

Current Trends in Biomarkers for Traumatic Brain Injury

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Abstract

Neurotrauma, especially Traumatic Brain Injury (TBI) is a major health concern not only for the civilian population but also for the military personnel. Currently there are no precision and regenerative therapies available for the successful treatment of TBI patients. Hence, early detection and treatment options may prevent the severity and untoward harmful effects of TBI. However, currently there are no effective biomarkers available for the rapid and robust diagnosis as well as prognosis of TBI. Several biomarkers in blood, cerebrospinal fluid (CSF), saliva and urine have been explored to assess the onset, progression, severity and prognosis of TBI recently. Present knowledge on the blood biomarkers including cytokines and chemokines and in vivo imaging modalities are useful to some extent to detect and treat TBI patients. Here, we review S100B, Glial Fibrillary Acidic Protein (GFAP), Neuron Specific Enolase (NSE), Myelin Basic Protein (MBP), Ubiquitin C-terminal Hydrolase L1 (UCHL1), tau protein, and alpha II spectrin break down products regarding their usefulness as a set of reliable biomarkers for the robust diagnosis of TBI. We suggest that these biomarkers may prove very useful for the diagnosis and prognosis of TBI.

Keywords: Alpha II spectrin; Biomarkers; Glial Fibrillary Acidic protein; Myelin basic protein; Neuron specific enolase; S100B; Tau protein; Traumatic brain injury; Ubiquitin C-terminal hydrolyase L1

Abbreviations: TBI: Traumatic Brain Injury; CSF: Cerebrospinal Fluid; GFAP: Glial Fibrillary Acidic Protein; NSE: Neuron Specific Enolase; MBP: Myelin Basic Protein UCHL1: Ubiquitin C-terminal Hydrolase L1; WHO: World Health Organization; PTSD: Post-Traumatic Stress Disorder; DVVIC: Defense and Veterans Brain Injury Center; GCS: Glasgow Coma Scale; CT: Computed Tomography; ATP: Adenosine Triphosphate; NSE: Neuron Specific Enolase; MBP: Myelin Basic Protein;

Introduction

Traumatic Brain Injury (TBI) is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force (Brain Injury Association, Vienna, VA). TBI may either be closed (non-penetrating) or open (penetrating) type. TBI may result due to military-related and terrorist activities, motor accidents, sports injuries, falls, assaults, domestic violence etc. TBI is a major health concern in today's world and is predicted to be the third leading cause of mortality and morbidity globally by the year 2020 according to the World Health Organization (WHO) [1-3]. In the military as well as in the civilian population, TBI is one of the most common injuries [4]. TBI is the leading cause of long-term disability and a significant cause of death worldwide. TBI constitutes approximately 2.4 million emergency department

visits annually in the United States, many of which result in hospitalizations and subsequent deaths (Centers for Disease Control and Prevention). In the United States, approximately 1.7 million people are diagnosed with TBI each year, creating an economic burden exceeding \$56 billion. Approximately 5.3 million Americans are currently living with TBI. On the combat field, TBI from explosive blast exposure is a significant challenge for our troops. TBI is also a major health hazard and a potential risk factor for Post-Traumatic Stress Disorder (PTSD) and chronic neurodegenerative diseases. As per the Defense and Veterans Brain Injury Center (DVVIC), more than 383,947 military personnel have been diagnosed with TBI since 2000. Furthermore, the reports emanating from the Department of Defense (DoD) and the Department of Veteran's Affairs (VA), suggest that nearly 82.3%

of the TBI cases are due to mild concussion and invisible injuries. Additionally, 56,695 veterans of Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF) enrolled with the VA have been evaluated or treated for conditions possibly related to TBI.

The categorization of TBI according to severity makes use of the Glasgow Coma Scale (GCS) score [5,6]. Although GCS remains a key and vital assessment tool to determine the plan of action in these patients, overestimation or underestimation of this score can occur due to confounding factors such as circadian rhythmicity, sedation, analgesia, drug intoxication and poor cooperation of the patient [7-9]. A pivotal intervention done in the early stages of TBI includes neuroimaging studies which are used in all hospitals as an initial diagnostic measure as well as repeatedly later on during the course of admittance to measure the progression of damage [10,11]. One of the most commonly used neuroimaging modalities - Computed Tomography (CT) scan is preferred more than others keeping in mind the cost, availability and the technical superiority it offers. There have been reports that have concluded the overuse of CT scans in the emergency department and up to one third of scans could be eliminated [12]. Repeated scans in patients with lack of neurological changes have negligible additive value in the management of patients with mild to moderate TBI [13-17]. Keeping these attributes in mind, the demand of a rapid, accurate, inexpensive and reproducible biomarker has risen which can help in determining the severity and progression of TBI. Such an entity can also help in predicting the outcome and help in planning therapeutic interventions according to the timeline of the injury.

Defined in 2001 by the Biomarkers Definition Working Group [National Institutes of Health (NIH)] as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention; an ideal biomarker should have the following characteristics: high sensitivity and specificity, reproducibility, inexpensive and non-invasive. To date there is no biomarker which satisfies all the above-mentioned criteria. This review paper aims to summarize the different biomarkers which have been assessed in the past and their potential usefulness in the long term.

Pathogenesis of TBI

TBI can be mild, moderate or severe. Mild TBI (mTBI) can occur due to an impact on the head which can induce rotational acceleration of the brain. At times, there is no impact to the head, for example, in a motor vehicle crash that causes a rapid rotational acceleration of the head in a restrained occupant. mTBI usually does not produce any gross changes in the brain but instead can produce a rapid neurophysiological or neurological dysfunction that mostly resolves in a short span of time. In 15% of the patients, persistent cognitive dysfunction can occur [18-

20]. The mechanisms of TBI consist of two different injuries. The primary injury is the consequence occurring immediately after the injury and the secondary injury includes the body's attempt to limit and repair the consequences and restore the functional and structural integrity [21,22]. The primary case of events causes necrosis, tissue deformation and shearing of the neurons, axons and glial cells [23]. It also causes excitotoxicity, oxidative damage and cerebrovascular derangements. There is also a decrease in the mitochondrial respiratory capacity, lysosomal damage, activation of the mechanisms involved in apoptosis and non-apoptotic delayed cell death, a triggered cascade of inflammatory and protein degradation events [24,25]. Also, disruption of the Blood Brain Barrier (BBB) after the initial injury can occur which increases the permeability within a few hours [26,27]. The initial injury eventually produces a loss of cerebral vascular autoregulation, an imbalance of the cerebral blood flow and metabolism. Ultimately, there is a lack of cerebral oxygen and ischemia which can lead to the mitochondrial dysfunction, increase in lactate levels, intramitochondrial Ca^{2+} ions, and a lower production of Adenosine Triphosphate (ATP) which leads to the failure of maintenance of ATP-dependent ion pumps and slow glutamate uptake [28]. The secondary cascade is initiated by glutamate which is released by the injured nerve cells and causes edema, pro-inflammatory cytokine release and ischemia [23,29]. Overall, many metabolic changes occur after a person suffers TBI which can include changes in the metabolism of amino acids, carbohydrates, and lipids hence affecting the functioning of the brain and other organs [30]. All of the above processes eventually lead to many clinical symptoms which can range from motor deficits to debilitating neurocognitive and personality changes [31]. Here, we discuss the role of S100B, Glial Fibrillary Acidic Protein (GFAP), Neuron Specific Enolase (NSE), Myelin Basic Protein (MBP), Ubiquitin C-terminal Hydrolase L1 (UCHL1), tau protein, and alpha II spectrin break down products in the pathogenesis of TBI.

S100 Calcium-binding protein B (S100B)

S100 protein was first identified in 1965 and its three subtypes (two related homodimeric and one heterodimeric) were identified later. These three proteins include S100A1 (two alpha subunits), S100B (two beta subunits) and the third S100 consists of both $\alpha\beta$ subunits. These three types have similar profiles of being released into the serum post traumatic brain injury [32-35]. S100B is a low affinity calcium-binding protein expressed in glial and Schwann cells that regulates intracellular calcium levels [32,36,37]. It is released during an astroglial injury and becomes elevated in the Cerebrospinal Fluid (CSF) and serum and has a good predictive power for prognosis. Apart from being found in astrocytes, S100B is also found in adipocytes, chondrocytes and in trauma patients without any head injuries [38-40]. It has been

shown to correlate with the GCS score and neuroradiological findings at the time of hospital admissions [41-44]. A high level of S100B during the initial TBI can predict a poor outcome, especially if it is accompanied by a second increase in levels of serum S100B that occurs during the subacute phase [45-46]. This second peak can be due to an ongoing damage to the astroglial cells exhibiting excitotoxicity and inflammation, while an initial lower level and the lack of second peak and other clinical measures suggest a mTBI and a good functional recovery [47,48]. The levels may also increase due to the BBB dysfunction [49]. Studies have shown that S100B can differentiate between mild and severe TBI [50,51].

Other studies have concluded a relationship between S100B levels and the outcome of TBI [41,43,44,50-54]. The serum levels of S100B have been used experimentally to rule out mTBI in the emergency room. In a clinical study of 1,560 patients with minor head injury, initial blood S100B levels had a high negative predictive value of 99.7% and therefore has a potential to be used as a screening tool to rule out mTBI [55]. Moreover, the utility of serum S100B levels is limited in mTBI or concussion which can be due to its low specificity and extracranial sources of S100B, for example; in muscle injury the moderate levels can rise and give a false positive lab test in mTBI [47,48,56]. In the Scandinavian literature, there has been a study demonstrating the sensitivity of S100B to predict significant intracranial pathology up to 100% but with specificity of only 28% [57]. Also, it is important to note that S100B lacks specificity in patients with hemorrhagic shock or circulatory arrest therefore making it an impractical screening tool for brain injury in the neuro intensive care unit [58,59]. Moreover, in children under the age of 2 years, S100B is not a useful marker due to high normal levels in this group [60,61]. Even though, S100B has been studied thoroughly and was included into the Scandinavian Neurotrauma Committee guidelines, its relative limited specificity can cause the overuse of imaging studies in brain trauma [62]. Overall, S100B is a factor that can be used as an adjuvant marker in a patient with TBI, but its diagnostic utility is not clear and still controversial.

Glial fibrillary acidic protein (GFAP)

GFAP is a monomeric intermediate filament protein which is present in the cytoskeleton of astrocytes in the brain [63]. It is also expressed by the Leydig cells of the testes [64]. After TBI, the concentration of this biomarker is increased in the CSF and serum [65,66]. This biomarker is more specific to the brain and its concentration is less likely to increase during trauma to other parts of the body [67]. A prospective study done in which GFAP in serum was measured in patients with severe head injury concluded that the levels were not elevated in those patients with multiple trauma that did not have TBI [68]. After a mTBI, serum levels of GFAP breakdown products (GFAP-BDP)

increase within an hour and correlate with the GCS ratings, CT lesions and neurosurgical interventions [69]. The increase of this biomarker suggests injury to the astrocytes and the BBB. It has a good sensitivity and specificity for TBI however, it is not a good predictor for return to work and Glasgow outcome score; which are used to assess the long-term outcome [69,70]. A study on patients with mTBI and abnormal findings on CT and MRI of the brain showed an elevated level of serum GFAP. However, the levels of this biomarker did not predict the patient's outcomes at 6 months after a TBI [70]. Another study demonstrated that serum GFAP levels show an unfavorable outcome in patients with moderate or severe TBI, however, in patients with mTBI this may not be the case due to the non-brain contamination playing a greater role in GFAP levels [71]. A study showed that the levels of serum GFAP did not differentiate mTBI patients with a negative CT scan from patients who had acute orthopedic trauma [72]. This could be due to the expression of GFAP outside the Central Nervous System (CNS) [73,74]. The levels of GFAP in the CNS have been suggested to improve TBI outcome prediction and may serve as an intracranial injury marker [75,76]. When compared to S100B, GFAP has been reported to have a higher diagnostic accuracy with an excellent accuracy in differentiating mTBI patients from non-TBI controls and it outperforms S100B and UCH-L1 as a predictor for positive computed tomography of the head in trauma subjects [77-79]. Even though, there is an advantage of GFAP over S100B and UCH-L1, the best biomarker still remains yet to be identified.

Neuron specific enolase (NSE)

NSE is a glycolytic enzyme which is released due to acute neuronal damage in the brain. It is known to have a high specificity to the brain but its accuracy to predict a brain injury is limited due to its release in the serum during hemolysis. For this very reason, it lacks specificity and sensitivity. The serum levels of NSE one-month post mTBI did not correlate with outcome as reflected by the Glasgow outcome scale [80-85]. This biomarker was initially identified in the serum and CSF of patients with head trauma and those in a state of coma, and its levels in CSF were proportional to the severity of TBI and were associated with an increased mortality rate in cases of moderate or severe TBI [84-86]. NSE is also present in erythrocytes and endocrine cells and therefore, in vitro lysis of erythrocytes from blood contamination in CSF samples can raise NSE levels which can be a confounder. The studies on CSF NSE levels in patients who have mTBI are lacking [32, 86]. A study done in boxers following a bout demonstrated that their serum levels of NSE were raised and persisted for two months [87].

Myelin basic protein (MBP)

MBP a component of oligodendrocytes happens to be the second abundant CNS proteins found in myelin sheath of neurons.

It is released into the blood due to axonal damage and has high brain specificity but a delayed release into the blood (24-72 h post-injury) which makes it temporally unfavorable. Elevated levels of MBP in the serum can also be related to a poor outcome [80, 88, 89]. MBP levels may be more specific for TBI than NSE levels (specificity 96% versus 64%, respectively); however, its sensitivity is suboptimal (44% for MBP versus 71% for NSE) [89]. There was no difference in initial levels of serum MBP in a pediatric population with mTBI when compared with controls, but there was a significant difference in the peak MBP levels between patients and controls [89]. Studies have shown a positive relationship between the severity of injury and MBP serum levels [90-92]. MBP is also expressed on the myelin of peripheral nerves and its transcripts are present in the bone marrow and immune system and therefore it is not specific to the CNS because in severe TBI peripheral nerves are almost always involved [93]. Therefore, we conclude that the predictive and diagnostic value of this biomarker level in TBI is limited. Even though, it takes around a day or two to appear in the serum, once elevated the peak levels of MBP can persist for up to two weeks and can be a specific indicator for future intracranial hemorrhage, which can occur after a TBI [90]. Also, a persistent elevated level after mTBI can suggest that this biomarker can be used as a screening tool for the pediatric population. This can be especially useful if the child cannot communicate the symptoms or the event that lead to the symptoms. Overall, not many studies on MBP are currently available but future studies may find a role of this biomarker in mTBI [92].

Ubiquitin C-terminal hydrolase L1 (UCHL1)

UCHL1 has been used as a histological marker for neurons because of its high abundance and expression in these cells. It is known to be involved in the addition or removal of ubiquitin from proteins that have to be metabolized. This makes it a pivotal protein in the removal of excess proteins in normal as well as neuropathological conditions [93]. Studies have demonstrated that UCHL1 levels were increased significantly in patients with TBI as compared to controls after the first 24 hours. A significant association was also found between UCHL1 levels and measures used to assess severity of TBI including GCS, evaluation of lesions on CT scans and 6-week mortality of patients with TBI. This study also reported that UCHL1 levels were significantly higher in patients with unfavorable outcomes 4 days and 8 days post TBI [94]. Yet another study reported that the maximum levels of UCHL1 during the first 7 days predicted the 3-month mortality independently while also being an independent predictor of hospital mortality [95,96]. UCHL1 and GFAP together have been reported to predict mortality at 6 months post TBI [96]. However, UCHL1 has been poor in predicting complete recovery but has been fairly predictive of unfavorable outcomes [97]. UCHL1 alone is unable to predict the outcome at 6 months although

adding other suitable biomarkers in combination with UCHL1 can strengthen its predictive value [75]. A pediatric study in 2011 reported significant differences in the levels of UCHL1 between controls and patients with severe or moderate TBI. There was a significant negative partial correlation between UCHL1 levels and GCS score while no relationship was established between concentrations of UCHL1 and clinical symptoms or abnormalities in head CT. This study also reported higher concentrations of UCHL1 in patients with worse outcomes [75]. A study aimed to discover if biomarkers such as UCHL1, GFAP and S100B were able to differentiate between normal and abnormal CT head findings in patients with mild and moderate TBI concluded that UCHL1 had a sensitivity of 100% and a specificity of 39% at a cut off value of >40pg/ml and it outperformed GFAP and S100B in reducing the use of CT head scan without any compromise in sensitivity [98]. Patients with full recovery had lower UCHL1 levels during the first two days post TBI when compared to patients with incomplete recovery or poor prognosis. A strong negative correlation was observed between outcome and UCHL1 levels during the first 3 days.

Tau Protein

Tau is a member of Microtubule Associated Protein (MAP) expressed predominantly in neurons and astrocytes. The key function of tau includes the stabilization of microtubule and the coordinated movement of molecules along the microtubule that are regulated by its phosphorylation [99,100]. Normally present in a stable, unfolded and monomeric morphology, tau exists in hyperphosphorylated state in several neurodegenerative diseases including Alzheimer's Disease (AD) which are collectively referred to as tauopathies [99,100]. TBI has also been associated with an increased risk of developing neurodegenerative diseases such as AD later in life [101-103]. Furthermore, prior TBI is associated with an earlier disease onset when compared to patients without prior TBI suggesting that TBI plays a pivotal role in acceleration of AD pathology [104-107]. This relationship of TBI and tau is further strengthened by various studies including a postmortem study that revealed diffuse tau pathology in patients many years after a TBI [35]. Studies on animal models concluded that TBI resulted in accumulation of hyper phosphorylated protein (p-tau) as well as neurodegeneration and progressive brain atrophy [102,108,109]. Keeping this evidence in mind, tau pathology is considered to be one of the key mechanisms of neurodegeneration related to TBI [103]. Further studies on the brains from boxers, US football players and blast exposed military veterans with Chronic Traumatic Encephalopathy (CTE) have reported the presence of intracellular Neurofibrillary Tangles (NFTs) as a common neuropathological denominator [102,110-114]. Rodent models mimicking TBI showed increased levels of tau and p-tau pre-tangle conformations with white matter degradation and increased neuroinflammation 2-3 months after injury [103].

Alpha II spectrin break down products

Alpha II spectrin is a cytoskeletal protein which is a substrate for caspase-3 and calpain which are calcium activated cysteine proteases. It plays a key role in neuronal development, synaptic plasticity and cytoskeletal remodeling [115]. The breakdown of alpha II spectrin by these enzymes leads to formation of breakdown products which include SBDP 145, SBDP 150 and SBDP 120. SBDP 145 which is 145 kDa protein formed after the cleavage is a marker of necrotic cell death activation process [116,117]. SBDP 145 levels have been reported to be increased after severe TBI in the adult population [118-122]. Studies have also shown SBDP 145 to be elevated in pediatric population with TBI [99]. Furthermore, increased levels of calpain and calcium have been reported to correlate with the magnitude of brain injury in animal models [123,124]. SBDP levels in CSF have also been reported to remain elevated for 5-7 days after penetrating TBI as compared to controls suggesting that the increase may surpass the initial time frame of injury as well [121]. SBDP 120 was found to be increased in the first few hours post TBI and is known to last for a few days [125,126] while the SBDP 145 and SBDP 150 types occur in the first few days and last for about 7 to 14 days [116,126-128].

Conclusion

We conclude that proteins S100B, GFAP, NSE, MBP, UCHL1, tau protein, and alpha alpha II spectrin break down products may be useful as an adjuvant biomarker in the diagnosis and prognosis of TBI.

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