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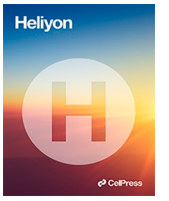

Review article

Mild traumatic brain injury as a pathological process

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ABSTRACT

Traumatic brain injury (TBI) is defined as dysfunction or other evidence of brain pathology caused by external physical force. More than 69 million new cases of TBI are registered worldwide each year, 80% of them - mild TBI. Based on the physical mechanism of induced trauma, we can separate its pathophysiology into primary and secondary injuries. Many literature sources have confirmed that mechanically induced brain injury initiates ionic, metabolic, inflammatory, and neurovascular changes in the CNS, which can lead to acute, subacute, and chronic neurological consequences. Despite the global nature of the disease, its high heterogeneity, lack of a unified classification system, rapid fluctuation of epidemiological trends, and variability of long-term consequences significantly complicate research and the development of new therapeutic strategies. In this review paper, we systematize current knowledge of biomechanical and molecular mechanisms of mild TBI and provide general information on the classification and epidemiology of this complex disorder.

1. Introduction

Traumatic brain injury (TBI) is defined as a disruption of normal brain function caused by a collision, shock, concussion, or penetrating head injury, according to the Centers for Disease Control and Prevention (2016). Mild trauma is defined as a closed head injury caused by acceleration or deceleration forces and resulting in one or more of the symptoms listed below (CDC, 2003): loss of orientation for a short period; a 0–30 min loss of consciousness; a seizure following a head injury; irritability, lethargy, or vomiting in babies and young children; headache, dizziness, and irritability in older children and adults. In most scientific sources, the concept of mild TBI is interchangeable with the concept of concussion [1] However, there is a difference between their definitions, which is as follows. Mild trauma is defined by the Glasgow Coma Scale, while concussion is a clinical syndrome that can overlap with mild, moderate, and severe trauma. The main causes of mild TBI are falls, traffic accidents, violence, contact sports (football, boxing, hockey, etc.), and participation in military actions (Brickell et al., 2020).

In some cases, acute symptoms of mild TBI do not include loss of consciousness, and structural disorders go unnoticed (if functional) [2], but it can lead to persistent cognitive, behavioral, and mental complications [3,4]. In addition, the recurrence of mild TBI increases the risk of delayed development of neurodegenerative pathologies such as Alzheimer's disease (AD) and Parkinson's disease, chronic traumatic encephalopathy (CTE), etc. [5,6].

Standard diagnostic methods, magnetic resonance imaging, computed tomography, and electroencephalography are insensitive to structural abnormalities in mild TBI and may show normal results [3,7]. However, Anne McKee, a well-known specialist in the field of

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sports injuries, found a build-up of hyperphosphorylated τ-protein in the brains of boxing and football players (45–80 years old) during a postmortem analysis [8]. Under physiological conditions, it is a stabilizer of neuronal microtubules, but in pathology, it undergoes hyperphosphorylation, which leads to the formation of neurofibrillary tangles that are toxic to neurons [9]. This process is most common in AD, but in the presence of recurrent concussions in medical history, the distribution of hyperphosphorylated τ-protein is more common in CTI [10,11]. It is assumed that the probability of development of the latter and the severity of its course depends on the sport, position, duration of exposure, age at the time of the first or repeated injury, genetic predisposition, etc. [12]. According to a study of late cognitive impairment due to several concussions, 61% of former American football players suffered a single concussion, while 24% had three or more cases [13]. Another major risk group for mild TBI is the military.

Often a person is unaware that he or she has suffered a concussion [14]. In this regard, educational programs have been created that provide students with information about the signs of mild trauma and the measures needed to prevent or neutralize its consequences [15]. These programs are especially relevant for athletes and parents of children who play sports. A special mobile questionnaire application has also been developed for athletes, which allows for determining the need to see a doctor after a possible concussion [16].

However, treatment for mild TBI is still based on its external manifestations [17], and the pathophysiology remains poorly understood. Knowledge of the effects of concussion at the tissue level is a prerequisite for finding effective and reliable treatments and prevention of neurodegenerative effects.

Table 1
A summary table of the latest clinical trials on traumatic brain injury. Treatment and diagnostics. Czeiter, Endre et al. 2 - Campos-Pires, Rita et al.

Clinical Trial ID /Author name	Purpose	Year	Sample size	Treatment	Results
NCT00623506	To test the possibility of using a neuroactive steroid as a multi-targeted treatment for TBI	2013	30 participants with TBI	Pregnenolone	Improvement in cognitive performance after TBI
NCT01750268	Testing topiramate as a possible treatment for TBI with concomitant alcohol abuse	2020	32 participants with TBI and Hazardous and Harmful Alcohol Use	Topiramate	Potential benefits in reducing alcohol use but had transient negative effects on cognitive function in veterans with AUD and mTBI
NCT01670526	To evaluate the effect of the cholinesterase inhibitor rivastigmine in the form of a patch on the cognitive abilities of veterans with TBI	2018	94 participants with TBI and Cognitive Impairment	Rivastigmine Transdermal Patch	No significant difference between treatment and placebo for TBI treatment
NCT01058395	Evaluation of the safety and efficacy of minocycline after TBI at two varying doses administered over a week	2018	15 participants with TBI	Minocycline	Treatment was safe for TBI at a dose twice that as recommended for treatment of infection, Disability Rating Scale improvement after treatment
NCT01990768	To determine the efficacy of Tranexamic Acid (TXA) at the prehospital stage in patients with severe and moderate TBI	2019	967 participants with TBI	Tranexamic Acid	Treatment does not improve neurological outcomes for patients with TBI after 6 months
NCT02957331	To test the effect of beta-blockade on mortality in traumatic brain injury patients and the ability of beta-blockade to suppress the catecholamine burst	2020	26 participants with TBI	Propranolol	Treatment does not affect catecholamine levels in patients with TBI
Czeiter, Endre et al.	To test the possibility of using serum GFAP as a marker for the biochemical diagnosis of traumatic brain injury	2020	2867 participants with TBI	–	The feasibility of using serum GFAP as a potential biomarker for the diagnosis of TBI within 24 h after injury was proved
NCT02210221	Establish a new possible classification of traumatic brain injury based on a combination of physical and biochemical factors, as opposed to the Glasgow Coma Scale	2022	1728 participants with TBI	–	Six possible persistent brain injury endotypes have been identified, which may provide a greater grading and treatment scope than GCS
NCT01676311	To investigate the effect of Huperzine A on the cognitive abilities of patients with moderate to severe traumatic brain injury	2020	14 participants with moderate/severe TBI	Huperzine A	There was no statistically significant difference between the improvements in cognitive abilities in the treatment group compared to the placebo group
Campos-Pires, Rita et al.	Effects of xenon on neuroinflammation and neurodegeneration in rats with severe traumatic brain injury	2020	22 adult male Sprague Dawley rats	Xenon	Xenon reduces neuronal death after severe TBI by increasing microglia and astrocytes activity due to the beneficial effect of early inflammation
NCT02161055	To evaluate the relationship between blood glucose levels and Glasgow Coma Scale score	2022	208 participants with TBI	–	It has been shown that both upward and downward deviations in blood glucose levels are associated with poor prognoses for TBI according to the GCS

1.1. Epidemiology of mTBI

TBI rates vary widely over the world, and there are severe gaps in trustworthy data for many areas where TBI rates are likely to be high (Bey, T., & Ostick, B., 2009). Population-based studies with a broad definition of TBI (811–979 per 100,000 people per year) show significantly higher rates of TBI than studies based on hospital discharge rates (47.5–643.5 per 100,000 people per year) [18]. Every year, more than 69 million new incidents of TBI are reported worldwide, with mild trauma accounting for more than 80% of the total [19]. The European Union estimates that at least 2.5 million cases of TBI occur each year; in the United States, the overall number of TBI patients is close to 3.5 million annually. According to a meta-analysis of 15 prevalence studies, 12% of the entire sample of 25,134 people had severe trauma that resulted in the loss of consciousness [20,21]. TBI is particularly common in young individuals; for example, one cohort research discovered that more than 30% of participants under the age of 25 experienced at least one TBI that required medical attention [22]. Mild TBI appears to be the most common out of all other types classified by the severity of symptoms. Because many patients with mTBI do not seek medical help, the true annual incidence of mTBI is likely to be higher than 600 per 100, 000 people (or around 42 million people worldwide) [23]. One of the key variables that can be used to separate TBI risk groups is age. Since falls are most common in the early and late stages of life, the highest rates of TBI in emergency departments were seen in age categories such as "0–4 years" (1618.6 per 100,000 people) and "75 and older" (1682 per 100,000 people) [21,24,25].

There are gender differences in the epidemiology of TBI. According to estimates from the national database TBI Model System for 2017, the number of cases of trauma in males much outnumbered those in females, accounting for more than 73% of all trauma reports. In sports brain injuries, however, the number of female cases outnumbers the number of male cases by a factor of about 2:1 [26].

The most prevalent causes of death related to trauma in the United States, according to the Centers for Disease Control and Prevention (CDC), are purposeful self-harm (32.5%), unintentional falls (28.1%), and car accidents (18.7%) [27]. The population mortality rate from trauma in the United States was 17.1 per 100,000 people in 2010 [28]; in China — 13.0 per 100,000 people in 2013 [29]; in the EU — 11.7 per 100,000 people in 2012 [19]. TBI is responsible for about a million deaths every year on average. TBI mortality varies depending on age and injury mechanisms and can fluctuate over time. Adults above the age of 60 have the highest mortality rate [25]. Improved clinical treatment of severe TBI has lowered mortality by more than 50% over the last 150 years, according to a study [30]. Sports-related concussion is a common source of trauma (Bey, T., & Ostick, B., 2009). Combat-related TBI is a leading cause of morbidity and mortality. It frequently combines explosive trauma and extracranial polytrauma, such as amputation, internal hemorrhage, and burns, which are uncommon in civilian cases [31]. TBI is 3–8 times more common in offender populations than in non-offending ones [21].

Thus, the problem of diagnosis and effective approach to patients with mTBI is one of the most important in modern medicine. In recent decades, there is a pandemic spread of TBI due to the increase in the pace of life, the increase in the number of high-speed vehicles, industrialization, as well as such phenomena as terrorism and military conflicts. Consequently, any inhabitant of the earth is at risk of TBI regardless of his age, place of residence, and social status (Table 1).

1.2. Classification of traumatic brain injuries

Traumatic brain injury is a quite challenging disorder to classify due to the high degree of heterogeneity, variability of localization, and severity of pathological lesions in most patients, and difficulty in replication and proper scaling in animal models [32,33]. The physical mechanism of injury, which divides injuries into closed and penetrating, is an important criterion in TBI classification. The biomechanics of injury are extremely different in both circumstances, and the risk of infection is increased with penetrating trauma [34]. Even though the physical mechanism classification gives limited information about the patient's actual injury, medical specialists can use it to identify or predict vascular impairment in the early stages of a patient's treatment [35].

The divide into primary (or immediate) and secondary (or delayed) injuries is another classification based on the physical mechanisms of injury. Primary trauma occurs when a force is applied to the brain, either directly or indirectly. Numerous mechanisms of primary brain injury (compression, rotation, displacement, rupture, and so on) can be classified as associated with contact trauma or acceleration-deceleration forces [36]. Contact injuries are more frequently linked with epidural hematomas and contusions, whereas injuries caused by acceleration/deceleration forces are more frequently related to subdural hematomas and diffuse axonal injury [37]. Progressive negative effects are thought to arise after the primary injury as a result of numerous molecular cascades that can be active for weeks after the initial impact. Because these mechanisms of secondary injury manifest later, they can be preventable or treatable [35,38].

TBI is characterized by a multitude of clinical alterations, including diffuse axonal injury, contusions, cerebral edema, and brain compression by extracerebral hematomas [39]. There are two types of pathoanatomical lesions: focal and diffuse. Contact is the most common source of focal injuries, while acceleration and deceleration forces are the most common cause of diffuse injuries. These lesions can also be considered when particular tissues and planes of the skull are taken into account. For doctors, pathological categorization is critical in developing emergency therapy methods [40]. In clinical practice, computed tomography (CT) data are now routinely employed in premorbid pathological categorization. In 1992, the Marshall Scale based on CT data was published, demonstrating the capacity to connect CT abnormality patterns with intracranial pressure (ICP) (Marshall et al., 1992). Despite its widespread use, the Marshall Score System has several flaws. It is unable to recognize subtypes of intracranial lesions, is one-dimensional, and is essentially based on only two features: the need for surgery and radiological signs of elevated ICP. The Rotterdam scale is a newer classification method that allows various CT components to be evaluated separately. It also determines the predictive value of clinical and anatomical aspects like traumatic subarachnoid hemorrhage and epidural hematomas [41].

Traumatic brain injury is frequently classified according to severity, which can be thought of as a symptom-based classification

system. The Glasgow Coma Scale (GCS) is a widely used scoring system in medicine that is frequently employed for this purpose (Teasdale & Jennett, 1974). The scale (range 3–15) is made up of the sum of three-component points (ocular, verbal, and motor scales) and can be used to quickly determine the severity of brain damage. Patients with GCS scores of 13–15, 9–12, or 9 are classed as having mild, moderate, or severe traumatic brain damage, accordingly. Both the clinical course and the prognosis of the disease differ significantly between these groups. Although the GCS damage evaluation is very precise, it is difficult to use effectively in the treatment of children [42]. The FOUR score scale is the most recent addition, and it solves GCS constraints such as the difficulty to calculate a verbal score in intubated patients or to examine the status of the brainstem directly [35,43].

There is a growing understanding that adequate characterization of the initial type and severity of TBI should not be limited to a single dimension (eg, GCS classification or CT Marshall scale), but should include several areas, such as clinical and pathophysiological features, neuroimaging findings, and other factors, which may affect the clinical outcome. It should also be noted that the development of a method of classification of human traumatic brain injury, which takes into account and corresponds to the models of TBI in rodents, would be of great use in translational studies.

1.3. Biomechanics of mild TBI

Various mechanisms, including impact, inertia, and explosive overpressure can lead to mTBI. The most common causes of civilian head injury - sports activity and vehicle crashes - are usually the result of impact to the head, which leads to a high rate of head acceleration or deceleration. Deformations in this case are transferred from the outer to the inner regions of the brain, which leads to diffusely distributed pathologies [44]. Although the role of linear acceleration in the primary injury of mild trauma has been understood for decades, more recent experimental studies have found that angular acceleration is much more harmful to the brain. It is shown that 90% of the total deformations in brain tissues during head acceleration are the result of the rotational component, and only 10% is generated by the translational component [45]. A third possible force, the probable basis of an explosive injury, is based on stereotactic theory, which states that as a result of the interaction of the spherical shape of the skull and the fact that brain tissue has the same density on concentric planes, pressure waves can propagate as a spherical wave which is more focused and direct energy reaches the deeper structures of the brain [46].

Kinematics such as angular acceleration, rotational speed, and acceleration duration has been identified as the major determinants defining the extent of rotationally induced diffuse brain injury. Peak rotational acceleration of the head was found to be highly connected with the occurrence of trauma in primates. The same research underlined the importance of rotational acceleration happening during a certain window (period) of time [47]. Because of the rising clinical recognition of chronic cognitive and emotional dysfunction from single or repeated mild TBI, understanding biomechanical tolerance for concussion in terms of measurable head kinematics is crucial.

Given the various proportions and structural properties of the head and skull contents of humans, primates, and rodents, scaling results to humans is a big challenge in studies that use animal models of TBI. Developments in this area are very important for the creation of valid small-animal experimental models and the scaling of biomechanics-based thresholds from rodents to humans [44,48].

1.4. Pathophysiology of mild TBI

We described some biomechanics of primary injury, but since most clinical assessments and therapeutic strategies focus on mechanisms of secondary injury, it is crucial to understand the timeline of events after mechanical impact. Pathophysiology of mild traumatic brain injury includes multiple molecular cascades with immediate and delayed consequences that lead to temporary or permanent neurological deficits.

2. Acute injury pathophysiology

2.1. Cellular homeostasis

The breakdown of cellular homeostasis caused by the mechanical force applied to the brain during trauma triggers a complex cascade of neurochemical and neurometabolic changes. Shearing and stretching forces generate mechanoporation of the plasma membrane after a physical impact of primary injury, resulting in an uncontrolled outflow of intracellular potassium ions and subsequent depolarization [49–51]. This rapid depolarization causes voltage-gated calcium channels to open and synaptic release of mostly excitatory neurotransmitters like glutamate. Previous research (which used a variety of methods, including microdialysis and proton magnetic resonance spectroscopy) has revealed that changes in neurotransmitter concentrations are region-specific and time-dependent. Immediately after mTBI, there is a rise in glutamate concentration in the brain, which returns to normal within hours. Increased levels of extracellular glutamate following trauma were linked to the severity of the injury and the complexity of the consequences [52–54].

Glutamate binds to kainate, N-methyl D-aspartate (NMDA), and D-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid ionic channels (AMPA), resulting in a further potassium efflux and creating a feedback loop of depolarization and hyperexcitability [55]. The release of excitatory neurotransmitters stimulates intracellular sodium and calcium influx and accumulation, causing cellular and mitochondrial structures to deteriorate [56]. Mutations in the CACNA1A and CACNA1E genes (which encode the voltage-dependent calcium channels) have been linked to an increase in the severity of post-TBI sequelae in concussed athletes. Calcium channel blockers used in animal models of mTBI have demonstrated the ability to limit post-traumatic calcium accumulation and improve the effects of

mTBI [57–59]. Other therapeutic strategies designed to combat trauma-induced excitotoxicity focus on targeting NMDARs, including NMDAR antagonists, NMDAR subunit inhibitors, and partial agonists of glycine/NMDAR [60].

2.2. GLT-1 changes

As noted above, excitotoxicity is one of the main consequences of traumatic brain injury, which in the long term can lead to delayed neurodegeneration. One of the main components involved in reducing extracellular glutamate levels in mammals is the glutamate transporter GLT-1. It has been previously shown that glutamate expression decreases after traumatic brain injury [61]. It should be noted that the transporter is currently perceived as being expressed only on astrocyte membranes. However, there are also arguments in favor of the ability of the glutamate transporter to "migrate" across the cell membrane (for example, during long-term potentiation) [62]. Due to this ability, GLT-1 is also able to form substrate-associated clusters with increasing sodium concentration. These clusters form inside the cell and are therefore unable to perform their primary function of glutamate reuptake [63]. However, if the increase in extracellular glutamate affects only glutamate transporter migration and cluster formation, the question of what causes the decrease in GLT-1 expression in the brain after TBI remains unexplored.

There is a study that suggests that GLT-1 can be expressed in neuronal dendrites in pathological conditions [64]. It should be noted that the specific pathologies in which this occurs are not specified in the study. However, since cellular excitation and excess glutamate can contribute to changes in GLT-1 expression and function, trauma may induce changes in the expression of the neuronal glutamate transporter.

We suggest that a detailed study of changes in the formation and functioning of GLT-1 in traumatic brain injury is key to the development of possible therapies. Thus, the use of ceftriaxone has shown positive results in reducing the effects of TBI, in particular, through the restoration of physiological indicators of glutamate expression [65].

The rationale for the assumption that the development of post-traumatic therapy should focus on a detailed study of the glutamate transporter is that the main cause of delayed neuronal death after mild TBI is excitotoxicity, which is poorly neutralized by physiological means due to disturbances in the expression (or transport) of GLT-1 (Fig. 1).

Thus, the detailed mechanisms of such disorders, as well as ways to correct them could help to treat patients with TBI.

2.3. Glucose metabolism

ATP-dependent Na/K pumps are at their most active after mTBI, attempting to reestablish ionic equilibrium. It causes the intracellular glucose reserves to quickly deplete. The neuronal glycolytic rate increases by 30–46% within 30 min of impact and can last for 4–6 h, according to the findings of a study on a fluid percussion injury model. Simultaneously, the described hypermetabolic period is accompanied by glucose hypometabolism (lasting 5–10 days after TBI), ineffective oxidative metabolism, and decreased cerebral

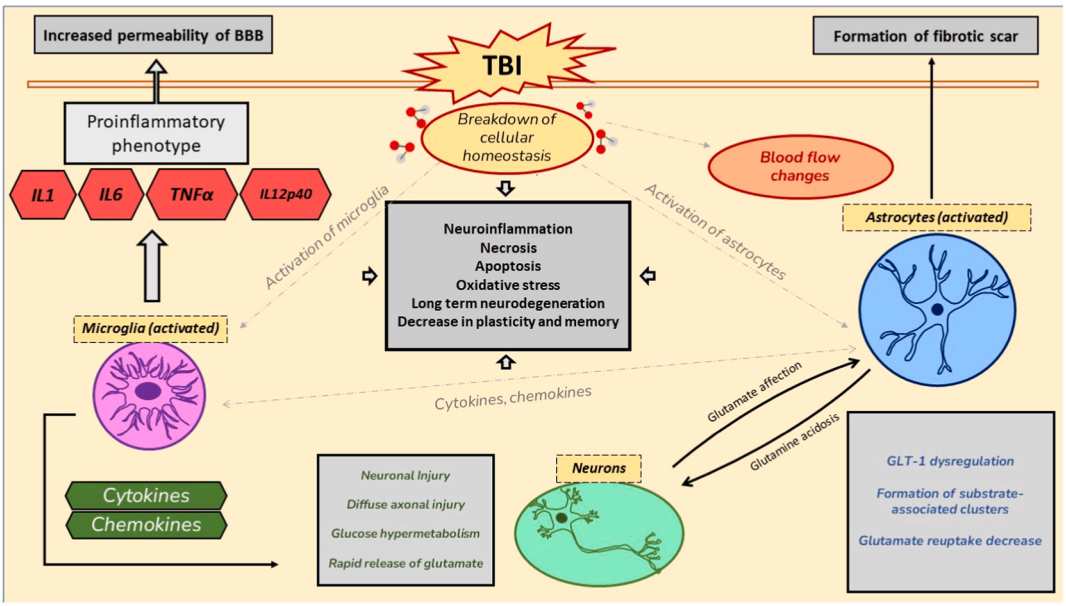

Fig. 1. Progress of traumatic brain injury events. TBI leads to the overall cellular homeostasis of the brain. Damage of cell membranes causes further activation of microglia and astrocytes; release of intracellular calcium; production of chemokines and cytokines that activates of immune system. In addition, there are changes in the functioning of GLT-1 as a glutamate transporter, while excess glutamate causes excitotoxicity. Taken together, these factors contribute to changes in blood flow, deterioration of oxidative stress consequences, loss of neuronal survival, and in the long term, cognitive decline and neuroinflammation.

blood flow [50,66,67]. Repeated brain injury within a window of glucose hypometabolism has been linked to poorer cognitive function in animal models [68]. Results like this were used as the basis for the "second impact syndrome" theory, which states there is a definite window of biological vulnerability to repeated mechanical impact. The duration of the metabolic vulnerability window after injury varies and requires additional research, but there have been developed prophylactic clinical practices that aim to reduce the likelihood of a second injury within this vulnerable timeframe.

All those factors combined contribute to the anaerobic metabolism of glucose with excessive lactate accumulation, which leads to the creation of an acidic microenvironment. Resulted acidosis in turn could lead to increased membrane permeability and cerebral edema [69,70]. Lactate serves as an alternative energy source for the brain and is utilized during the post-traumatic energy crisis, demonstrating neuroprotective effects in models of mild and severe TBI in rats [71]. There are also several other available alternative energy sources, such as creatine, creatine phosphate, and ketone bodies. Animal studies show that a ketogenic diet is associated with lower brain contusions and improved behavioral outcomes after sustaining TBI [57,72].

2.4. Mitochondrial dysfunction

The main reason for mitochondrial dysfunction after sustained mTBI is the influx and accumulation of calcium through voltage-gated calcium channels and NMDARs [73]. Those changes in calcium homeostasis are reflected by decreased levels of metabolic biomarkers, including ATP/ADP ratio, NAD/NADH ratio, and N-acetyl aspartate (NAA) [57,74]. Neural tissue is very sensitive to free radical-mediated damage because of the presence of abundant polyunsaturated lipids, so generated after glutamate-induced excitotoxicity free radicals and reactive oxygen species (ROS) contribute greatly to secondary injury after TBI [75]. Reactive oxygen compounds include superoxides, hydrogen peroxide, nitric oxide, and peroxynitrite [76]. Astro- and microglia, in the end, do not cope with the elimination of free radicals, and their activation occurs [75].

2.5. Blood flow and axone damage

The triphasic (hypo-hyper-hypo) response in the cerebral blood flow (CBF) was first observed after severe cases of trauma but now is proposed as a possible mechanism of secondary injury in mTBI. Researchers suggest that this triphasic response is caused by impaired brain metabolism resulting in carbon dioxide production which in turn leads to vasoactive disturbances and regional perfusion variability [50,77,78]. Recent animal studies provide structural evidence of these hemodynamic alterations, showing a decrease in vascular junction and length, as well as suggesting a parallel between the decrease in global and regional cerebral blood flow with the window of metabolic vulnerability after mTBI [77,79]. MRI-based studies on concussed adult athletes during the first week after injury showed a decrease in regional blood flow in the frontal and temporal lobes [80]. It was also shown that changes in cerebral blood flow correlate with the initial severity of symptoms. Results of recent research suggest that changes in cerebral blood flow after traumatic brain injury are area- and time-dependent and may persist after the disappearance of clinical symptoms [81]. Although cerebral edema was observed in MRI-based studies of severe TBI, it was not registered in mild TBI experimental models [57,82].

A rapid decrease in head acceleration causes the transfer of linear and rotational forces to the neuron and results in microstructural axonal damage [83]. One of the initial changes is the change in permeability of the axolemma due to focal microscopic mechanoporation. These microscopic gaps can provide a path of the intra-axonal influx of calcium, which leads to the activation of calpain and structural changes in the cytoskeleton of axons resulting in disruption of both anterograde and retrograde transport, as well as accumulation of beta-amyloid precursor protein (b-APP) [67,84,85]. C-Jun N-terminal protein kinases (JNKs) mediate axonal transport disruption by phosphorylating the kinesin-1 heavy chain subunits [86,87]. Although diffuse axonal injury (DAI) is more pronounced in severe trauma, it can be observed after mild TBI, albeit with less severity and potentially reversible effects. Studies have shown that impact velocity is the most useful characteristic in predicting axonal injury due to the viscoelastic properties of the tau protein [88].

3. Subacute injury pathophysiology

3.1. Axonal damage

Axonal damage peaks within the first 24 h following injury, with a gradual restoration to baseline after that [89]. The quantitative assessment of selective loss of white matter has taken center stage in the research of traumatic brain injury, thanks to the advancement of neuroradiology techniques. Unmyelinated axons from the young brain are more prone to injury than myelinated fibers impacted by repeated mTBI, according to animal studies [78]. Fractional anisotropy (FA) is a measure of linear water diffusion that decreases when the directionality of white matter tracts is disturbed. It has been hypothesized that FA alterations after sustained mild injury are related to transient axonal swelling [67,90]. Using diffusion tensor imaging, researchers reported a decrease in FA in the ipsilateral corpus callosum, hippocampus, and external capsule after mTBI compared to the control group [91]. Contradictory to this, results of the pediatric study demonstrated a post-traumatic decrease of FA in inferior frontal, superior frontal, and supracallosal subcortical regions and no difference in corpus callosum [92]. The death of oligodendrocytes may be a symptom of diffuse damage if neurons are destroyed locally [93]. Due to the ongoing process of remyelination after contact sports, contact sports players demonstrated an increase in the aqueous fraction of myelin compared to non-contact sports players during the season and 3 months after the season [94].

3.2. Plasticity and memory

Rat model-based research registered changes in ligand-controlled excitatory NMDA receptors and inhibitory GABA-ergic interneurons after sustained injury. Those alterations affected the development of plasticity and memory [95]. Comparing the development of immature rodents raised in an enriched environment after TBI has shown that animals from the group that got injured did not show anatomical or cognitive improvement in adulthood, which was observed in intact ones [96]. Considering the role of glutamate in post-traumatic calcium regulation, it is no wonder that the NMDA glutamate receptor is a subject of particular interest. It has been reported that higher expression of the NR2A subunit protected neuronal connectivity after sustained trauma, suggesting the importance of NMDAR in the post-traumatic rebuilding of the neuronal network [97]. Another animal study showed downregulation of the NR2A subunit following lateral FPI. At the same time, there was no difference in the expression of NR2B and NR1 subunits [57,60,98].

Both long-term potentiation (LTP) and long-term depression are dependent on the activity and subunit composition of NMDA receptors. So, it is expected to observe LTP impairment 2 days following experimental mTBI with partial recovery by the seventh day. One animal study described 28 days of post-injury neuronal loss and alterations of LTP in the female hippocampus compared to the male [99,100]. Later studies have shown that environmental enrichment strategies improve memory and reduce anxiety after sustaining mTBI, which can be explained by moderate synaptic changes in NMDA subunits after injury [101]. We observe similar patterns in LTP changes in college football players with a history of two or more concussions. It was concluded that GABA-mediated intracortical inhibition reduces LTP and long-term depression-like plasticity [102]. Patients who have had concussions frequently have cognitive and behavioral problems as a result of aberrant brain circuit activation [67]. While human research is scarce, it has been hypothesized that environmental interventions and external adjustments may be advantageous during a period of decreased brain activation and neuroplasticity following mTBI.

3.3. Gliosises

According to experimental studies, rmTBI has chronic astro- and microgliosis (Loane & Kumar, 2016; Anyaegbu et al., 2021). Gliosis processes were reflected in an increase in the number of astrocytes and microglia cells and were recorded in such areas of the hippocampus as the fimbria and the CA1 zone, 3 months after the last injury. The activated form of astrocytes is determined by the increased expression of GFAP protein, which in clinical studies is considered a potential marker of mild trauma in the blood and spinal cord (Zetterberg et al., 2013). Another compound whose expression depends on the intensity of gliosis is the calcium-binding protein S100B. Reactive astrogliosis is also characterized by astrocyte hypertrophy. Astrocytes, activating in response to inflammatory processes, produce microfilaments and neurotrophins to synthesize scar tissue at the site of injury (Werner & Engelhard, 2007). Migrating to the site of injury and forming a glial scar, the latter, on the one hand, limit the area of further damage to neurons, and on the other hand, prevent the recovery of their processes, which reflects their negative role (Fawcett & Asher, 1999). The biochemical function of astrocytes in nerve tissue damage is to produce such growth factors as NGF, erythropoietin, etc. (Chen et al., 2022). These compounds have neuroprotective value for neurons.

3.4. Neuroinflammation

Neuroinflammation, which is observed at mTBI, involves the activation and increased regulation of inflammatory cytokines and microglia and can contribute to cellular damage. Microglia, activating in response to signals from damaged cells, acquire an amoeboid shape and migrate toward the affected areas [103]. These activated cells produce both proinflammatory mediators and anti-inflammatory cytokines, playing a dual role in the development of TBI.

Outside the core of the injury site in case of severe TBI, microglia, and macrophages (MG/M) are shown to be the primary propagators of tissue inflammation [104]. Studies show gender differences in MG/M response; male mice display faster microglial activation and astrogliosis compared to females [105]. Following mTBI, interleukin 1β (IL-1B) and interleukin 6 (IL-6) are expressed to mediate a neuroinflammatory response [67,106]. Like astrocytes, microglia cells are involved in BDNF signaling and the release of other neuroprotective factors [107]. In addition, trauma among its functions includes the elimination of dead cell residues (through phagocytosis) and the production of anti-inflammatory cytokines and chemokines (CD206, CD163, FcyR, arginase 1, Ym1, and TGFβ) [108]. However, microglia are also characterized by the start of inflammatory processes that lead to neuronal dysfunction and death. Inflammatory substances of microglia are interleukin-1β, tumor necrosis factor-α, interleukin-6, inducible nitric oxide synthase, and interleukin-12p40. The ambiguity of microglial activity, in particular, is explained by the presence of two molecular phenotypes in these cells – M1 and M2. The latter promotes such regenerative processes after TBI as neurogenesis, angiogenesiss, oligodendrogenesis, and remyelination, and the M1 phenotype causes further tissue damage and neurodegeneration. In addition, within 1 day after injury circulating neutrophils, monocytes, and lymphocytes cross the damaged blood-brain barrier, exacerbating neuroinflammation [109]. The neuroinflammatory response following mTBI has been hypothesized to correlate with symptom severity and duration [110]. In one study there was described a correlation between an initial increase in the concentration of highly sensitive C-reactive protein (hsCRP), an inflammatory biomarker, and the probability to experience cognitive deficit and other long-term complications [67,111].

The blood-brain barrier (BBB) is a sophisticated capillary system that controls the flow of compounds from the bloodstream to the brain. According to previous studies, the number of endothelium caveolae increases and the expression of adhesion binding proteins decreases hours to days after mTBI [112,113]. Secondary metabolic problems such as ischemia, hypoxia, and vascular spasm develop after direct shear injury [114]. Animal studies have shown differences in the length of post-injury recovery period: some demonstrate

dysfunction discarding within a few hours after mTBI, while others maintain a biphasic pattern with an early phase (3–6 h after injury), followed by delayed one (1–3 days after injury) [115,116]. During the assessment of BBB disruption caused by the experimental mTBI, researchers found a pronounced acute (6–72 h) permeability of BBB accompanied by an acute astroglial response [117]. Various inflammatory genetic markers have been reported in a subgroup of individuals after mTBI. There is more than enough evidence to support post-traumatic dysfunction of the BBB, but the extent of disruption and its timeline after mTBI in humans is not fully understood yet [67,118].

Animal models of mTBI have shown limited cell death compared to moderate and severe cases [119]. In juvenile rats, both single and repetitive impacts trigger neuronal death in the cortex and anterior thalamus, which leads to cognitive deficits [120,121]. Human research is limited, but quantitative MRI has progressed in recent years to assess long-term changes in brain volume. One human study using quantitative MRI showed greater diffuse volume loss after a single mTBI compared with age-appropriate controls 1 year after injury. Limbic system atrophy was also detected, which coincided with the results of neuropsychiatric tests [122]. Hippocampal volume is reduced in middle-aged males after a single distant trauma compared to the control group, as well as in boxers and football players after repeated mTBI [6]. Patients with recently acquired mTBI had significantly reduced volumes of caudate, putamen, and thalamus 2 months after injury, according to research. However, a year after the damage, the early discrepancies in brain volume vanished, indicating that brain tissue had normalized progressively [57,123].

4. Conclusion

Traumatic brain injury is a worldwide concern and a leading cause of disability and injury-related mortality, putting a significant financial and social burden on patients, their families, and society. There are no ways to detect mild traumatic brain injury promptly because it hardly ever appears at the level of the whole brain. Speaking of mild trauma, we mean exclusively processes occurring at the cellular and molecular levels such as glial reactivity and excitotoxicity as a consequence of it. Understanding the pathological processes that take place both immediately after injury and long afterward is necessary to find new ways of early diagnosis, as well as ways to block the neuropathological changes that contribute to the onset of neurodegenerative diseases.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

No data was used for the research described in the article.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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