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Review Article

The role of biomarkers in the early diagnosis of traumatic brain injury

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ABSTRACT

Traumatic brain injury (TBI) is a leading cause of mortality worldwide. It is caused by blunt force, explosive blasts, sudden head acceleration or deceleration, or penetrating trauma to the skull. TBI can be classified according to GCS into mild (GCS 13-15), moderate (GCS 9-12), and severe (GCS 3-8). Symptoms of TBI vary from mild symptoms to neurodegenerative diseases. Neuroimaging is the most utilized diagnostic tool in cases of TBI. However, its complex pathophysiology mechanisms make it difficult to diagnose TBI early. Biomarkers of TBI, such as glial cell injury biomarkers, axonal injury biomarkers, and inflammation biomarkers, are emerging as diagnostic and prognostic tools in TBI. However, the diagnostic and prognostic values of biomarkers showed mixed results. The aim of this review is to discuss the role of biomarkers in the early diagnosis of TBI in adults and children. Pathophysiology of TBI includes disruption of blood-brain barrier (BBB), inflammatory response, mitochondrial dysfunction, and oxidative stress. Various biomarkers have been reported as potential diagnostic biomarkers for TBI, including neuron-specific enolase (NSE), S100B, neurofilament proteins (NFs), and tau proteins. Identifying the role of biomarkers in the diagnosis of TBI in children is challenging due to age-dependent baselines, sampling limitations, and funding gaps. Future research should focus more on investigating kinetics of TBI biomarkers before their application in clinical settings.

Keywords: Traumatic brain injury, Biomarkers, S100B, Neurofilament proteins

INTRODUCTION

Traumatic brain injury (TBI) is one of the most common causes of physical impairment, cognitive impairment, and death worldwide.[1] About 50 million cases experience TBI annually, with 1.7 million cases in the United States alone.[1,2] Common causes of TBI include impact injuries such as blunt force, explosive blasts, sudden head acceleration or deceleration, or penetrating trauma to the skull.[3] Multiple classifications for TBI are available, including anatomical classification, Glasgow coma scale (GCS)-based classification, and CT abnormalities classification. Anatomical classification includes focal injuries, such as penetrating trauma and epidural and subdural hematomas, or diffuse injuries characterized by extensive involvement of the cerebrovascular system and/or white matter.[4] TBI can also be classified according to GCS into mild (GCS 13-15), moderate (GCS 9-12),

and severe (GCS 3-8). Moderate to severe TBI affects about 10% of hospitalized TBI patients, while mild TBI affects about 90% of TBI patients.[5]

Symptoms of TBI vary from mild headache and temporary confusion to neurodegenerative disorders, chronic behavioral problems, and long-term neurological impairments. TBI can result in impaired cognition and attention, anxiety and depression, and aggression and personality changes.[6] Additionally, TBI is believed to increase the risk of developing neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease.[7] The pathophysiology of TBI includes initial mechanical injury, including distortion, compression, and rupture of brain tissues and blood vessels, and secondary brain injury, including excitotoxicity, inflammation, and increased ROS production.[8-10] The detection of reactive astrocytes is considered a hallmark of TBI, as they significantly control tissue damage and repair.[11]

Assessment of TBI typically involves a thorough medical history and examination, a neurological examination, and brain CT. Currently, neuroimaging is the most utilized diagnostic tool in cases of TBI; however, its sensitivity to all types of TBI is low.[12] The diagnosis of TBI and its secondary adverse effects is challenging due to the complex nature of its pathophysiology and the variety in its clinical presentation. Biomarkers have shown potential in the early diagnosis of TBI. Previous studies have identified various types of biomarkers, such as glial cell injury biomarkers, axonal injury biomarkers, and inflammation biomarkers, in the CSF and blood of TBI cases. However, the diagnostic value of biomarkers is still unreliable due to the differences in findings between studies, lack of standardized clinical application, and limitations in research methods. Thus, this review aims to explore current evidence focused on the role of biomarkers in the early diagnosis of TBI in adults and pediatrics, highlighting the pathophysiological mechanisms of TBI.

LITERATURE SEARCH

A comprehensive literature search was conducted in Medline (via PubMed), Scopus, and Web of Science databases up to September 8, 2025. Medical subject headings (MeSH) and relevant free-text keywords were used to identify synonyms. Boolean operators (AND', OR') were applied to combine search terms in alignment with guidance from the Cochrane handbook for systematic reviews of interventions. Key search terms included: "Traumatic brain injury" AND "Biomarkers". Summaries and duplicates of the found studies were exported and removed by EndNoteX8. Any study that discusses the role of biomarkers in the early diagnosis of traumatic brain injury and published in peer-reviewed journals was included. All languages are included. Full-text articles, case series, and abstracts with the related topics are included. Case reports, comments, and letters were excluded.

DISCUSSION

Pathophysiological mechanisms of TBI

Biomarkers of TBI have different onsets and durations, with some having rapid onset and short half-lives, such as S100B and GFAP, and some having a slow and delayed increase peaking, such as NF-L.[13] These differences can be attributed to different pathophysiological mechanisms of secondary TBI, hence different releases of biomarker mechanisms. Disrupted BBB and glymphatic system are considered main routes for blood biomarkers to transfer from brain to blood. The BBB is formed of endothelial cells and astrocytes, which are tightly connected by tight junctions. The main function of the BBB is to keep harmful substances out of the brain and to maintain a homeostatic environment. It can be significantly disrupted in cases of TBI, leading to the influx of different harmful agents, resulting in secondary brain injury.[14]

Various mechanisms harm the brain following TBI, including early inflammatory response, ionic imbalance leading to secondary neuronal death, glial and immune cell activation, cytokine and chemokine release, increasing the accumulation of parenchymal and peripheral immune cells in the injured brain region, and BBB disruption causing edema, excitotoxicity, and neuroinflammation.[15-19] TBI is also associated with an increase in oxidative stress, which can induce secondary brain damage. The production of reactive oxygen species is increased due to the acidic cytoplasmic condition caused by TBI, which contributes to lipid peroxidation, mitochondrial dysfunction, and ATP depletion.[20-22]

Mitochondrial dysfunction is a major pathophysiology of TBI, which can result in secondary brain injury. This mitochondrial dysfunction arises from disturbances in fusion and fission processes, inducing apoptosis and disrupting repair processes.[23] Fusion is controlled by some proteins, such as opa1, mfn1, and mfn2, and when these proteins are inhibited, fusion fails, resulting in the formation of undersized mitochondrial fragments with reduced functioning. These events contribute to neurodegeneration.[23,24] The mitochondrial fragments resulted from fission under the effect of dynamin-related protein 1 (Drp1) significantly contribute to intrinsic apoptosis by releasing various pro-apoptotic proteins, including cyto C.[25] It has been reported that TBI increases the cellular level of DRP1.[26] Inhibition of mitochondrial fission, for example through post-TBI administration of mitochondrial division inhibitor-1 (Mdivi-1), a pharmacological Drp1 inhibitor, prevents the shortening of mitochondria, improves memory and cognition, and reduces neuronal loss.[27,28]

One of the major pathophysiological mechanisms of TBI is inflammation. TBI provokes an inflammatory response, leading to the secretion of various inflammatory markers, such as neutrophils, activated microglia, and macrophages. Inflammatory cells increase the

permeability of the BBB, leading to the formation of cytokines, which contribute to neurodegeneration and contribute to oxidative stress. Persistent inflammation leads to white matter degeneration, axonal injury, and synaptic dysfunction.[6]

TBI BIOMARKERS

Neuronal cell body injury biomarkers

NSE is a neuronal cytoplasmic enzyme, which contributes to the glycolytic pathway of nerve cells. Its presence in the extracellular space indicates neuron cell injury.[29] In cases of TBI, a rise in serum NSE in the first 12 h occurs and then declines within hours or days. Serum NSE levels show a persistent rise in moderate and severe TBI patients; thus, patients with persistent elevated serum NSE levels have a high risk of adverse neurological outcomes and mortality.[30,31] However, the use of NSE as a TBI diagnostic tool involves a major limitation, which is its high erythrocyte concentrations. Thus, serum NSE increases in case of hemolysis, without the presence of TBI.[30]

Ubiquitin C-terminal hydrolase-L1 (UCH-L1) is an enzymatic protein in the cytoplasm of nerve cells. This protein aids in eliminating altered neuronal proteins in physiological and pathological conditions.[32,33] CSF and serum UCH-L1 levels are elevated in the first 6-24 h following TBI, which can be attributed to BBB disruption in cases of moderate to severe TBI.[34,35] In cases of severe TBI, elevated serum and CSF levels of UCH-L1 within the first 6 hours post-injury are associated with increased mortality within 3 months.[34]

Glial cell injury biomarkers

S100B is a calcium-binding protein present in astroglial cells.[36] Astroglial cells release the S100B protein into the extracellular space following brain trauma.[37] S100B protein contributes to neurodegeneration by increasing the phosphorylation of tau proteins.[38] Elevated levels of S100B have been linked to unfavorable clinical outcomes and high mortality.[32,39,40] The occurrence of post-concussion syndrome following mild TBI can be predicted by S100B protein level.[36,40] While numerous studies support S100B as a prognostic biomarker following TBI, others have reported it to be a weak predictor, particularly for long-term outcomes.[38,39,41] The release of S100B protein from other tissues, such as adipose tissue, cardiac muscles, and skeletal muscle, is another major drawback of its use as a diagnostic tool.[36]

Glial fibrillary acidic protein (GFAP) is an intermediate filament in astroglial cells.[36,38] The release of GFAP and its breakdown products is increased in blood and CSF following TBI.[42] GFAP levels are positively correlated with TBI severity.[32] GFAP can be used to evaluate the need for CT, MRI, and intensive monitoring. It also serves as a predictor of adverse prognosis and high risk of cognitive and psychiatric disorders.[43]

Axonal injury biomarkers

NFs form a major part of the neuronal cytoskeleton, ensuring structural stability and mechanical support. Intracellular calcium levels increase following TBI, stimulating different calcium-dependent enzymes, including proteases, calpains, and phosphatase calcineurin, resulting in proteolysis, dephosphorylation, and dissociation of NFs.[6] These events lead to the release of NF and its subunits into extracellular space, then to CSF and blood.[44] NF levels remain elevated for days following trauma, potentially serving as predictors of chronic complications and cognitive impairment.[36]

Tau is a microtubule-associated protein found mainly in the neurons to stabilize axonal microtubules.[36] Reports found increased levels of tau protein in CSF, and these increased levels were associated with poor outcomes. The severity of TBI is correlated with tau levels in the CSF.[45] Cerebral ischemia resulting from TBI increases the process of tau phosphorylation, increasing the risk of neurodegenerative diseases.[46]

Inflammation biomarkers

As mentioned, TBI leads to an elevation in the production of inflammatory cells, mainly cytokines.[47] These cytokines include interleukin (IL)-1, IL-6, IL-8, IL-10, and TNF-α. Cytokines increase risk of neurodegenerative diseases, especially with prolonged secretion.[48] Adiponectin and high-mobility group box 1 (HMGB1) are markers of inflammation that were found to be elevated in the plasma of TBI patients. Adiponectin is considered an independent indicator of adverse prognosis and mortality in TBI, while HMGB1 is an important predictor for 1-year mortality in TBI patients.[49,50]

Micro RNA

MiRNAs are evolutionarily conserved non-coding RNAs that regulate gene expression and protein synthesis at the post-transcriptional level.[51] Various neurodegenerative diseases and several brain injuries, such as TBI, were associated with miRNA abnormalities. Multiple studies evaluated the effect of TBI on miRNA profile in the CSF and serum plasma.[6] Redell et al found a downregulation of miR-92a and miR-16 in severe TBI cases and an upregulation of miR-765 in mild and severe cases during the first 24 h of injury.[52] Additionally, Bhomia et al detected 18 and 20 miRNAs in the serum plasma and CSF of mild and moderate TBI and severe TBI patients, respectively.[53]

TBI in pediatric

The role of biomarkers in the early diagnosis of TBI in pediatrics has been evaluated by multiple studies. It has

been shown that S100B and NSE can play a key role in predicting prognosis.[54] When measured together, their serum levels may improve differentiation between moderate/severe TBI patients and healthy controls. Findings regarding GFAP are inconsistent; however, GFAP can be effective in predicting worse outcomes and classifying the severity of the trauma.[55] Furthermore, studies showed inconsistent results regarding the role of UCH-L1 in the early diagnosis of TBI. Elevated biomarker levels correlate with injury severity, poor outcomes, and long-term cognitive or behavioral deficits.[56] Non–CNS-specific markers, including IL-6, IL-8, albumin, miRNAs, and mtDNA, are also implicated.[56]

TBI and the role of biomarkers in pediatrics face multiple challenges. A major challenge facing pediatric TBI research is limited funding. Adult TBI research funding is disproportionate to pediatric TBI research funding, with resources more directed towards adult research.[57] Another challenge is the specific attributes of physiological and neurological development in children, which makes it hard to implement findings from adults' research on them.[57] Given the evolving nature of the pediatric brain, it is crucial to examine TBI effects across developmental stages, requiring longitudinal studies to assess both acute and long-term outcomes, often spanning decades.[57]

FUTURE DIRECTIONS

Future research should focus more on investigating the kinetics of TBI biomarkers before their application in clinical settings. Large, high-quality studies focusing on age and sex differences and using sequential biomarker sampling should be conducted. Furthermore, a standardized assay with good sensitivity and specificity in multiple clinical groups and with well-established thresholds for abnormality should be developed. Global research networks should develop standardized methods for the validation of TBI biomarkers and generate robust and comprehensive data through the promotion of international collaborative science. The CENTER-TBI and TRACK-TBI studies are current trials investigating the role of TBI biomarkers in clinical practice.

CONCLUSION

TBI is a complex condition that has been a global burden for years. Early diagnosis of TBI is critical to improve outcomes and guide treatment decisions. Biomarkers have shown potential as a diagnostic and prognostic tool for TBI, as they can predict long-term outcomes, mortality, and recovery potential. Currently, NF-L, GFAP, Tau, and brain-derived Tau are the most validated biomarkers for prognostic assessment in TBI. Identifying the role of biomarkers in the diagnosis of TBI in children is challenging due to age-dependent baselines, sampling limitations, and funding gaps. Future research should focus on exploring the pathophysiological mechanisms of TBI in order to develop standardized methods for the validation of TBI biomarkers.

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