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Traumatic brain injuries in sports - neurological aspects

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Abstract

Aim: Traumatic Brain Injury (TBI) was characterized as alternation in brain function or any other sign of brain pathology resulting from external force. Sport-related traumatic brain injury (SR-TBI) calculated as up to 20% of all TBA. Different diagnostic tools, such as CT scan or MRI, are utilized in clinical assessment of the patients, however there is a necessity of further investigation of new diagnostic methods such as biomarkers. A long-term repetitive brain injury can lead in consequence to a Chronic Traumatic Encephalopathy (CTE). Neuroprotection, treatment and rehabilitation play a crucial role in both prevention and recovery of TBI patients.

Methods: The research methodology involved a comprehensive review of scientific articles accessed through databases like PubMed and Google Scholar. This study is based on scientific reports published between 2002-2024.

Results: The scientific studies presented in this work underscore the clinical importance of sport-related brain injuries, including their pathophysiology and associated consequences. Detection methods and biomarkers for these injuries are highlighted. Additionally, it covers strategies for neuroprotection, treatment, and rehabilitation. The review indicates that many rehabilitation methods for patients with brain injuries require further research before being integrated into clinical practice.

Conclusions: An increase in TBI cases is observed globally with documented harsh consequences for further well being or even life. In light of this we should concentrate on proper classification methodology of the TBI types as well as evaluation of the effectiveness of existing diagnostic methods. Potentially promising diagnostic method is usage of bioflud biomarkers. Attention should also be given to proper prevention, which encompass also societal education about threats arising from cerebral injuries and rehabilitation of patients with TBI injuries in order to avoid long-term health consequences.

Keywords: Traumatic Brain Injury, Chronic Traumatic Encephalopathy, Biomarkers, Neuroprotection, Sport-related TBI

1. Introduction

In recent years the incidence of traumatic brain injury (TBI) and chronic traumatic encephalopathy (CTE) is increasing globally. Sport related TBI (SR-TBI) are estimated to account for up to 20% of all TBIs (3).

Brain injuries area heterogeneous group varying in severity, ranging from mild to moderate to severe. Rather than being a single condition, they represent a diverse set of disorders triggered by various causes, each with different impacts on survival outcomes [2].

A long-term consequence of a repetitive brain injury is a CTE, a neurodegenerative disorder where clinical symptoms typically develop progressively, often starting several years after retiring from the sport. The condition is characterized by the abnormal accumulation of tau protein, which is its key histological marker [5].

The aim of this study is to provide review of the epidemiology, pathophysiology and management of a TBI and a CTE with emphasis on sport-related injuries.

2. TBI: Definition and Initial Evaluation

Traumatic Brain Injury (TBI) was characterized as alternation in brain function or any other sign of brain pathology resulting from external force such as: bump, blow, or jolt to the head, or a penetrating head injury [1]. TBI falls into two categories: chronic TBI caused by repeated head trauma or acute TBI, comprising mild TBI (mTBI) or concussion and catastrophic brain injury [4]. Both acute and chronic TBI symptoms can manifest as cognitive and balance difficulties, fatigue, dizziness or headaches as well as emotional disturbance (increased irritability or low mood) and sleep difficulties. It is estimated that mTBI accounts for 58-88% of all TBIs [5]. Common acute SR-TBIs are epidural and subdural haematoma, ruptured vertebral artery with subarachnoid hemorrhage and skull fractures. Catastrophic brain injuries refer to severe brain trauma associated with cerebral contusions or intracranial bleeding, which may result in long term neurological consequences or death [4]. The most prevalent cause of death in SR-TBI, especially in boxers, is subdural haematoma [5].

The most frequently utilized TBI assessment system has been based on the Glasgow Coma Scale (GCS),a clinical score based on level of consciousness. In general, a GCS score of 13-15 is diagnosed in patients with mTBI, a GCS score of 9-12 in those with moderate TBI ; and GCS score 8 for severe TBI [2].

It is estimated that theyearly incidence of TBI is 50 million cases worldwide [2] with the sport-related traumatic brain injury (SR-TBI) calculated as up to 20% of all TBI. According to sport-specific studies, higher incidence of TBI occurs in match play than in training with elevated risk in females. Other factors impacting risk of injury are position played, discipline or involvement in the sport [3]. The meta-analysis consisting of 84 articles suggested that boxers have a significantly increased risk of sustaining a brain injury compared with other combat sports (risk ratio [RR]: 0.253 vs RR: 0.065, $P < 0.001$ [11]. Underreporting of sports-related injuries, inconsistent definitions or limited recognition of milder injuries likely contributes to underestimation of the actual incidence of TBI [3].

3. Pathophysiology of sports-related TBI

Brain injuries resulting from trauma are classified into two main categories: focal and diffuse. Focal injuries, such as contusions, lacerations, and intracranial hemorrhages, result from direct, severe impacts and are typically observed in severe cases of traumatic brain injury (TBI). Diffuse injuries, including diffuse axonal injury (DAI), arise from stretching and tearing of brain tissue without requiring skull fractures or direct impacts and can occur even in milder TBI cases [18].

Sudden acceleration and deceleration forces on the brain, both linear and rotational, are the primary mechanisms behind concussions and microtraumas. Rotational acceleration, as seen in lateral impacts during boxing, [16] results in stretching of the brain and its components, such as neurons, glial cells, and blood vessels, which can disrupt their normal functioning and lead to diffuse axonal injury, contributing to the symptoms of concussion [17]. Studies on biomechanical forces acting on the head in boxing have shown that rotational acceleration of punches is greater in higher weight classes, with impact force increasing with the athlete's weight. A punch from a professional boxer can generate significant force comparable to being struck in the head by a 6-kilogram bowling ball traveling at 20 miles per hour.

Mechanisms that increase the brain's susceptibility to repeated injuries are complex and involve metabolic dysfunctions, such as reduced mitochondrial energy levels and disturbances in ATP/ADP and lactate/pyruvate ratios. Additionally, mild injuries can induce sodium channelopathies in axons, enhancing sensitivity to subsequent injuries. Repeated concussions can exacerbate axonal damage and increase the brain's vulnerability to further trauma [18].

According to a 2009 study by the AANS, the top 10 sports-related head injuries among children aged 14 and under are: [19]

1. Cycling
2. Soccer
3. Baseball and Softball
4. Basketball
5. Water Sports
6. Electric-Powered Recreational Vehicles
7. Football
8. Skateboarding and Scooters
9. Winter Sports (Skiing, Luge, Snowboarding, Snowmobiling)
10. Trampolines

4. Medical management

The on-scene medical management following an acute TBI consists of medical evaluation and stabilization including assessment of the airway, breathing, and circulation. Acquiring and frequently repeating GCS score help guide further treatment as mental status can decline in a short period of time. In occurrence of moderate to severe TBI cases intubation and mechanical ventilation maybe required for airway protection (8). In many studies it was highlighted that rapid use of hypertronic saline could be beneficial for maintaining good CPP by decreasing ICP and increasing MAP [12].

The first-line imaging assessment to uncover an intracranial pathologic condition is head CT scan. This method holds similar information on the injury as MRI, however CT scan is more accessible, affordable and faster; furthermore, it provides clearer imaging of acute bleeding and skull fractures. Routine MRI is the preferable tool in presence of more subtle injuries due to its higher sensitivity [9]. When CT scan is not available medical staff uses worldwide criteria such as : Canadian CT Head Rule or New Orleans Criteria [12].

Functional MRI (fMRI) detects oxygen extraction of specific brain tissues, this allows to detect activation of specific brain areas during an experimental task or resting state. Consciousness of patients with TBI can be divided into two groups. First one is called unresponsive wakefulness syndrome, second are intermittent periods of increased awareness. In those two stages, fMRI has shown that associations are altered when compared with the conscious, resting brain. Different cognitive disorders are typical formTBI, hence a fMRI is a valuable tool in identifying functional patterns related to brain injuries [8].

Magnetic resonance spectroscopy (MRS) provides metabolic information of the brain tissue in vivo. This method recognises magnetic interactions between protons detecting altered metabolism in mTBI. One of the early indicators of brain injury is reduction in the levels of N-acetylaspartate (NAA) and increase of choline (Cho). Those changes often occur in TBI patients and the proportion of these metabolic changes associate with the acuteness of TBI. As this method relies on quantifying the metabolites, it is considered more sensitive and can be utilized in absence of visible injury on routine anatomic imaging [10].

5. Biofluid Biomarkers in TBI

TBI is a dynamic condition followed by complex pathophysiological events, main clinical tools in TBI diagnosis, as CT scan or MRI either lacks sensitivity or are difficult to access in the acute phase. This diagnostic gap could be potentially bridged by biofluid biomarkers [13].

Biofluid biomarkers are biochemical or chemical measurements that may serve as indicators of the biological state of the patient. Measuring biomarkers could potentially provide insight into cellular and molecular pathophysiology of TBI, serve as a way of monitoring disease progression, improving the classification of TBI severity and predicting long-term outcome [14,15].

Despite being subject of much investigation, many requirements need to be met by biofluid-based TBI protein biomarkers in order to be clinically useful [15]. Hence only few biomarkers have been approved for clinical use [13]. In the section below we provide general characteristics of top biomarkers connected with TBI studies. S100 calcium-binding protein B- is the most investigated TBI biomarker to date. It is expressed predominantly in glial cells but lower concentrations can be also found in other cells such as adipocytes, melanocytes, and chondrocytes [14]. However it has been noted that elevated levels of this biomarker can be also present in cases of orthopedic trauma without head injury [13]

- Neuron-Specifc Enolase (NSE)- glycolytic enzyme predominantly originating from mature neurons and neuroendocrine cells as a homodimer [13]. Elevated levels of NSE have been documented in cases of mTBI. The major drawback of this biomarker is that it is also expressed in red blood cells thus hemolysis correction is required to measure NSE level in blood [15].

- Interleukin-6 (IL-6)- this glycoprotein and prototypical cytokine expressed by both resident glial and neuronal cells within the CNS has been described as significantly increasing in the acute phase of TBI. IL-6 has been considered as a major contributor to the inflammatory process after TBI. However, as IL-6 could be produced by extracranial injuries, lack of brain specificity is a disadvantage for clinical use [14].

- Platelet count – due to the microvascular damage done by the TBI coagulation pathway is activated. Platelet count is a negative prognostic marker for TBI. Many studies have shown that reduced platelet count increases the risk of mortality. On the other hand, it seems that this test oversimplifies coagulopathy mechanism not highlighting its complexity [13].

- Cortisol – this hormone is used primarily to assess early identification and treatment of post-TBI adrenal crisis. Several studies mentioned a higher risk of adrenal insufficiency in more severe TBI; however, there were others with contrary findings. AS cortisol is a fine indicator of early stage TBI it is not an excellent marker [15].

6. Chronic Traumatic Encephalopathy

Chronic Traumatic Encephalopathy (CTE) is aneurodegenerative disorder primarily seen in individuals who experience repeated head injuries, such as athletes and military personnel. The disease develops gradually and can manifest decades after the last trauma. Clinically, it presents with cognitive impairments (e.g., memory loss, dementia), behavioral disturbances (e.g., impulsivity, aggression), and mood disorders (e.g., depression, anxiety). In later stages, parkinsonism symptoms may occur.

The pathology of CTE involves the accumulation of hyperphosphorylated tau protein in neurons and astrocytes, primarily in perivascular regions and around the cerebral cortex. This process is often asymmetric and localized to specific brain areas, such as the cingulate gyrus and medial temporal structures. In advanced cases, tauopathy extends to other brain regions, leading to generalized neuronal degeneration. Characteristic changes also include gliosis and brain atrophy.

Currently, there are no effective treatments, and management focuses on symptomatic care and injury prevention. CTE differs from other tauopathies, such as Alzheimer's disease, by its distinct distribution of tau pathology and the absence of early amyloidosis features [20].

CTE diagnosis relies primarily on post-mortem brain examination, revealing deposits of hyperphosphorylated tau in perivascular and deep cortical structures. Research is ongoing to improve in vivo diagnostics, focusing on biomarkers like light neurofilaments and tau proteins in cerebrospinal fluid, as well as neuroimaging technologies such as PET scans with tau-binding ligands. MRI may show atrophy in specific brain structures but is not specific for CTE. In vivo diagnostics rely heavily on a history of head trauma and clinical symptoms, including cognitive, behavioral, and emotional changes. However, widely available and definitive diagnostic tests that could replace neuropathological evaluation are currently lacking [21].

Growing awareness of CTE has led to research into biomarkers and neuroimaging techniques that could enable earlier diagnosis and a better understanding of pathogenic mechanisms [20].

7. Neuroprotection, treatment and rehabilitation

The World Health Organization (WHO) defines rehabilitation as "a set of interventions designed to optimize functioning and reduce disability in individuals with health conditions in interaction with their environment" [22]. Classical rehabilitation after brain injury involves three key aspects:

1. Complication Prevention: Regular evaluations help treat and avoid complications.
2. Neuroplasticity Stimulation: Rehabilitation therapies, such as physical therapy, speech and language therapy, and neuropsychology, support the brain in regaining functions.
3. Compensatory Solutions: Assistive tools and adjustments improve the quality of life, although they may limit functional recovery (e.g., using a wheelchair).

The goal is a harmonized approach that combines treatment, recovery, and adaptation to new living conditions [23].

Recent studies have begun to explore the importance of new approaches to rehabilitation in TBI patients. Neuromodulation, pharmacotherapy, and new technologies are promising techniques, although the current evidence is insufficient to incorporate them into routine clinical practice [24].

Pharmacological methods supporting neuroplasticity are drawing significant interest. A randomized, placebo-controlled trial evaluated the impact of fluoxetine on rehabilitation in ischemic stroke patients. In this double-blind study, patients from nine centers in France were randomly assigned to receive fluoxetine or a placebo for three months, starting treatment 5–10 days post-stroke. Combined with physical therapy, fluoxetine improved motor function inpatients with moderate to severe motor deficits, indicating the promising potential of treatment through neuroplasticity modulation [25]. Also creatine supplementation may support brain metabolism following

concussions, with preclinical studies suggesting that creatine may both prevent the onset of symptoms when administered prior to injury and enhance recovery when taken post-injury. Beyond its role in maintaining ATP levels and cellular bioenergetics, creatine is also believed to help stabilize mitochondrial membrane potential and reduce the production of reactive oxygen species and calcium ions within mitochondria [31,32].

Increasing research suggests that electrical and magnetic brain stimulation can enhance motor function and motor learning after brain injury. Experiments in rodents and primates have shown that combining cortical stimulation with appropriately tailored rehabilitation training results in better motor function recovery after stroke. Although brain stimulation after traumatic brain injury (TBI) is less studied, early preclinical and pilot studies in humans suggest its potential as a promising therapy for patients with motor impairments following TBI [24].

Another critical but under-researched aspect of pharmacological influence on neuroplasticity is the potential adverse effects of medications commonly used to treat symptoms during recovery from moderate to severe TBI. For example, the use of typical neuroleptics, such as haloperidol, in treating post-traumatic agitation, despite studies in animals suggesting they may negatively affect neuroplasticity processes, hindering neuronal recovery and complicating complete recovery [26].

Interest in technology for rehabilitation is growing, especially in supporting traditional rehabilitation methods aimed at functional improvement, such as exoskeletons that support motor functions. These technologies can also serve as powerful compensatory tools, helping patients cope with functional loss and improving daily functioning. A study analyzing the technical and clinical feasibility of an integrated hybrid robotic system in upper limb rehabilitation, particularly in reaching movements, in patients with brain injury affecting motor function revealed high patient satisfaction and acceptance of the hybrid robotic system. However, the research base remains relatively small [27].

The Role of neuroinflammation and anti-inflammatory drugs

Neuroinflammation is a natural response to injury, but in TBI, it can lead to prolonged and excessive inflammatory reactions. This results in the production of pro-inflammatory cytokines and chemokines that further damage neurons and glial cells. Microglia and astrocyte activation, key immune cells in the brain, leads to the release of reactive oxygen species (ROS) and nitric oxide, which, in turn, exacerbate oxidative stress and cause further damage to brain tissue. Early pharmacological interventions with anti-inflammatory drugs aim to reduce pro-inflammatory cytokine production, inhibit microglial activity, and decrease oxidative stress. For example, corticosteroids have potent anti-inflammatory effects, reducing microglial activity and cytokine production, but their long-term use can lead to severe side effects. Selective COX-2 inhibitors can reduce the production of prostaglandins, which are mediators of inflammation, without affecting COX-1, minimizing the risk ofside effects. Anti-cytokine drugs that block specific pro-inflammatory cytokines, such as IL-1β or TNF-α, can mitigate the inflammatory response but require precise modulation to avoid compromising natural defense mechanisms.

In addition to reducing inflammation, anti-inflammatory drugs may support neuroprotection, or the protection of existing neurons from further damage, as well as neurogenesis, the creation of new neural cells. By reducing inflammation, they also decrease the risk of secondary brain injury, which is crucial for improving neurological outcomes in TBI patients [28].

Ceramidep17/c18-dependent mitophagy

Among neuroprotective mechanisms, attention is drawn to research on ceramide p17/C18-dependent mitophagy. It plays a crucial role in protecting neurons from damage caused by oxidative stress and other factors leading to neurodegeneration. In response to brain injury, ceramides p17/C18 activate the mitophagy pathway, which selectively removes dysfunctional mitochondria, thereby minimizing the accumulation of reactive oxygen species (ROS). This reduces oxidative stress and the risk of apoptosis, promoting neuron survival. This mechanism operates in both preclinical and clinical brain injury settings, highlighting its therapeutic potential.

Ceramidesp17/C18 regulate key proteins associated with mitophagy, such as PINK1 and Parkin, which facilitate the degradation of damaged mitochondria in lysosomes. This action is critical for maintaining energy homeostasis and cellular stability, especially under stress conditions such as hypoxia or excessive ROS production. By eliminating damaged mitochondria, neurons are protected from further harm, contributing to better clinical outcomes inpatients with brain injuries. In addition to protecting against oxidative stress, ceramidesp17/C18 may also influence inflammatory processes, further enhancing their neuroprotective effect. The increase in ceramide p17/C18 levels in response to brain injury suggests that they are part of an endogenous defense mechanism that could be exploited as a therapeutic target in treating various neurodegenerative conditions [29].

Ketogenic diet and neuroprotection

The ketogenic diet, by drastically reducing carbohydrate intake and increasing fat consumption, induces a state of ketosis in which the body begins to produce ketones, including BHB, as an alternative energy source for the brain. In the context of neuroprotection, BHB plays a key role in several protective processes that can counteract the negative effects of brain injuries.

One of the main mechanisms by which BHB exerts its neuroprotective effects is its ability to reduce oxidative stress. Brain injury leads to the production of reactive oxygen species (ROS), which damage nerve cells. BHB acts as an antioxidant, neutralizing ROS and preventing neuronal damage.

After brain injury, an inflammatory response often occurs, which can lead to further damage to nervous tissue. BHB exhibits anti-inflammatory properties by modulating signaling pathways, such as NF-kB, which is crucial in the inflammatory process. BHB can reduce microglial activation, which plays a role in the brain's inflammatory response. Neurons, after brain injury, may have impaired abilities to efficiently use glucose as an energy source. BHB can serve as an alternative fuel source for the brain, stabilizing nerve cell functions and supporting their survival. Increased BHB availability can improve energy metabolism in neurons, which is crucial for their recovery.

Evidence suggests that BHB may support neurogenesis, the formation of new neurons, and aid in the regeneration of damaged neural networks. This may occur through the activation of signaling pathways associated with cell proliferation and neuronal differentiation.

In the context of studies on fruit flies, BHB supplementation after brain injury reduced aggressive behaviors that can result from neuronal damage. This indicates that BHB not only protects brain structures but also modulates cognitive and emotional functions, which are often disrupted after injuries [30].

8. Challenges and limitations research

Despite significant advances in the understanding and management of traumatic brain injury (TBI) and chronic traumatic encephalopathy (CTE), several challenges and limitations persist in the research landscape. One major challenge is the variability in TBI definitions and diagnostic criteria across studies, which can complicate comparisons and generalizations of findings. The reliance on established diagnostic tools like CT and MRI, while crucial, also presents limitations insensitivity and specificity, particularly in detecting subtle or early-stage injuries. The emerging use of biofluid biomarkers offers promising potential, yet these biomarkers face hurdles in terms of validation, standardization, and integration into routine clinical practice. Additionally, many rehabilitation and neuroprotection strategies require further investigation to confirm their efficacy and safety before they can be widely adopted. Variability in study methodologies, small sample sizes, and the heterogeneity of injury types and severities further complicate the interpretation of research results. Addressing these limitations requires a concerted effort to standardize research protocols, enhance diagnostic techniques, and rigorously evaluate new therapeutic approaches. Only through overcoming these challenges can the field move toward more effective prevention, diagnosis, and treatment of TBI and CTE.

9. Conclusions

The rise in cases of traumatic brain injury (TBI), particularly those related to sports, underscores a significant global health issue with severe implications for long-term well-being. The findings of this study emphasize the critical need for precise classification methodologies and effective diagnostic tools to enhance the assessment and management of TBI. Current diagnostic approaches, including CT scans and MRIs, while valuable, are complemented by emerging methods such as biofluid biomarkers, which show promise for improving diagnostic accuracy and understanding the disease's progression. Effective prevention strategies, encompassing public education on the risks of brain injuries and robust rehabilitation programs, are essential to mitigate the long-term health consequences of TBI. Continued research is necessary to validate new rehabilitation techniques and ensure they are integrated into clinical practice to better support recovery and minimize enduring damage.

Disclosures

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