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Biomarkers in Traumatic Brain Injuries: Narrative Review

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Abstract

Traumatic brain injury (TBI) is a multistep interaction of brain antigens, cytokine-mediated humeral, and cellular immune reactions. Because of the limitations of clinical and radiological evaluation in TBI, there has been a considerable advancement toward the need for developing biomarkers that can predict the severity of TBI. Blood-based brain biomarkers hold the potential to predict the absence of intracranial injury and thus decrease unnecessary brain computed tomographic scanning. Various biomarkers have been studied that detects neuronal, axonal, and blood–brain barrier integrity. Biomarkers are still under investigation and hold promise in the future evaluation of TBI patients. They can be used for grading as well as a prognostication of head injury.

Keywords

- traumatic brain injury
- biomarkers
- UCHL-1
- GFAP
- inflammatory markers

Introduction

Traumatic brain injury (TBI) is a slow epidemic in India as well as in the world. About 25% of global deaths due to TBI occur in India. It is one of the major causes of morbidity and mortality in India. High-quality research is lacking and is the need of the hour. The increased incidence of TBI in a productive population is of serious concern.[1] The Glasgow coma scale (GCS) has been used to assess severity of TBI. This is purely clinical and does not give any information about the underlying pathology. Computed tomographic (CT) scan is used to diagnose TBI for immediate evaluation but does not correlate with long-term outcomes particularly in mild head injury.[2] Biomarkers are used for diagnosis, risk stratification, and predicting outcomes in TBI patients.[3] The TBI results in neurologic, neuropsychological, or behavioral changes caused by mechanical trauma.[4] The entire spectrum of sequelae of TBI cannot be predicted by GCS and CT scan alone; hence, there is need of addition of serum biomarkers for the evaluation of TBI.[5–9]

Biomarkers in TBI

Improvement in scientific advances and knowledge of TBI biomarkers has improved our understanding of complicated pathological processes related to TBI. Various drugs in animal experiments are neuroprotective but similar results in humans are not satisfactory.[10–13] Failure in clinical trials is due to a lack of temporal measurement of biomarkers and heterogeneous pathophysiological processes involving TBI. It is a combination of an acute and chronic event resulting in a progressive delayed degenerative process involving reactions at the cellular level. As the axons are lengthy, they are particularly susceptible to direct trauma to the brain.[14,15] Hence, a thorough understanding of these processes in greater detail is important for further research and knowledge for therapeutic intervention.

TBI Biomarker Requirement

For a serum biomarker to be useful, it should have the following characteristics:

1. It should be easily measured in serum /plasma or cerebrospinal fluid (CSF),
2. Their levels must change in TBI patients after an injury as compared with the normal population,
3. It should have some baseline level in the control population,

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4. It should be derived from the brain as the main source,
5. Their levels can be easily quantified by using sandwich enzyme-linked immunosorbent assay or similar assays.
6. Their levels should be able to classify the severity of TBI, should correlate with CT and GCS findings.[16]

There are currently two hypotheses as to how the brain proteins reach the peripheral circulation: first is damage to blood–brain barrier (BBB), and second is following the bulk movement of fluids through central nervous system (CNS) that may clear the proteins from the central to a peripheral system called as glymphatic system.[17] These biomarkers can be classified as below:

1. Inflammatory markers like interleukin-1β (IL-1β), IL-10, and tumor necrosis factor-α (TNF-α).
2. Markers of astrocyte activation: glial fibrillary acidic protein (GFAP), S100β.
3. Markers of neuronal injury: myelin basic protein (MBP), neuron-specific enolase (NSE), ubiquitin carboxy-terminal hydrolase-l (UCHL-1).

(a) Interleukin-1β

IL-1 is an important mediator of inflammation in the CNS as well in the peripheral nervous system. These molecules of the IL1 family are the widely studied cytokines about TBI in different models of focal and diffuse injury.[18–21] The most commonly studied isoform in TBI is the IL-1β. The mature human IL-1β is 17.5 kDa.

IL-1β is the main endogenous mediator of multiple hosts. Response to injuries like fever, alterations of neuroendocrine, immune, and cardiovascular systems affect IL-1 levels. IL-1β induces various responses such as alteration of BBB, migration of inflammatory cells, the release of membrane arachidonic acid metabolites, free radicle generation, and complement-mediated damage.[22]

Clinical Evidence

IL-1β is normally absent in the blood–cerebrospinal fluid of healthy individuals. Its detection in patients with TBI has been difficult.[23–25] The studies that correlated the levels of IL-1β with the outcome have found that serum levels of IL-1β taken within 6 hours of TBI correlated well with TBI severity in a cohort of 48 patients.[26] In recent studies of severe TBI, patient's increase in CSF levels of IL-1β has been linked with worse outcomes.[27,28]

(b) Tumor Necrosis Factor-α

TNF-α is another prime chemokine involved in initiating and upregulating the inflammatory response and other cytokine production. It is a 17-kDa active cytokine derived from a 26 codon precursor molecule after being cleaved by the converting enzyme.[29] Normally this cytokine is not expressed in a healthy brain. Because of this fact, its role in physiological conditions is not understood. But in a state of inflammation or disease, it is produced in abundance along with other inflammatory cytokines by activated microglia.[30]

Laboratory Evidence

Results from previous studies on injured rat brain show that mRNA of TNF-α can be identified before the cytokine production and this upregulation precedes the leukocyte infiltration itself.[31,32] This is suggesting that it is produced in the initial stages of injury by the brain cells as a response to trauma.

Clinical Evidence

It has been proven that the serum and CSF levels of patients with TBI at 24h intervals are significantly elevated as compared with controls. It was found in patients that died within 17 minutes of trauma, they had increased TNF-α mRNA and proteins.[33] Hayakata et al have investigated CSF of 23 patients with GCS <8, and they have noted a peak of 20 to 30pg/mL within 24 hours. No significant correlation is seen with TNF-α levels and intracranial pressure (ICP) or Glasgow outcome scale (GOS) outcomes after 6 months.[27] In a recent study by Stein et.al, the blood and CSF samples of 24 patients with severe grades of TBI at 12 hours intervals for 7 days have been investigated. They have also monitored the ICP and cerebral perfusion pressure (CPP) in the same patients. Their study has shown a correlation with serum levels of TNF-α and subsequent change in ICP or CPP, but not associated with any prediction for the outcome.[34]

(c) Interleukin-10

It is a chemokine with a weighing around 40 kDa. IL-10 is synthesized in the brain by the microglia and astrocytes. In the periphery, it is mainly generated by the lymphopoietic cells.[35–37] It is a main anti-inflammatory cytokine and considered to be neuroprotective.

Laboratory Evidence

There is limited information from animal studies on the expression profiles of IL-10 following TBI. Knoblauch and Faden have documented an increase IL-10 level in animal models of TBI during the first 4 hours postinjury, and it is observed to persist for at least 20 hours. It has been noted that decreased levels of IL-1β and TNF-α are seen in rats when given IL-10.[38]

Clinical Evidence

Csuka et al have measured IL-10 in serum and CSF of 28 patients with GCS <8. They have found increased levels in CSF and serum. In CSF, it ranged from 1.3 to 41.7pg/mL and in serum, the levels ranged from 5.4 to 23pg/mL. The temporal variation has been such that there was an early rise followed by a slow decline. This is noted both in CSF and serum. The BBB function was also assessed using the CSF/serum albumin ratio and then correlated with the IL-10 levels. But they did not find a significant correlation.[39] When considering outcome after 6 months, it is reported that the IL-10 levels have been higher in patients with poor outcome (GOS < 4).

The IL-10 levels alterations in polytrauma patients could be the reason for the poor association between IL-10 and grades of TBI.[28,40]

Though there are contrary reports on IL-10 in TBI, it is established that it reduces neuroinflammation centrally and causes peripheral immune-suppression. This plays a role especially in secondary brain injury by increasing the chances of infection.[24]

(d) S-100β

S-100β is the most commonly studied biomarker in TBI. S-100 family has a low molecular weight of 10.5 kDa; it regulates intracellular calcium levels. It is synthesized mainly by astrocytes microglia, oligodendrocytes, and neurons.[41,42] Their effect seems to be dependent on their levels in serum, regardless of its spatial distribution. It is toxic at higher concentrations and protective at minimal concentrations in healthy subjects. S-100β is nonspecific to the brain, as it is secreted in extra-CNS areas such as adipose tissue, cartilage cells, cardiac cells, and pulmonary alveolar cells.[43] Variations in levels of S-100β have been seen in conditions such as heart failure, musculoskeletal damage, fractures, and obesity.[44] Low serum levels of 0.05 ng/mL are noted in healthy humans; also levels are not affected by gender or age of patients.[41] Increased S-100β is expressed by astrocytes and considered as a marker for impaired BBB, and an increased level of S-100β corresponds to BBB damage.[45]

In a recent study, it was shown that increased CSF/ serum albumin suggests disruption of BBB; also increased concentrations of S-100β predicted the severity of TBI subjects.[46] Another author studied 14 TBI patients posttrauma with magnetic resonance imaging and single photon emission computed tomography for BBB disruption; data showed well correlation with the severity of BBB damage; however, it did not show a positive correlation of serum S-100β levels.[47]

S-100β levels of nearly 5ng/mL are seen after TBI. Higher levels are useful in predicting outcomes after 3 to 6 months of injury. Values between 2.0 and 2.5ng/mL were considered predictive for worse outcomes.[48]

In a recent study, it was observed that S-100β did not increase after patients were subjected to exercise, which may suggest that serum levels may be more specific to mild TBI (mTBI)/concussion. In another study, serum levels of S-100β with effects of soccer ball heading at a particular speed were assessed. It was seen that levels of S-100β showed no differences in irrespective of the speed of the soccer ball.[49] One of the studies measured S-100β levels in three groups, only head injury, head injury with other trauma, and those with trauma other than a head injury, it was noted that blood levels were more in subjects with polytrauma with a head injury, which suggests extra CNS source of S-100β.[50] Some studies did not find an association between blood levels of S-100 β and the amount of adipose tissue. Also, S-100β levels do not change in various diseases such as epilepsy, bladder, lung liver, and renal cancers, which further support that the levels may correlate with brain injury. The half-life of S-100β is 97minutes; hence, temporal measurement may be used to identify various grades of TBI and predict outcomes.[51,52]

(e) Glial Fibrillary Acidic Protein

Astrocytes are the major source of GFAP that is one of the important structural proteins of cytoskeletal-intermediate filaments. There are 10 GFAP isoforms identified till now. GFAP-α is produced by astrocytes, while GFAP-β is produced by Schwann cells in peripheral nerves; GFAP-γ is seen in the reticuloendothelial system such as spleen and bone marrow.[53] GFAP maintains the integrity of the astrocytes cytoskeleton in response to injury.[54] After trauma and astrocyte activation, there is increased migration of GFAP to extracellular space and levels correlate well with TBI severity.[55,56] In normal healthy subjects, levels of GFAP are below the detection limit of 0.012ng/mL, while certain studies have not shown any detectable levels.[57] Interestingly, in one of the study, it was analyzed that GFAP levels are increased more in diffuse axonal injury than local injury.[58] These findings were similar to another study which showed that patient with focal injury had higher levels when compared with diffuse injury, but when diffuse axial injury (DAI) was further divided in to mild, moderate, and severe, GFAP levels were higher in moderate and severe types of injury, thus limiting its usefulness in distinguishing the type of injuries.[59]

Recent studies have shown that GFAP levels are increased in mTBI patients with abnormal radiological findings compared with those with normal scans.[60]

(f) Neuron Specific Enolase (NSE)

Enolase is an important enzyme in the glycolytic pathway for ATP production.[61] This enzyme is a protein in the cytoplasm and is expressed depending upon the energy requirement in a neuron. The levels may be increased in injured axons for homeostasis. In postmortem examination, NSE is specific for DAI patients with injured axons in the corpus callosum and is not seen in control groups.[62]

NSE has mainly produced by neurons in normal patients and baseline levels are present in red blood cells (10ng/mL).[63] Raised levels are seen in stroke, cerebral hemorrhage, and TBI.[64] Many studies have shown that the level of NSE correlates well with moderate and severe TBI and its outcome after 6 months.[65,66] In one of the pediatric TBI studies, it was shown that serum NSE levels were able to predict poor outcome. Also, the levels in moderate and severe TBI correlate well with a neurological examination.[67]

In a recent study involving ice hockey players with GCS of 14–15, there was no significant difference in blood levels of NSE in patients as compared with preinjury status; thus, it can be concluded that NSE assays may be not specific in detecting altered levels of NSE after mild injury. Raised NSE levels have been reported in abdominal injuries, migraine, and femur fracture patients, making it less specific for TBI.[58] In one of the studies with boxers, serum levels of NSE were in a higher range following 2 months of rest as compared with the nonboxers group that suggests impaired neuronal

recovery. Persistent levels of raised NSE even after its half-life of 24 to 48 hours could suggest repeat TBI.[68]

(g) Myelin Basic Protein

MBP is one of the most abundant proteins in the CNS and is produced by oligodendrocytes. In one study involving the pediatric population, the levels of MBP did not differ significantly when compared with mTBI patients with, but the peak MBP levels differed significantly in both groups. MBP in the blood is absent in the initial 48 to 72 hours of trauma making it unreliable as a screening tool. Once elevated the levels of MBP persisted beyond 14 days and helped to predict future cerebral bleed after injury. Increased MBP levels following mild injury are promising and can be used to screen pediatric populations for mTBI, who are unable to tell symptoms of TBI-related events.[69] Many studies have shown that MBP is released in CSF spaces and then into peripheral circulation following acute neuronal damage in stroke and multiple sclerosis. In one of the studies, it was seen that serum MBP levels correlated well with severe TBI patients.[70] In one of the studies it was shown that in postmortem examination of the brain of blunt head injury patients, MBP was detected in 17 out of 22 patients.[71]

(h) Ubiquitin Carboxy Hydrolase-1

UCHL-1 is a 24 kDa enzyme with protease activity and constitutes 10% of neuronal proteins and is used as a histological marker for neurons. UCHL-1 could be detected in the blood and CSF with a t1/2 of 7 to 9 hours after severe TBI.[72] It has an special role in the ATP-dependent proteasome pathway for the elimination and the ubiquitination of proteins destined for this pathway and removes the oxidized and misfolded proteins. The UCHL-1 can be used for the detection of neuronal injury. But it is not CNS specific as it is produced in extra CNS sites such as endocrine cells, endothelial cells, aortic endothelium, muscle, and tumors cells. Despite its presence in other tissues, UCHL-1 is highly expressed in CSF and serum. Due to the abundance of this biomarker in neuronal tissue and CSF, it was used as a histological marker to discriminate patients with TBI from patients without traumatic injury to the head. It is reported that patients, who suffer from head injuries with a consequent intracranial lesion, had higher levels within the first 4 hours, and the levels are higher in patients who required surgical management. It demonstrated that UCHL-1 has an association with injury severity and in-hospital prognosis of mortality and clinical outcome. It is a good biomarker for diagnosing TBI and intracranial lesions, and it can differentiate injured TBI from noninjured TBI patients when GCS is altered by any substance due to unclear cause. TBI patients had significantly elevated serum and CSF levels of UCHL-1 after injury compared with control patients after injury. As expected, CSF values of UCHL-1 were substantially higher and more sustained than levels of UCHL-1 in serum. The mechanism by which UCHL-1 is transported from the brain compartment into the circulation is unknown. Mondella et al evaluated the exposure and biokinetic parameters of UCHL-1 in CSF and serum. They found a statistically significant increase in the median amount and peak concentration of UCHL-1 in serum, and a shorter time to peak concentration in survivors compared with nonsurvivors.[73]

Recently, Puvenna et al researched subconcussive head injury in 15 American football players. Serum samples were collected before and after every two different games. No significant differences were observed between the levels of UCHL-1 between controls and positive individuals for mild injury within 6 hours regardless of CT brain findings.[45]

Also, there was no correlation between the levels of UCHL-1 and the number of impacts received. After each game, the levels of S 100β and UCHL-1, markers of BBB disruption, and neuronal injury, respectively, both were elevated. Only S-100β, unlike UCHL-1, was correlated with the number of hits received and the UCHL-1 elevation did not correlate with the increase in S-100β levels. Hence, it was suggested that elevated levels of UCHL-1 may be due to the release of this protein from the neuromuscular junction .

Panel of Biomarkers

Various novel brain proteins have been identified that potentially identify complicated mTBI. UCHL-1 and GFAP have emerged as promising biomarkers for use in clinical practice.[74] Initial evidence suggests that both proteins are predictors of CT-scan positive patients, but were limited by retrospective study, the small size of the cohort, and variability in the timing of serum sampling. All of these probably biased the estimate of diagnostic accuracy.

In a recent ALERT-TBI trial, validation of a biomarker test combining UCHL-1 and GFAP to predict CT-positive patients within 12 hours of TBI was studied. Results showed the high sensitivity and negative predictive value of the UCHL-1 and GFAP test. This supports its potential clinical role for ruling out the need for a CT scan among patients with TBI presenting at emergency departments in whom a head CT is felt to be clinically indicated.[75] In the United States, the U.S. Food and Drug Administration (FDA) has approved the Banyan BTI (Brain Trauma Indicator) to predict CT scan abnormalities after mTBI. Blood is sampled within 12 hours of head injury. Test sensitivity is 97.5% and specificity is 36.5% on the FDA application.[76] The FDA has recently approved a handheld testing platform for GFAP and UCHL-1 levels with results available within 15 minutes.[77] ►**Table 1** lists sensitivity, specificity, and timing of common biomarkers.[78,79] This table shows the sensitivity and specificity of biomarkers to detect an abnormal CT scan after mTBI.

Clinical Utility of Biomarkers TBI

A point-of-care test could be used on the field to help detect a concussion. It could also be used to determine the severity of concussion and be used to screen patients for neuroimaging (computed tomography and/or magnetic resonance imaging) and further neuropsychological testing. Biomarkers could have a role in monitoring recovery and in managing patients with prolonged postconcussion syndrome, a potential of being incorporated into guidelines for return to work.

Table 1 Sensitivity, specificity, and timing of common biomarkers[78–79]

Biomarker	Sensitivity	Specificity	AUROC	Method for estimation	Optimal time of testing after TBI
S100B	100%	35%	0.55–0.78	ELISA	1–3 hours
UCHL-1[a]	97.5%	36.5%	0.52–0.77	ELISA	2–8 hours
Tau	92%	100%	0.5–0.74	Single molecule array (Simoa) assay	2–8 hours
GFAP[a]	97.5%	36.5%	0.65–0.94	ELISA	6–18 hours

Abbreviations: AUROC, area under receiver operating curve; ELISA, enzyme-linked immunosorbent assay; GFAP, glial fibrillary acidic protein; TBI, traumatic brain injury; UCHL-1, ubiquitin carboxy hydrolase-1.
[a]Combined sensitivity and specificity for UCHL-1 and GFAP.

Currently available biomarkers reflect injury severity, and serum GFAP, measured within 24 hours after injury, outperforms clinical characteristics in predicting CT abnormalities.

The current clinical utility of the biomarkers lies in detection of intracranial injury defined as abnormal CT scan following mTBI. Most patients with a suspected head injury are examined using GCS, followed by a CT scan of the head to detect traumatic intracranial lesions, that may require treatment; however, a majority of patients evaluated for mTBI/concussion do not have detectable intracranial lesions after having a CT scan. Availability of a blood test for concussion will help health care professionals determine the need for a CT scan in patients suspected of having mTBI and help prevent unnecessary neuroimaging or prompt an urgent neuroimaging if the blood test report is abnormal.[75] Among all the biomarkers UCHL-1 and GFAP have been tested and have been approved. In the ALERT_TBI study, UCHL-1 and GFAP were measured in serum and analyzed using prespecified cutoff values of 327 and 22 pg/mL, respectively. UCHL-1 and GFAP assay results were combined into a single test result that was compared with head CT results. For 1,920 patients with GCS 14–15, the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio were 0.973 (0.924–0.994), 0.367 (0.345–0.390), 0.088 (0.073–0.105), 0.995 (0.987–0.999), 1.5 (1.457–1.618), and 0.07 (0·00–0·159.[76]

The biomarkers may improve prediction of neurological outcomes and mortality in patients with moderate-to-severe TBI over clinical characteristics alone. GFAP appears to be the most promising for this.

Conclusion

A panel of several different biomarkers, all associated with injury severity, with the different cellular origin and temporal trajectories, can help in the prediction of CT abnormalities after mTBI, and severity and outcome of moderate and severe TBI.

Note
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Conflict of Interest
None declared.

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