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REVIEW ARTICLE

Research Progress of Traumatic Brain Injury and Its Related Markers

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ABSTRACT

Background: **Traumatic brain injury (TBI) represents a leading global cause of mortality and disability, imposing substantial economic burdens on societies worldwide. Recent advances in molecular biology have identified several biomarkers with potential to improve TBI prognosis, yet these discoveries necessitate more comprehensive analysis and systematic summarization of their underlying mechanisms of action.**
Methods: **This article systematically collates and reviews recent research on key molecular biomarkers in TBI, including AQP4, NF-κB, ICAM-1, GFAP, UCH-L1, NF-L, NGF, and tau protein. We have synthesized existing evidence and provide a narrative synthesis regarding these biomarkers' mechanisms of action, diagnostic accuracy, and prognostic utility in TBI.**
Results: **The biomarkers summarized in this review play pivotal roles in the pathological processes of traumatic brain injury, including edema, inflammation, axonal injury, and neurodegeneration. Accumulating evidence indicates that these biomarkers demonstrate substantial potential to facilitate early diagnosis, enable accurate monitoring of disease progression, and improve assessment of long-term patient outcomes.**
Conclusions: **Monitoring these biomarkers holds significant clinical importance, as it enables early clinical intervention, optimization of therapeutic strategies, and ultimately reduction of disability and mortality rates. The translation of these biomarkers into routine clinical practice represents a crucial step toward improving outcomes for TBI patients.**
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INTRODUCTION

Traumatic brain injury (TBI) has emerged as a pressing global health concern, representing one of the leading contributors to global mortality and disability statistics. Annually, TBI accounts for a substantial number of fatalities and workforce losses, particularly affecting young adults, with millions of TBI cases presenting to emergency departments worldwide each year. TBI survivors frequently experience long-term cognitive, physical, and psychological impairments, imposing substantial economic burdens on both families and society at large.

Traumatic brain injury (TBI) is categorized into primary and secondary injury. Primary cell death results directly from mechanical forces at the time of trauma. Subse-

quently, a secondary injury cascade - driven by oxidative stress, excitotoxicity (glutamate), calcium overload, and inflammation - is activated. The pathophysiological complexity of TBI renders accurate diagnosis, monitoring, and prognosis particularly challenging. Conventional assessment tools, such as the Glasgow Coma Scale (GCS) and neuroimaging, offer certain clinical utility but exhibit limitations in sensitivity, specificity, and predictive value for individual outcomes. In contrast, advances in molecular biology have opened new avenues for TBI diagnosis and treatment. A growing body of research has focused on molecular biomarkers released into biofluids following neural injury. These biomarkers provide a window into underlying pathological processes, including neuroinflammation, astrocytic activation, axonal injury, and neurodegeneration. Despite promising advances, the translational potential of these biomarkers from laboratory research to clinical practice requires systematic evaluation.

Therefore, this review aimed to achieve two primary objectives: first, to provide a concise overview of the main types of traumatic brain injury; second, to systematically summarize recent research advances regarding eight key molecular biomarkers. We elucidated their biological functions, evaluated their potential clinical applications in diagnosis and treatment, and ultimately demonstrated how monitoring these biomarkers can contribute to improved patient outcomes.

EPIDEMIOLOGY

Current estimates suggest that nearly 5 million people suffer from TBI annually, with low- and middle-income countries accounting for roughly 90% of related fatalities and injuries. This issue poses a serious threat to public health while also carrying major economic and social consequences. The primary contributors to TBI are falls and road traffic accidents [1,2]. In China, the annual incidence of TBI is markedly higher than in other nations, positioning it as a significant public health issue. Epidemiological data indicate that males are twice as likely to sustain a TBI compared to females, with the highest incidence observed in adults aged 75 years and older. Additionally, among the pediatric and adolescent populations, the age groups most at risk are those between 0 - 4 years and 15 - 19 years [3]. Notwithstanding the enhancement of medical resources and the ongoing advancements in contemporary healthcare systems, the prevention and management of TBI continue to encounter considerable obstacles. There exists a pressing necessity for the development of more effective strategies for early identification and intervention to mitigate the associated risks of disability and mortality.

COMMON PRIMARY TYPES OF TRAUMATIC BRAIN INJURY AND THEIR PATHOPHYSIOLOGICAL CHARACTERISTICS

Subdural hematoma (SDH)

Following head trauma, the bridging veins of the dural venous sinuses may rupture [2], leading to blood accumulation between the dura mater and arachnoid membrane, thereby forming a subdural hematoma (SDH) [3]. In cranial computed tomography (CT) imaging, subdural hematoma (SDH) is characteristically identified as a crescent-shaped hyperdense lesion. Acute subdural hematoma (aSDH), which occurs as a consequence of trauma, may elicit localized inflammatory responses that are associated with elevated osmotic pressure. This condition has the potential to evolve into chronic subdural hematoma (cSDH) over an extended period. Patients typically present with headache, gait disturbance, hemiparesis, and cognitive impairment [4]. The fundamental pathophysiological mechanisms are predominantly characterized by three essential processes: the inflammatory response, angiogenesis, and fibrinolysis [5]. The presence of extravasated blood in the subdural space initiates a significant inflammatory response, which can intensify secondary brain injury and contribute to the transition from acute subdural hematoma (aSDH) to chronic subdural hematoma (cSDH). Ongoing inflammatory stimuli facilitate the development of new capillaries and the exudation of fibrin, further damaging the dural border cells. Simultaneously, the blood clots within the hematoma activate the fibrinolytic system. Although this hyperfibrinolytic condition accelerates the liquefaction and absorption of the hematoma, it also poses the risk of persistent or recurrent hemorrhage. The management of subdural hematoma (SDH) primarily involves two strategies: conservative treatment and surgical intervention. For patients diagnosed with acute subdural hematoma (aSDH), surgical intervention is advised in cases where there is a large hematoma volume (greater than 30 mL), a significant midline shift (exceeding 5 mm), or a Glasgow Coma Scale (GCS) score below 12. The preferred surgical techniques for hematoma evacuation include burr hole drainage and craniotomy [6]. In contrast, minimally symptomatic chronic SDH (cSDH) patients, particularly elderly individuals with multiple comorbidities, may benefit from middle meningeal artery embolization as an alternative treatment. Conservative management [7] is appropriate for neurologically intact patients or those with only mild consciousness disturbance, encompassing bed rest, corticosteroid administration, and high-dose mannitol infusion therapy.

Subarachnoid hemorrhage (SAH)

Subarachnoid hemorrhage (SAH) is characterized by bleeding into the subarachnoid space, the area bounded by the arachnoid and pia mater layers. Traumatic SAH typically results from blood infiltration into the subarachnoid space following head trauma, whereas non-

traumatic SAH is predominantly caused by rupture of intracranial aneurysms [8], with the latter being more prevalent in clinical practice. Patients diagnosed with subarachnoid hemorrhage (SAH) commonly exhibit a sudden and intense headache, although some may also display atypical manifestations, such as epileptic seizures. These individuals are at a heightened risk for various complications, including rebleeding, delayed cerebral ischemia, and cerebral edema [9]. The identification of subarachnoid hemorrhage (SAH) fundamentally relies on cranial computed tomography (CT) scanning. In instances where CT results are ambiguous, a lumbar puncture may be conducted to establish a definitive diagnosis. In spontaneous subarachnoid hemorrhage cases, digital subtraction angiography remains the diagnostic reference standard for definitive confirmation. This condition induces blood-brain barrier compromise, initiates neuroinflammatory cascades, and results in cerebrovascular constriction [10]. The secretion of inflammatory cytokines subsequent to subarachnoid hemorrhage (SAH) intensifies vasospasm and enhances early brain injury, which is closely linked to unfavorable clinical outcomes. Microglia and astrocytes are crucial in the process of neuroinflammation, as they not only exacerbate neuronal apoptosis but also facilitate delayed cerebral ischemia and the systemic inflammatory response syndrome (SIRS) [11]. SIRS [12] significantly increases the risk of systemic complications and demonstrates a strong correlation with SAH-related mortality [13]. Therefore, early identification, prompt treatment, and complication prevention are critical for improving outcomes in SAH patients. Given the inflammatory cascade triggered by immune cells following SAH, immunotherapy [14] is now recognized as a promising therapeutic approach with significant clinical potential. Novel therapeutic strategies are being developed, such as cell adhesion molecule-targeted therapy (CAM-targeting therapy) and circulatory factor-targeted therapy, which have the potential to influence critical pathological mechanisms associated with subarachnoid hemorrhage (SAH). Emerging therapeutic approaches utilizing endothelin receptor blockers, MMP inhibitors, and nitric oxide-based therapies have demonstrated potential in alleviating cerebral vasospasm, attenuating neuroinflammatory processes, and improving clinical outcomes [15]. In the management of aneurysmal subarachnoid hemorrhage (SAH), surgical intervention is a fundamental component of treatment. Commonly utilized techniques, including clipping and endovascular coiling, are routinely implemented to attain hemodynamic stabilization and mitigate the risk of rebleeding.

Diffuse axonal injury (DAI)

As a clinically important form of TBI, diffuse axonal injury (DAI) is characterized by widespread disruption of cerebral tissue integrity, predominantly involving axonal tracts in the brainstem, cerebral parasagittal white matter, corpus callosum, and gray-white matter interfaces [16]. Approximately 50% of patients with moderate-to-severe TBI demonstrate DAI in combination with other intracranial injuries, highlighting its frequent coexistence with multiple neuropathological findings. This condition is characterized by post-traumatic unconsciousness lasting for six hours or more, along with a range of neurological deficits of varying severity [17]. Diffuse axonal injury (DAI) can be categorized into three clinical grades according to the duration of coma experienced by the patient: Mild DAI is characterized by a coma lasting between 6 to 24 hours; moderate DAI is defined as a coma that persists for more than 24 hours, but without the presence of brainstem signs; severe DAI is indicated by a coma that lasts longer than 24 hours and is accompanied by brainstem signs [18]. Pathologically, diffuse axonal injury (DAI) is classified into three grades: Grade I involves microscopic changes in the cerebral cortex, corpus callosum, and white matter of the brainstem, with occasional involvement of the cerebellum; Grade II is characterized by distinct focal lesions in the corpus callosum; and Grade III includes additional focal lesions in the dorsolateral quadrant of the rostral brainstem, typically located at the superior cerebellar peduncles. Recent research suggests that dysregulation of calcium homeostasis is a critical factor in the pathogenesis of DAI. Following TBI, mechanical shearing forces disrupt axonal integrity, inducing membrane rupture that triggers pathological calcium influx and excessive reactive oxygen species generation, culminating in oxidative stress-mediated cellular injury [19]. As a result, calcium channel blockers are regarded as promising therapeutic agents for the reduction of axonal degeneration and secondary brain injury, exhibiting considerable potential for clinical application. Furthermore, the accumulation of β-amyloid precursor protein (β-APP) in injured axons has been associated with neuroinflammation, alongside the role of calcium ions. Oehmichen et al. [20] conducted an immunohistochemical analysis that revealed moderate infiltration of CD68-positive microglia in areas of axonal injury characterized by β-amyloid precursor protein (β-APP) reactivity. This finding suggests a significant relationship between β-APP and the activation of microglia. As a precursor for amyloid-β peptide (Aβ), β-APP facilitates the formation of Aβ plaques, which may initiate a gradual and insidious progression of neurodegenerative processes, including Alzheimer's disease (AD) [21]. In preclinical studies utilizing animal models, an increasing array of molecular biomarkers has exhibited significant associations with the prognosis of Disease Activity Index. The panel of significant biomarkers encompasses glial markers (GFAP, S100β), neuronal cytoskeletal components (pNF-H, NF-L, tau), metabolic enzymes (NSE), membrane proteins (AQP4, NCX), and the amyloidogenic peptide Aβ42 [22]. These molecules may serve as significant therapeutic targets for pharmacological intervention.

RELATED MARKERS

Aquaporin-4 (AQP4)

AQP4, chiefly expressed on astrocytic membranes, functions as the CNS's dominant water transport protein, facilitating crucial homeostatic regulation of water and potassium fluxes through the blood-brain and blood-spinal cord barriers [23], while also being significantly involved in both cerebral edema formation and neuroinflammatory responses. The water channel protein AQP4 contributes significantly to the pathophysiology of various neurological conditions. Following TBI, blood-brain barrier dysfunction leads to enhanced vascular permeability, where AQP4 mediates critical pathological processes. This condition is associated with elevated expression of AQP4 at the end-feet of astrocytes. Consequently, this upregulation facilitates the influx of water into cells via the activated water channels, which initiates cytotoxic edema and exacerbates the progression of cerebral edema associated with TBI. In Alzheimer's disease (AD), AQP4 may facilitate amyloid-β clearance [24], suggesting its dual roles in both pathological and protective mechanisms. In a rat model of hypoxic-ischemic encephalopathy [25], Dan et al. provided evidence that the knockout of the AQP4 gene enhances long-term neurobehavioral outcomes through the upregulation of growth-associated protein 43 (GAP43) expression, indicating a potential role for AQP4 in the neural repair processes following ischemic events. Additionally, Aquaporin-4 (AQP4) is critically involved in the disease mechanisms underlying neuromyelitis optica spectrum disorder (NMOSD). Jarius et al. identified AQP4 antibodies (AQP4-Ab) in both animal models of NMO and in the sera of patients, thereby confirming their immunopathogenic significance in the context of NMO [26]. The collective findings underscore the importance of AQP4 as a notable target for autoimmune responses. Recent investigations have delineated three principal regulatory mechanisms governing AQP4 within the central nervous system [24]: First, microRNA-mediated gene regulation: miR-19a and miR-224 directly target AQP4, modulating astrocytic connectivity and blood-brain barrier permeability. Notably, miR-320a exhibits dual regulatory effects - it downregulates AQP4 expression in cerebral infarction, exacerbating ischemic injury, while suppressing glioma cell invasion and migration in gliomas. Second, heavy metal ions participate in AQP4 regulation. Mercury ions (Hg^{2+}) have been shown to inhibit AQP4 function [27], with zinc (Zn^{2+}) and copper ions (Cu^{2+}) demonstrating similar inhibitory effects [28]. Finally, small-molecule inhibitors [24] can directly modulate AQP4 functional activity, with acetazolamide and TGN-020 being currently reported as representative agents. Considering the significant function of AQP4 within the nervous system, it is clearly an important therapeutic target for the clinical management of cerebral edema and neuroinflammation. Studies have shown that the serum AQP4 concentration in patients with TBI is elevated, and there is a strong association between the increase in AQP4 levels and the severity of neurological function impairment as well as a poorer clinical prognosis. These results highlight AQP4's potential value as a prognostic biomarker for tracking TBI progression and predicting recovery trajectories.

Nuclear factor-kappa B (NF-κB)

Following TBI, the transcription factor NF-κB becomes activated through IκB phosphorylation and proteasomal degradation, subsequently upregulating expression of inflammatory mediators. This mechanism results in the release of NF-κB dimers, which then translocate to the nucleus, thereby promoting the transcription of various pro-inflammatory factors and initiating neuroinflammatory responses. Liu et al. [29] conducted a study utilizing a murine model of TBI and observed an increase in nuclear levels of the P65 protein, alongside a decrease in its cytoplasmic levels. This alteration was associated with a marked upregulation of pro-inflammatory factors, underscoring the pivotal role of P65 nuclear translocation in the activation of pro-inflammatory pathways following TBI. Additionally, their research indicated that pharmacological inhibition of NF-κB activation mitigated inflammatory responses and diminished neuronal damage within the hippocampal region. In a separate animal study, Jiang et al. [30] further validated the therapeutic potential of NF-κB inhibition, demonstrating that suppression of NF-κB activity promotes microglial polarization toward the M2 phenotype. These studies collectively demonstrate that NF-κB not only occupies a central position in post-TBI inflammatory responses but also represents a clinically promising therapeutic target.

Intercellular adhesion molecule-1 (ICAM-1)

Under normal physiological conditions, the cerebral parenchyma exhibits only basal expression of ICAM-1 (intercellular adhesion molecule-1), a member of the immunoglobulin superfamily of cell adhesion molecules. Through the application of immunohistochemical analysis, research by Hang and colleagues [31] demonstrated substantial upregulation of intercellular adhesion molecule-1 specifically in injured cortical vasculature after TBI, reaching maximal expression levels at 3 days post-trauma. Their research also established a positive correlation between the upregulation of ICAM-1 and the activation of nuclear factor kappa B (NF-κB), indicating that ICAM-1 may play a role in mediating inflammatory responses via the NF-κB signaling pathway. Additionally, the oxidative stress induced by TBI leads to an excessive release of reactive oxygen species (ROS), which in turn enhances the permeability of the blood-brain barrier (BBB) and further promotes the expression of ICAM-1. Expanding on this mechanism, in their seminal work, Lutton et al. [32] established a standardized controlled cortical impact (CCI) protocol for inducing TBI in murine models. Their findings indicated that the targeted administration of anti-ICAM-1/

catalase conjugates effectively maintained blood-brain barrier (BBB) integrity and mitigated neuronal damage. Additionally, co-staining for glial fibrillary acidic protein (GFAP) provided further evidence of the neuroprotective and anti-inflammatory properties of anti-ICAM-1/catalase during the acute phase of injury.

Glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1)

Cellular distribution analysis reveals GFAP's predominant localization in glial cells, while UCH-L1 shows specific neuronal cytoplasmic expression. Korley et al. [33] undertook a prospective study that examined blood samples obtained from patients with TBI on the day of their injury. Elevated plasma levels of GFAP and UCH-L1 demonstrated strong predictive value for both mortality risk and poor functional recovery at the 6-month follow-up interval. Shahim et al. [34] performed both cross-sectional and longitudinal studies that revealed baseline serum levels of GFAP, as well as their subsequent changes, serving as independent predictors of future alterations in brain volume. This finding indicates the potential of GFAP to function as a non-invasive prognostic biomarker for the progressive neurodegeneration that may occur following TBI. Additionally, a prospective multi-center study [35] assessed the clinical utility of glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase L1 (UCH-L1) in cases of mild TBI. The findings indicated that the simultaneous measurement of both biomarkers demonstrated enhanced sensitivity and specificity in detecting intracranial lesions following mild TBI, thereby underscoring their potential for clinical application.

Neurofilament light chain (NF-L)

Neurofilament light chain (NF-L), a protein associated with the axonal cytoskeleton, has been associated with a range of acquired neurological disorders. Graham et al. [36] indicated that neurofilament light chain (NF-L) is the sole biomarker for neural injury that exhibits prolonged elevation in serum levels for up to six weeks following moderate to severe TBI, after which it gradually reverts to baseline levels. Building on this finding, Wang et al. [37] conducted a multi-cohort investigation that involved daily sampling of cerebrospinal fluid (CSF) and serum during the initial week following TBI, followed by biweekly serum collections over a six-month period. Their findings indicated distinct temporal profiles for neurofilament light chain (NF-L) levels: CSF concentrations peaked between 5 to 10 days post-injury, whereas serum levels exhibited an acute increase followed by a sustained elevation lasting from 1 to 12 months post-injury. The investigation revealed strong associations between neurofilament light chain (NF-L) concentrations in serum and cerebrospinal fluid with 6- and 12-month clinical outcomes, as assessed by both GOS-E and DRS measures. These findings position NF-L as a promising prognostic biomarker for long-term functional recovery trajectories after TBI. In a complementary prospective investigation, Shahim et al. [38] determined that serum neurofilament light chain (NF-L) serves as the exclusive biomarker correlated with the rate of cerebral atrophy quantified through magnetic resonance imaging (MRI) and the advancement of traumatic axonal injury assessed via diffusion tensor imaging (DTI). This finding further reinforces the relevance of NF-L in the assessment of structural brain damage following TBI.

Nerve growth factor (NGF)

Nerve growth factor (NGF) functions as a crucial modulator of neuronal development within both the peripheral and central nervous systems. NGF promotes neuroprotection and enhances cell survival by engaging various established signaling pathways, such as MAPK/PI3K/AKT. In a study conducted by Tu et al. [39] utilizing a chronic constriction injury-traumatic brain injury (CCI-TBI) model in Sprague-Dawley rats, polymerase chain reaction (PCR) and Western blot analyses indicated a marked decrease in both nerve growth factor (NGF) mRNA and protein levels within hippocampal tissues when compared to sham-operated controls. Additionally, the findings of the study illustrated that the administration of nicorandil led to an upregulation of NGF expression and an enhancement of cognitive function in the TBI rat model. These results suggest that NGF may play a significant role in mitigating oxidative stress and neuroinflammation. In a prospective study carried out by Chiavetta et al. [40], cerebrospinal fluid (CSF) samples were obtained from pediatric patients suffering from severe TBI. The findings revealed a significant correlation between early levels of nerve growth factor (NGF) expression and the severity of brain injury. Furthermore, an increase in NGF levels was positively associated with improved neurological outcomes. These results collectively suggest that NGF is not only crucial for neuroprotection following TBI but may also function as a reliable biomarker for evaluating injury severity and predicting prognosis, underscoring its considerable importance in both research and clinical settings.

Microtubule-associated protein Tau

Tau, a microtubule-associated protein primarily found in axonal structures, is essential for preserving the structural integrity of microtubules, ensuring their functional stability, and modulating axonal transport mechanisms. Studies have reported [41] that Tau can activate brain macrophages, leading to blood-brain barrier disruption and subsequent neuroinflammatory responses, while also impairing endothelial cell function. Building upon the established phenomenon of tau protein hyperacetylation in TBI, Parra et al. [42] conducted a study examining two antibodies that target acetylated tau in PS19 tau transgenic mouse models. Their therapeutic intervention revealed substantial neuroprotective effects, successfully mitigating neurodegeneration induced by TBI while maintaining cognitive function. These results

highlight the significant relationship between pathological modifications of tau and neurodegenerative processes associated with cognitive decline, suggesting that tau may serve not only as a potential diagnostic biomarker but also as a viable therapeutic target. Furthermore, *in vitro* investigations [43,44] have revealed that the overexpression of 4-repeat tau (4R-tau) in astrocytes heightens their vulnerability to oxidative stress, consequently intensifying neuronal injury. These results imply a possible involvement of tau in the modulation of interactions between astrocytes and neurons. Overall, the existing evidence underscores the substantial role of tau protein in the pathophysiology of neurological impairments subsequent to TBI, thereby necessitating additional research and clinical validation to assess its diagnostic and therapeutic potential.

SUMMARY AND PROSPECT

Recent trends indicate that TBI is increasingly affecting younger demographics. The pathological progression of TBI typically transitions from an initial primary injury to a secondary brain injury characterized by neuroinflammation and cerebral edema, which are closely linked to functional impairments and unfavorable prognoses. A significant proportion of patients with moderate to severe TBI experience various neurological sequelae during the post-acute phase, including disorders of consciousness, hemiplegia, and cognitive dysfunction, all of which considerably diminish their quality of life and hinder social reintegration. While current medical interventions can partially alleviate symptoms and slow disease progression, they are largely ineffective in preventing secondary brain injury or associated complications, highlighting the considerable limitations of existing therapeutic approaches. Consequently, it is essential to identify molecular biomarkers that are closely related to the pathogenesis of TBI. The dynamic monitoring of these biomarkers could enhance the assessment of injury severity, facilitate clinical stratification, guide early interventions, and enable personalized treatment strategies, ultimately improving adverse outcomes. Moreover, comprehensive research on these biomarkers will provide critical theoretical insights and innovative perspectives for the development of targeted therapeutic strategies, potentially shifting TBI management from a focus on symptomatic treatment to a model of precision medicine.

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