. With an increased risk of PTE under normal circumstances, TBI patients may be particularly vulnerable to neurologic dysfunction if infected with COVID-19.

The time period after TBI, in which secondary injury processes are initiated, is critical in the development of epilepsy and research has shown that inflammatory molecules, including pro- inflammatory cytokines like IL-1β and TNF - α, may initiate early seizures (7). In the nervous system, astrocytes regulate neuronal synapses, and during neurotrauma, they protect uninjured tissue by a process termed reactive gliosis (8). The elimination of a population of reactive astrocytes leads to increased neurodegeneration and BBB deficits, suggesting the neuroprotective effects of gliosis (8). Gliosis can also lead to an overproduction of inflammatory cytokines and a hyperexcited environment conducive to seizure development (7).

Given the challenges and cost burden of screening for TBI and epilepsy, recent research has focused on the potential use of biomarkers to diagnose injury and predict patients at risk of developing PTE (9). Common biomarkers between TBI and PTE include GFAP, IL-1, HMGB-1, UCH-L1, tau, and S100B (3). While each marker can be associated with the processes underlying TBI, more research is needed to establish relationships with epileptogenesis.

CONCLUSION

To conclude, there are many factors to consider when exploring the relationship between TBI and PTE. Diagnostic and prognostic biomarkers may offer insight into secondary injury processes and provide a preventative advantage. The interplay of several neuropathophysiological processes related to neuroinflammation may contribute to PTE. Further research should seek to establish causal relationships and identify targets for therapeutic intervention.

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