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

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ABSTRACT

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 (CDC, 2020). TBI is a disruption in the brain's normal function, caused by a bump or blow to the head or by penetrating head injury (CDC, 2020). These injuries range in severity and can cause damage to one or multiple areas of the brain (Oleksii et al., 2019). Mild TBI, often used synonymously with concussion, comprises more than 90% of TBI cases (Pitkänen et al., 2020). Additionally, secondary TBI processes can result in several long-term neurological disabilities (Webster et al., 2017). Post-Traumatic Epilepsy (PTE) is defined as a recurrent seizure disorder secondary to trauma to the brain and has been described as one of the most devastating complications associated with TBI, as it can lead to neurodegenerative and neurocognitive symptoms (Keith & Huang, 2019). Most cases of PTE are resistant to existing anti-epileptic drugs, making treatment extremely difficult (Webster et al., 2017).

The objective of this review is to explore the relationship between TBI and the development of PTE. A review of relevant literature from peer-reviewed publications, was focused on TBI, development of PTE, and potential diagnostic biomarkers for these conditions. It was found that elements of the neuroinflammatory response, including reactive astrogliosis and pro-inflammatory cytokines, may offer valuable insight into the development of PTE. Further research is needed to establish causal relationships, identify targets for therapeutic intervention, and ultimately prevent, manage, and treat PTE.

INTRODUCTION

The Centers for Disease Control and Prevention (2020) defines traumatic brain injury (TBI) as a disruption in the brain's normal function, caused by a bump or blow to the head or by penetrating head injury. These injuries can be caused by various events, which determine the characteristics and severity (CDC, 2020). Secondary processes related to TBI can result in short or long-term neurological disabilities, including post-traumatic epilepsy (PTE) (Webster et al., 2017). While the exact relationship between TBI and PTE remains unknown, various pathophysiological processes may be involved. Furthermore, there is currently no definitive test to evaluate TBI patients to determine the neurological conditions that may arise (Mahan et al., 2019). Characterizing the damage caused by mild TBI is also challenging, given the subjectivity of diagnosis (Meier et al., 2020). Research suggests the utilization of biomarkers associated with neurological damage as a means of diagnosing patients presenting with head trauma (Thelin et al., 2019). These biomarkers may also give insight into the secondary physiological processes occurring after injury (Thelin et al., 2019). Understanding the pathogenesis of PTE is the foundation for developing and evaluating therapeutic interventions. This review will focus on the neuropathophysiological mechanisms of PTE following TBI and potential biomarkers for diagnosis of injury.

BACKGROUND

Epidemiology

TBI is a global public health problem, as approximately 50 million people worldwide sustain TBI every year (Maas et al., 2017). As the leading cause of death and disability across all ages in all countries, it is predicted that nearly half the world's population will sustain at least one TBI in their lifetime (Maas et al., 2017). In the United States, 2.87 million TBI-related emergency department visits, hospitalizations, and deaths were documented in 2014 (CDC, 2020). This estimate includes the 812,000 children treated in emergency departments for concussion or TBI alone and TBI along with other injuries (CDC, 2020). While age-adjusted rates for TBI-related hospitalizations and deaths decreased between 2006 and 2014, rates of emergency department visits increased by 54% and continue to rise (CDC, 2020).

Risk factors

Among the risk factors for TBI, age plays a large role. Rates of ED visits are highest for people over the age of 75 years old and for children younger than four years old (CDC, 2020). Accounting for nearly half of TBI-related ED visits, falls disproportionately affect children and older adults (CDC, 2020). Following falls, motor vehicle accidents were the second leading cause of TBI-related hospitalizations across age groups (CDC, 2020). Children under the age of eight years old are mainly injured by falls, abuse-related injuries, motor vehicle accidents, and transportation-related accidents (Araki et al., 2017). Additionally, injuries related to participation in sports and trauma

contribute to the high prevalence during childhood and adolescence (Agarwal, MD et al., 2021). Other risk factors across age groups may include male gender and participation in sports (Agarwal, MD et al., 2021).

Pediatric Traumatic Brain Injury

According to the CDC, approximately 475,000 children ages 14 years and under sustain TBI annually, with up to 90% sustaining mild injury (Araki et al., 2017). As the leading cause of death and disability in children, injury patterns in pediatric patients are distinctively different from those observed in adults (Araki et al., 2017). Even within the pediatric population, age-related anatomical and physiological differences contribute to varied injury patterns (Araki et al., 2017). For example, as age decreases, the thickness of the scalp also decreases, thereby reducing the scalp's protective ability (Araki et al., 2017). In infants specifically, the skull plasticity and open sutures allow for movement during trauma, leading to stretching that can injure brain parenchyma (Araki et al., 2017). Other differences in children include weak neck musculature, increased head size, and lack of myelin (Araki et al., 2017).

Between 2007 and 2014, there was a 60% increase in concussion, a mild TBI, in the general population, with pediatric and adolescent patients accounting for the majority of this increase (Smith et al., 2019). Approximately 1.9 million individuals under 18 years old sustain a sports-related concussion each year, with rates of pediatric sports-related and non-sports-related concussion being highest in individuals between the ages of 15 and 19 years old (Smith et al., 2019). While symptoms of concussion usually resolve within one month of injury, up to 30% of pediatric patients have symptoms extending past one month (Smith et al., 2019). Further, concussion can lead to changes in cerebral

homeostasis that may contribute to secondary injury processes (Smith et al., 2019). Impairment in cerebrovascular autoregulation can leave the brain vulnerable to post-traumatic hyperemia and ischemia, which can contribute to neurologic dysfunction. (Smith et al., 2019). Given the prevalence of TBI in the pediatric population and the stark anatomical and physiological differences, identifying the consequences of secondary injury processes is vital.

Sport-Related Concussion

The CDC estimates between 1.6 million and 3.8 million sports-related TBIs occur each year (CDC, 2020). Actual numbers may be higher, as many individuals sustaining mild TBI do not seek medical attention (McKeithan et al., 2019). Concussions are considered mild TBIs characterized by diffuse injury that alters mental status, while sport-related concussion (SRC) refers specifically to TBI induced by biomechanical forces (Agarwal, MD et al., 2021). These sport-related injuries include sub-concussive injures that are usually produced by acceleration-deceleration forces (VanItallie 2019). SRC and mild TBI are often used synonymously, but an important distinction should be differentiated. Both SRC and mTBI overlap on the Glasgow Coma Scale, but any condition with positive neuroimaging is no longer categorized as a concussion and is instead considered a mTBI (McKeithan et al., 2019). Sports such as American football, soccer, boxing, rugby, and cheerleading frequently contribute to concussion rates, as the forces involved can subject the brain to secondary injury processes (VanItallie 2019). While most symptoms associated with SRC result from a functional disturbance rather than a structural disturbance, neuropathological changes may occur (Agarwal, MD et al., 2021). SRC can potentially cause long-term neurological dysfunction, yet current

evidence does not show a causal relationship between SRC and neuropathological sequelae (McKeithan et al., 2019). Of the associations found between SRC and long-term cognitive changes, one of the strongest predictors in determining the duration of persistent symptoms is the severity of symptoms associated with the initial injury (McKeithan et al., 2019). Another factor contributing to long-term cognitive defects is prior concussion or TBI history (Oleksii et al., 2019). Some studies have found a cumulative effect in patients sustaining repetitive head injuries (Lasry et al., 2017). Approximately 5.5% of patients experience recurrent TBI within one year of the index case, with even more experiencing recurrence after one year (Lasry et al., 2017). Furthermore, approximately 16% of youth experience recurrent injury within 2 years (Eyolfson et al., 2020). Given the frequency and increasing incidence of mild TBI and recurrent injury, exploration of the long-term consequences is critical.

Post-Traumatic Epilepsy

PTE, a common consequence of TBI, is a recurrent seizure disorder secondary to trauma to the brain (Keith & Huang, 2019). PTE can contribute to progressive and long-term neurodegenerative and neurocognitive symptoms in adults and children (Webster et al., 2017). While immediate and early seizures can occur within one week of injury, a diagnosis of PTE is made after the observation of two or more unprovoked seizures occurring later than one week after injury (Park & Chugani 2015). Most cases of PTE are resistant to existing anti-epileptic drugs, making treatment extremely difficult (Webster et al., 2017). While the exact etiology of PTE remains unknown, many secondary neurobiological processes are thought to be involved (Keith & Huang, 2019). Moreover, age-dependent factors may contribute to differences in seizure activation and mechanisms

inducing epileptogenesis, the process by which epilepsy develops (Webster et al., 2017). Epilepsy occurs when a normally functioning brain becomes abnormally electrically activated, decreasing the threshold for spontaneous, recurrent seizures (Webster et al., 2017). Along with age; injury type, severity, and individual factors also contribute to the development and pathogenesis of PTE (Webster et al., 2017). In PTE development, there is an initial trigger, a latency period, and the onset of spontaneous seizures (Webster et al., 2017). The latency period is of particular interest, as this is the time when secondary neurological processes leading to PTE occur (Webster et al., 2017). Following TBI, the latency period may last weeks or even years (Webster et al., 2017).

The incidence of PTE following TBI ranges greatly, as estimates range from 4% to 53% (Webster et al., 2017). Patients with more severe injury and younger age have the highest risk for developing PTE (Webster et al., 2017). For example, studies show that children under the age of five-years-old are at the highest risk for developing PTE, in comparison to older children and adults (Park & Chugani 2015). Most PTE research investigates focal or penetrating injuries, with little research focused on mild or diffuse injuries (Oleksii et al., 2019). Only about 10% of TBI patients experience focal injury, as most TBIs are a combination of focal and diffuse injuries (Oleksii et al., 2019). Difficulties with diagnosis and follow-up are potential causes for the wide reported range of PTE and lack of research into diffuse injury (Webster et al., 2017).

Further consideration should be given to the pediatric population, as age-related differences may drastically alter the characteristics of PTE. Research shows that seizures are particularly harmful during brain development and can cause permanent neurological deficits (Webster et al., 2017). Given the increased vulnerability of the pediatric brain to

injury, the long-term consequences of PTE on the developing brain should be further explored.

Neuroinflammation in PTE

Inflammation is a physiological process that protects against foreign pathogens, and the term “neuroinflammation” describes the inflammatory process occurring in the CNS (Sharma et al., 2019). The main components of the cerebral inflammatory response include the release of inflammatory factors like cytokines, microglial and astrocytic activation, edema, blood-brain barrier (BBB) disruption, and the recruitment of blood-derived leukocytes (Webster et al., 2017). The period after TBI in which secondary injury processes are initiated is critical in the development of epilepsy and research has shown that inflammatory molecules may mediate early seizures (Webster et al., 2017). Seizures, themselves, can also further increase the presence of inflammatory mediators by upregulating inflammatory genes (Webster et al., 2017). Chronic overexpression of pro-inflammatory molecules may alter neuronal networks and ultimately reduce seizure threshold (Webster et al., 2017). When examining the brain tissue of epileptic patients, researchers found elevated levels of pro-inflammatory cytokines and high mobility group box-1 (HMGB-1) protein in neurons and glia (Webster et al., 2017). When the infiltration of microglia and monocytes was inhibited, an electroconvulsive shock-induced seizure was reversed (Webster et al., 2017).

Neuroinflammatory Cytokines

The interleukin-1 (IL-1) family of cytokines, including IL-1ß, are important mediators of the neuroinflammatory response (Sharma et al., 2019). IL-1ß is known to be

involved in focal and diffuse brain injuries, as it regulates edema, leukocyte recruitment, the release of neurotoxic mediators promoting glial activation, and disruption of the BBB (Sharma et al., 2019). Both adult and pediatric patients suffering from severe TBI show an increase in IL-1ß, which is associated with worse outcomes (Webster et al., 2017). In rodent models of TBI, both interference with IL-1ß synthesis and the use of IL-1 receptor antagonists demonstrate neuroprotective qualities (Sharma et al., 2019). The use of an IL-1ß neutralizing antibody was also found to reduce some of the effects of TBI, such as cerebral edema, microglial activation, and cognitive deficits (Webster et al., 2017). Since interference with IL-1ß synthesis, IL-1ß neutralizing antibody, and IL-1 receptor antagonists showed similar results, it can be concluded that the IL-1 family of cytokines mediates some of the secondary injury processes following TBI (Webster et al., 2017).

Research has suggested ictogenic properties of IL-1ß, as elevated serum and CSF levels are associated with several epileptic conditions (Sharma et al., 2019). It is thought that IL-1ß may interfere with gamma-Aminobutyric acid (GABA)-mediated neurotransmission, inhibit glutamate uptake by astrocytes, and regulate neuronal excitability via α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors, which are involved in glutamate-mediated neurotransmission (Perron et al., 2001). In the specific case of PTE, antagonism of the IL-1 receptor in young TBI mice resulted in decreased susceptibility for provoked and unprovoked seizures, as well as decreased cortical tissue loss (Sharma et al., 2019). The same experimental model also showed that inhibition of IL-1ß synthesis resulted in reduced seizure activity, suggesting IL-1ß involvement in the initiation of post-traumatic seizures (Sharma et al., 2019).

Tumor necrosis factor-alpha (TNF-α), considered a pro-inflammatory cytokine, may also be involved in the development of PTE via pro- and anti-inflammatory mechanisms (Webster et al., 2017). While elevated TNF-α levels lead to leukocyte infiltration, neurodegeneration, and BBB damage, the absence of this cytokine or its receptor was associated with increased neurodegeneration, longer recovery time, and even mortality in mice (Sharma et al., 2019). This suggests that while TNF-α can increase CNS damage, it can also be neuroprotective in the later stages of the inflammatory response, occurring weeks after TBI (Webster et al., 2017). TNF-α also displays dual functionality in the context of seizures, being both pro- and anti-convulsive (Sharma et al., 2019). There is, however, a discrepancy in describing the role of TNF-α. Some studies concluded that elevated TNF-α levels resulted in shorter seizures, and lack of the TNF-α receptor led to longer seizures (Sharma et al., 2019). Other studies have shown the opposite: elevated TNF-α resulted in seizures and early death (Sharma et al., 2019). This contrasting evidence may be attributed to two different TNF-α receptors, TNF-α-R1 (p55) and TNF-α-R2 (p75) (Sharma et al., 2019). Research showed that mice lacking the p75 receptor had increased epileptic activity, while mice lacking the p55 receptor showed decreased epileptic activity (Sharma et al., 2019). Considering PTE specifically, the role of TNF-α has not been defined (Sharma et al., 2019).

Other cytokines and proteins worth mentioning in the context of PTE include IL-6, HMGB-1, and IL-10 (Sharma et al., 2019). IL-6 is expressed by many cells in the CNS, including astrocytes and microglia (Sharma et al., 2019). Similar to TNF-α, IL-6 appears to have a dual role in neuroinflammation (Sharma et al., 2019). IL-6 can enhance

the inflammatory response but can also inhibit the production of TNF-α, reduce NMDA toxicity, and promote neuronal differentiation and survival (Sharma et al., 2019). Of the inflammatory cytokines IL-6 often presents in the highest concentrations following TBI and is considered to be ictogenic, correlating with the severity of epileptic seizures (Sharma et al., 2019). Clinical findings have shown adults with tonic-clonic seizures had a corresponding increase in IL-6 and IL-1 receptors (Webster et al., 2017). HMGB-1 is a DNA-binding protein that serves as a damage-associated molecular pattern following tissue injury (Sharma et al., 2019). Suspected in neurodegeneration, edema, TBI, and epilepsy, HMGB-1 promotes the immune response and the release of pro-inflammatory compounds (Sharma et al., 2019). Experimental animal models showed that inhibition of HMGB-1 reduced the development of acquired epilepsies (Sharma et al., 2019). HMGB-1 may interact with NMDA receptors and IL-1ß to result in abnormal electrical activity (Sharma et al., 2019). The cytokine IL-10 is considered anti-inflammatory, as it inhibits the actions of many pro-inflammatory molecules, like IL-1ß and TNF-α (Sharma et al., 2019). Therefore, IL-10 can regulate processes like leukocyte infiltration and glial cell activation, thus preventing CNS damage (Sharma et al., 2019). Several animal studies have shown the anti-seizure effect of IL-10 in cases of hypoxia- and hyperthermia-induced seizures (Sharma et al., 2019).

While not explored in detail in this review, several other cytokines and proteins have been implicated concerning PTE, including but not limited to transforming growth factor-alpha (TGF-α), ciliary neurotrophic factor (CNTF), and leukemia inhibitory factor (LIF) (Pekny & Pekna, 2016). In addition, some cytokines, like TNF-α and IL-6, play a

dual role in neuroinflammation. Future studies should seek to identify the factors influencing the effects each cytokine may have.

Reactive Gliosis

Astrocytes are involved in maintaining homeostasis in the CNS (Pekny & Pekna, 2016). Astrocytes communicate with neurons and the endothelium to influence processes like the regulation of blood flow and BBB function (Pekny & Pekna, 2016). Additionally, astrocytes are involved in the formation and function of neuronal synapses (Pekny & Pekna, 2016). Protoplasmic astrocytes are found in gray matter and may regulate up to 2 million neuronal synapses (Pekny & Pekna, 2016). Astrocytes are connected via gap junctions and form an interconnected network, allowing communication between neighboring cells (Pekny & Pekna, 2016). During neurotrauma, including epilepsy, stroke, or neurodegenerative disease, astrocytes respond by a defensive process termed reactive gliosis (Pekny & Pekna, 2016). During injury, astrocytes respond to changes in gene expression resulting in alterations in astrocyte shape and function (Pekny & Pekna, 2016). The most severe form of reactive gliosis leads to the formation of a glial scar that is responsible for creating a seal around injured brain tissue, thus protecting the surrounding healthy tissue (Pekny & Pekna, 2016).

According to recent studies, the elimination of a population of reactive astrocytes can lead to increased neurodegeneration and BBB deficits, suggesting the neuroprotective effects of gliosis (Pekny & Pekna, 2016). Several cytokines, including transforming growth factor-alpha (TGF-α), ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), and IL-6, are thought to activate reactive gliosis (Pekny & Pekna, 2016).

While mediating tissue repair, astrocytes can sometimes over-produce cytokines and alter BBB and neuronal function (Webster et al., 2017). This may lead to an inflammatory response and a hyperexcited environment conducive to seizure development (Webster et al., 2017). In the case of spinal cord injury, inhibition of transcription of these cytokines results in inhibited astrocyte migration, increased migration of inflammatory cells into injured brain tissue, and larger lesions (Pekny & Pekna, 2016). On the other hand, allowing the transcription of cytokines, such as IL-6, resulted in increased astrocyte migration, smaller lesions, and better recovery following spinal cord injury (Pekny & Pekna, 2016). Importantly, these results relate to fibrous astrocytes in white matter and have not been tested in relation to protoplasmic astrocytes in gray matter (Pekny & Pekna, 2016).

The astrocyte intermediate filament proteins glial fibrillary acidic protein (GFAP) and vimentin (Vim) are both known to be involved in reactive gliosis and glial scar formation (Pekny & Pekna, 2016). GFAP and Vim are upregulated during reactive gliosis (Pekny & Pekna, 2016). When examined in mice, the elimination of both GFAP and Vim led to reduced gliosis and glial scar formation, which resulted in slower wound healing, increased loss of neuronal synapses, and lower resistance of the CNS to mechanical stress (Pekny & Pekna, 2016). These results demonstrate the important role of astrocytic intermediate filament proteins in limiting the effects of neurotrauma. It is also important to note that adolescent mice had lower levels of reactive gliosis following brain injury (Pekny & Pekna, 2016). Even in the absence of GFAP and Vim, when younger mice underwent hypoxic-ischemia normal size injury areas resulted (Pekny & Pekna, 2016). This not only suggests that reactive gliosis plays an important role in the developing brain

but also highlights the potential stark differences between adult and pediatric TBI (Pekny & Pekna, 2016). Lastly, the astrocytic intermediate filament network is connected to the efficiency of glutamate transport and astrocyte gap junctional communication, both of which have important implications in the development of epilepsy (Pekny & Pekna, 2016).

Diagnosis and Management of Traumatic Brain Injury

TBI can produce a combination of diffuse injury, focal injury, and various secondary processes (Thelin et al., 2019). Current diagnostic criteria involve clinical examination and evaluation using the Glasgow Coma Scale. In cases of mild TBI, like SRC, clinical diagnoses depend largely on self-reported information provided by the patient (Meier et al., 2020). With the subjectivity of current TBI diagnostic practices, more objective and universal diagnostic techniques are needed. Although there are objective criteria in place for PTE diagnosis, guidelines should be established to identify at-risk patients and prevent epilepsy development.

Biomarkers

Given the challenges and cost burden of screening for TBI and epilepsy, recent research has focused on the potential use of biomarkers as a means of diagnosis (Thelin et al., 2019). A biomarker is an objectively measurable indicator of a biological process (Liang et al., 2019). To be considered useful in the context of neurological processes, a biomarker must exhibit specific qualities, for example, it should be low or undetectable in serum, it should exist in the CNS, and it should be detected in brain injury (Liang et al., 2019). In relation to TBI, a successful biomarker should identify patients with injury,

predict the injury severity, and help determine which patients may need neuroimaging or further intervention (Thelin et al., 2019). In addition to initial TBI diagnosis and classification, biomarkers can also be used to monitor emerging secondary injury processes that may lead to long-term consequences, such as PTE (Thelin et al., 2019). Serum protein biomarkers associated with TBI include S100 calcium-binding protein B (S100B), GFAP, ubiquitin carboxy-terminal hydrolase 1 (UCH-L1), neurofilament light (NF-L), and tau (Thelin et al., 2019). All of these biomarkers were positively correlated with TBI severity (Thelin et al., 2019).

Biomarkers for epilepsy should identify the presence, development, severity, progression, or localization of abnormal electrical activity (Liang et al., 2019). Biomarkers are of great importance when considering patients with seizures that do not respond to typical anti-epileptic treatments (Liang et al., 2019). Various biomarkers have been suspected concerning PTE, including protein and genetic markers (Pitkänen et al., 2020). Since biomarkers associated with processes such as neuroinflammation, oxidative stress, and metabolic dysfunction, which may occur following TBI, potentially correlate with the development of epilepsy, research should further explore potential connections. (Liang et al., 2019).

TBI Biomarkers

The S100B protein is found in the CNS, melanocytes, chondrocytes, and adipocytes (Liang et al., 2019). It has many functions, including regulation of cell cycle progression, stimulation of cell proliferation and migration, and inhibition of apoptosis and differentiation (Liang et al., 2019). In the CNS, S100B is mainly of astrocytic origin and

is described as a robust predictor of outcome in TBI (Thelin et al., 2019). Elevated S100B in serum may be a sign of damaged neurons or glial cells or even the result of secondary brain injury (Shulte et al., 2014). Because of this, S100B is a part of the Scandinavian Neurotrauma Guidelines to reduce the number of unnecessary computed tomography (CT) scans in mild TBI patients (Thelin et al., 2019). S100B has also been implicated in the management of SRC, a mild form of TBI (Shulte et al., 2014). S100B increases in concentration following cerebral insult, but the protein usually remains in the CNS due to its size and lack of a transporter to cross the blood-brain barrier (Shulte et al., 2014). Studies have suggested that finding S100B in peripheral circulation indicates damage to the endothelial tight junctions of the BBB during mTBI (Shulte et al., 2014). It is also important to consider extracranial sources that contribute to peripheral increases in concentration (Shulte et al., 2014). Researchers reported significant increases in peripheral protein levels following competitive and vigorous physical activity without head injury (Shulte et al., 2014). Before this biomarker can be used, reference values must be determined, and the influence of extracranial sources evaluated (Shulte et al., 2014).

While using the S100B protein in TBI management is promising, GFAP may provide more accurate information (McCrea et al., 2020). GFAP is an astrocytic intermediate filament protein involved in the regulation of neuronal synapses and is often associated with increased intracranial pressure and axonal injury (Mahan et al., 2019). Upregulation of GFAP following cerebral insult, due to damage-induced hypertrophy in glial cells, is associated with TBI (Mahan et al., 2019). Additionally, GFAP-breakdown products identify the presence of traumatic lesions and characterize their severity (Mahan

et al., 2019). In cases of concussed athletes, serum GFAP concentrations were significantly increased during the acute post-injury period and 24-48 hours post-injury when compared to controls (McCrea et al., 2020). GFAP levels of concussed athletes who lost consciousness (LOC) and those who developed post-traumatic amnesia (PTA) were even further increased when compared to concussed athletes with no LOC or PTA (McCrea et al., 2020).

Through ubiquitination, the enzyme UCH-L1 maintains neuronal health by removing abnormal proteins and preventing secondary brain injury (McCrea et al., 2020). Studies report increased serum UCH-L1 in cases of TBI. (Mahan et al., 2019). When compared to control groups, athletes presenting with concussion had significant serum increases in UCH-L1 levels during the acute post-injury period (McCrea et al., 2020). By 24-48 hours post-injury, UCH-L1 levels were similar in the concussion and control groups (McCrea et al., 2020). In contrast to other protein biomarkers, UCH-L1 levels were significantly lower in concussed athletes at the asymptomatic time point (McCrea et al., 2020). The United States Food and Drug Administration approved both GFAP and UCH-L1 for clinical use in determining whether or not an intracranial injury is present (McCrea et al., 2020). If intracranial injury is predicted, future studies should aim to identify levels of GFAP and UCH-L1 that may correspond with neurological deficits.

Some of the other serum biomarkers indicated in TBI management are neuron-specific enolase (NSE), NF-L, and tau. Similar to UCH-L1, concussed athletes showed significant increases in tau during the acute post-injury period, while at 24-48 hours post-injury, levels were significantly lower than control groups (McCrea et al., 2020). While tau correlated strongly with TBI, NSE and NF-L correlated to a lesser extent (Thelin et

al., 2019). Notably, all biomarkers associated with TBI, except NF-L, decreased over time following injury (Thelin et al., 2019). Since NF-L levels continued to increase in the weeks after injury, this biomarker may be useful in evaluating TBI in later stages (Thelin et al., 2019). Additionally, the long-lasting effects of NF-L should be explored in relation to sequelae associated with TBI (Thelin et al., 2019).

PTE Biomarkers

Several protein biomarkers have been used to characterize patients with epilepsy in comparison to controls with convulsive seizures initiated by other events (Pitkänen et al., 2020). Examples of protein markers with this ability are soluble intercellular adhesion molecule 5 (sICAM-5), the IL-6 cytokine, and S100B, which distinguishes between patients with focal seizures and controls (Pitkänen et al., 2020). Studies also found that patients with epilepsy had significantly elevated serum levels of S100B (Liang et al., 2019). Additionally, an animal model demonstrated that an oral anti-epileptic reagent reduced glial cell proliferation and S100B proteins (Liang et al., 2019). This decrease in S100B correlated with reduced epileptic seizures (Liang et al., 2019). The proteins GFAP and UCH-L1 are associated with initial TBI severity, and both differentiated epileptic seizures from psychogenic nonepileptic seizures (Pitkänen et al., 2020). Complement components such as C3, C4, and C1 inhibitor also identify epileptic patients (Pitkänen et al., 2020). Proteins HMGB-1 and IL-1ß, both associated with TBI, predicted seizure frequency (Pitkänen et al., 2020). The tau protein is known to correlate to longer recovery following mild TBI, and studies have shown increased tau levels following seizures and status epilepticus (Pitkänen et al., 2020). This increase could be both indicative and predictive of underlying neurophysiological processes (Pitkänen et al., 2020).

Genetic biomarkers may offer insight into genetic mutations related to disease development and severity (Pitkänen et al., 2020). In TBI patients, genetic biomarkers may allow providers to identify patients with an increased risk for the development of PTE (Pitkänen et al., 2020). Early identification of these patients may lead to trials of antiepileptic agents, decreasing the occurrence of PTE in patients with known genetic variants (Pitkänen et al., 2020). Several potential genetic markers have been identified, including GAD1, SLC1A1, and SLC1A3 (Pitkänen et al., 2020). The GAD1 gene encodes the enzyme glutamic acid decarboxylase 1, which is responsible for the synthesis of the inhibitory neurotransmitter GABA (Pitkänen et al., 2020). Genetic variants in the GAD1 gene were associated with an increased risk of developing post-traumatic seizures (Pitkänen et al., 2020). The chief excitatory neurotransmitter is glutamate, and mutations in the glutamate transporter genes SLC1A1 and SLC1A3 were also associated with increased post-traumatic seizure risk (Pitkänen et al., 2020). Lastly, mutations in the IL-1 gene, coding for the cytokine IL-1ß, were also associated with an increased risk of PTE (Pitkänen et al., 2020).

Common serum biomarkers between TBI and PTE include GFAP, IL-1, HMGB-1, UCH-L1, tau, and S100B (Pitkänen et al., 2020). While each marker can be associated with the processes underlying TBI, more research is needed to establish relationships with epileptogenesis. Future studies should also aim to qualitatively and quantitatively characterize these biomarkers in relation to preventable TBI sequelae.

RESEARCH STRATEGIES

To complete this literature review, 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 AND DISCUSSION

During the coronavirus 2019 (COVID-19) pandemic, consideration should be given to the impact of the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) virus on TBI patients. Early research shows that the virus can enter the CNS, either via the ACE2 receptor on olfactory neurons or by infecting immune cells with the ACE2 receptor that eventually cross the BBB (Nikbakht et al., 2020). Once in the CNS, neurological symptoms, including epilepsy, may be mediated by the upregulation of pro-inflammatory cytokines by astrocytes and microglia (Nikbakht et al., 2020). Neuropathological changes in infected patients included microglial activation and astrogliosis (Lou et al., 2021). This provides further evidence for the connection between neuroinflammation and epileptogenesis. Given the increased risk of PTE under normal circumstances, TBI patients may be particularly vulnerable to neurologic dysfunction if infected with the COVID-19 virus. Further information is needed regarding the mechanisms of SARS-CoV-2-induced epilepsy, especially in TBI patients.

To conclude, there are many factors to consider when exploring the relationship between TBI and PTE. Diagnostic biomarkers may offer insight into secondary injury processes and provide a preventative advantage. The interplay of several neuropathophysiological processes and mediators may contribute to PTE development. Further research should seek to establish causal relationships and identify targets for therapeutic intervention. With most cases of PTE being resistant to existing treatments, it is vital to identify the processes and ways to prevent, manage, and treat PTE.

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