Mini Review

Traumatic Brain Injury III: Diagnosis Challenges and the Role of Biomarkers

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Abstract

Traumatic brain injury (TBI) affects approximately 70 million people worldwide, yet its diagnosis remains challenging due to the limitations of traditional neuroimaging techniques and symptom-based assessments. Standard imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) are effective for detecting severe TBIs but often fail to identify mild TBIs (mTBIs) or concussions. Additionally, endocrine dysfunction and neuropsychiatric disturbances further complicate diagnosis and patient management. This review explores the limitations of current diagnostic methods for TBI and highlights the potential of biomarkers in improving detection, monitoring, and treatment outcomes.

Introduction: Beyond the Individual—The Societal Organism and Mental Illness

Traumatic brain injury (TBI) occurs when an external force damages the brain, resulting in significant medical, social, and economic consequences. Each year, traumatic brain injury (TBI) affects approximately 70 million people globally and results in 70,000 fatalities in the United States [1,2]. These injuries can be classified into penetrating TBIs, where an object breaches the brain's surface, and concussive TBIs, which involve internal damage without penetration. Common causes include falls, motor vehicle accidents, and blunt force trauma [3]. Certain populations, such as young children and older adults, are more susceptible to concussion TBIs due to falls, while penetrating TBIs are more prevalent among adolescents and adults. Additionally, the TBI-related death rate is three times higher in males than in females [4].

Currently, no definitive treatment exists for TBI. The injury initiates an inflammatory response that releases cytokines, exacerbating brain damage beyond the initial loss of neural tissue. This secondary injury process makes treatment complex, requiring a multifaceted approach that addresses both neural loss and inflammation [5]. Both the initial loss of neural tissue and the secondary inflammatory response should be considered in treatment strategies to minimize long-term complications.

Diagnosis of TBI

Diagnosing TBI presents significant challenges due to its diverse manifestations and varying severity. Symptomatology is influenced by factors such as pre-existing health conditions, injury severity, and the immediacy of medical care. Historically, diagnosis relied on symptom severity and imaging techniques such as CT scans and MRIs. However, these methods have limitations in detecting mild TBIs or concussions, which often lack visible structural damage. Instead, clinicians rely on patient-reported symptoms, neurological examinations, and cognitive assessments. These subjective measures introduce variability and potential misdiagnosis, emphasizing the need for objective diagnostic tools [6].

Balance deficits are a common symptom following TBI, affecting about half of those recovering. Individuals with TBI may experience dizziness, vertigo, or difficulties in coordination, increasing the risk of falls and further injury. Factors, such as medication side effects, brainstem injuries, and nerve damage contribute to these deficits. Addressing these issues requires a multidisciplinary approach, including neurologists, physiatrists, and physical therapists, to tailor individualized rehabilitation programs. Despite improvements in motor function within three months post-injury, many individuals continue to struggle with mobility and agility, necessitating prolonged therapy [7].

Cognitive impairments also complicate diagnosis, with affected individuals experiencing difficulties in attention, memory, and problem-solving. TBI may affect prospective memory, making it difficult for individuals to remember plans and intentions long enough to act on them. Challenges in processing information, following conversations, and retaining new knowledge impact daily functioning, making objective diagnostic criteria essential for effective treatment planning [8]. Traditional severity scales for concussions have been replaced with an all-or-none classification, recognizing that symptom

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severity does not always correlate with recovery time. This shift was prompted by inconsistencies in recovery times and outdated grading systems [9]. Personalized treatment strategies are now emphasized over rigid classification systems.

Challenges in Imaging and Endocrine Deficits

Standard neuroimaging techniques, such as CT and MRI scans, are instrumental in diagnosing severe TBIs but often fail to detect subtle changes associated with mild TBIs or concussions. Advanced imaging techniques, including functional MRI (fMRI), magnetic resonance elastography (MRE), and functional near-infrared spectroscopy (fNIRS), offer insights into brain activity changes but remain costly and inaccessible for widespread clinical use [10]. Diffusion tensor imaging (DTI) has emerged as a promising tool for detecting white matter injuries, yet its clinical application is still under development [11].

Endocrine dysfunction is another under-recognized complication of TBI. Damage to the hypothalamic-pituitary axis can disrupt hormone regulation, leading to symptoms, such as fatigue, mood disturbances, and metabolic irregularities. These symptoms overlap with typical post-TBI manifestations, complicating diagnosis. Approximately 27% of TBI patients develop major depression or dysthymia, highlighting the need for routine endocrine screening to ensure early intervention and comprehensive patient care [12].

Biomarkers as the Strongest Evidence for TBI Diagnosis

Biomarkers have emerged as a promising avenue for objective TBI diagnosis, providing measurable biological indicators of brain injury. Biomarkers are crucial for improving diagnostic accuracy, allowing early detection of injuries in a non-invasive manner. Additionally, they provide a method to monitor injury progression and better understand the underlying biological processes of TBI.

Salivary small non-coding RNAs (sncRNAs) have shown potential in identifying concussions, as demonstrated in studies on male rugby players. A panel of 14 sncRNAs effectively distinguished concussed athletes from control groups, with Let-7f-5p demonstrating the highest diagnostic accuracy at 36–48 hours post-injury. Let-7f-5p, a small microRNA that regulates gene expression, has been used as a biomarker for cancer and other conditions, further supporting its utility in TBI diagnostics. These findings support the use of saliva-based biomarkers for non-invasive, rapid concussion diagnosis in sports settings [13].

The Investigation into Repetitive Concussion in Sport (RECOS) study highlights the need for improved concussion diagnostics. By integrating neuroimaging, neurophysiological tests, biological markers, and neuropsychological assessments, the study aims to develop comprehensive diagnostic criteria. The use of biomarkers in this context can facilitate early detection, monitor injury progression, and guide return-to-play decisions, reducing the long-term risks associated with repetitive concussions. Biomarkers may also play a role in detecting second impact syndrome (SIS), which occurs when a person sustains a second head injury before fully recovering from a previous concussion. This condition has been linked to neurodegenerative disorders such as Parkinson's and Alzheimer's, particularly in athletes and individuals with repeated head trauma, such as American football players [14].

Beyond sports, biomarkers hold promise for broader clinical applications, including emergency settings and routine screenings for individuals at risk of TBI. Correlations between biomarkers, neuroimaging (1H-MRS, fMRI, MRE, DTI, fNIRS), neuropsychological scores, and motor coordination parameters will be assessed using standardized statistical analyses. The ability to objectively measure injury severity and predict outcomes could revolutionize TBI management, shifting reliance away from subjective assessments.

Continued research and validation of biomarker-based diagnostics are essential for integrating these tools into standard clinical practice

Conclusion

TBI diagnosis remains a complex challenge due to its diverse symptomatology and the limitations of traditional assessment methods. While imaging techniques provide valuable insights, they often fail to detect mild TBIs and concussions. Endocrine dysfunction further complicates diagnosis, necessitating more comprehensive screening approaches. Emotional disturbances, including anxiety, depression, anger, and irritability, are also prevalent in TBI patients due to both direct brain injury and difficulties in coping with cognitive changes. Sleep disturbances affect nearly 60% of individuals with TBI, with women being more affected than men, further underscoring the need for improved diagnostic tools.

Biomarkers represent the strongest evidence for advancing TBI diagnostics, offering objective, non-invasive, and reliable indicators of brain injury. Ongoing research, such as the RECOS study, underscores the importance of integrating biomarkers into clinical practice to enhance early detection, treatment, and long-term management of TBI. By prioritizing biomarker development, the medical community can improve diagnostic accuracy and ultimately enhance patient outcomes in TBI care.

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