Chapter

The Neuropathology of Concussion

Ioannis Mavroudis, Ioana-Miruna Balmus, Lucian Gorgan and Alin Ciobica

Abstract

This review provides a detailed analysis of the pathophysiology involved in traumatic brain injury (TBI), with an emphasis on mild TBI and chronic traumatic encephalopathy (CTE). It explains the dynamic interaction between mechanical trauma and the neuroinflammatory response, especially the crucial role of microglia in post-TBI inflammation. Moreover, the review discusses the significance of dendritic and spinal changes as indicators of a regenerative response. The role of transactive response (TAR) DNA-binding protein 43 and tau protein in the pathogenesis of mild TBI and CTE is assessed, with tau protein changes being a potential biomarker for acute and chronic TBI-related conditions. The study also investigates syndromes commonly found in young athletes, such as second impact syndrome and juvenile head trauma syndrome. The review addresses the complex inflammatory response after mild TBI, focusing on pro-inflammatory and anti-inflammatory mediators, including IL-1, IL-6, TNF-α, and CRP as potential indicators of injury severity and outcome. The review calls for further research to elucidate the exact relationship of these factors in TBI and its long-term effects.

Keywords: traumatic brain injury, chronic traumatic encephalopathy, microglia, tau protein, second impact syndrome, inflammatory response

1. Introduction

The definition of concussion remains controversial and lacks universal agreement. The 2012 Zurich Consensus Statement on Concussion in Sport proposed that concussion and mild traumatic brain injury (TBI) should be regarded as distinct entities, and defined concussion as a "complex pathophysiological process affecting the brain" that can cause neuropathological damage. However, the statement acknowledged that concussive symptoms typically resolve spontaneously and do not produce imaging abnormalities. In contrast, recent American Academy of Neurology guidelines for sports concussion in 2013 did not differentiate between concussion and mild TBI, defining concussion as "a clinical syndrome of biomechanically induced alteration of brain function, typically affecting memory and orientation, which may involve loss of consciousness." These guidelines noted that the terms concussion and mild TBI are often used interchangeably, highlighting a lack of consensus in their use. Therefore, concussion is currently employed in two distinct ways: (1) to describe a specific

pathophysiological entity with unique diagnostic and management implications, commonly observed in the context of sports injuries; and (2) to describe a constellation of symptoms that arise after different types of TBI [1, 2].

2. The pathophysiology of concussion

Concussion and subconcussion injuries are caused by the acceleration and deceleration linear or rotational forces acting on the brain. This results in the elongation and deformation of the brain, causing stretching of neurons, glial cells, and blood vessels and altering membrane permeability. Although all cell compartments and blood vessels are affected by the injury, axons are especially vulnerable as they often extend long distances from the neuronal cell bodies. Axons may be injured even in the absence of the death of the neuron of origin [3, 4].

In addition to structural deformation, acceleration-deceleration forces produce a rapid release of neurotransmitters, influx of calcium, efflux of potassium, and acceleration of the cellular sodium-potassium (Na^+-K^+) pump to maintain membrane homeostasis, requiring large increases in glucose metabolism. These changes are referred to as the "neurometabolic cascade of concussion."

Post-concussive hypermetabolism in the setting of decreased cerebral blood flow produces a disparity between glucose supply and demand and a cellular energy crisis [5]. Pathological studies of acute concussion and post-concussion syndrome (PCS) have shown multifocal diffuse axonal injury (DAI), microhemorrhage, astrocytosis, and perivascular clusters of activated microglia. The severity of axonal injury is generally parallel to the severity of the TBI, with mild injury producing only microscopic multifocal axonal damage and moderate and severe TBI producing more severe, widespread axonal injury. Mild TBI produces multifocal and perivascular axonal injury in the corpus callosum, fornix, subcortical white matter, and cerebellum, physical changes that may contribute to the severity of symptoms after mild TBI [3, 6]. Focal perivascular accumulations of hyperphosphorylated tau (p-tau) as neurofibrillary tangles (NFTs) and neurites and TDP-43 immunopositive neurites in the white matter have also been found after concussion, suggesting that focal axonal injury may be mechanistically associated with the development of p-tau and TDP-43 pathology. Evidence of microhemorrhage as hemosiderin and hematoidin-laden macrophages may also be present after concussion, indicating loss of microvascular integrity and breach of the blood-brain barrier following mild TBI. Structural changes in the brain after concussive injury, such as DAI and microhemorrhages, are best detected with diffusion tensor imaging (DTI) and susceptibility-weighted imaging (SWI) and are not detectable with conventional structural imaging studies, including computed tomography (CT) scan and magnetic resonance imaging (MRI) [7–10].

3. Diffuse axonal injury

Diffuse axonal injury (DAI) is a major neuropathological consequence of TBI and is caused by the acceleration/deceleration forces that shear fragile axons during the trauma [11–14]. Although DAI is more commonly seen in moderate to severe TBI, it can also occur in mild TBI, and its severity is proportional to the deceleration force

[15, 16]. DAI is difficult to identify in patients with TBI using CT and conventional MRI, but novel MRI techniques, such as diffusion tensor imaging (DTI) have been found to be useful for assessing axonal integrity and identifying DAI, particularly in mild TBI patients and athletes with mild sports-related concussive or sub-concussive TBI [17–19]. Histological techniques have shown that DAI can be identified within hours after trauma while being characterized by sequential changes that begin with an acute shearing of axons, disrupted axonal transport with axonal swellings, and secondary disconnection, leading to Wallerian degeneration [11].

Diffuse axonal injury (DAI) with axolemmal disruption leads to calcium influx, neurofilament compaction, and microtubule disassembly. Calcium influx triggers microtubule disassembly, while neurofilament compaction is an early event caused by calpain-mediated proteolysis of neurofilament side arms or phosphorylation [20, 21]. Disruption of calcium homeostasis is the primary regulator of calpain activation, leading to increased intracellular-free calcium, and proteolytic degradation of essential cytoskeletal proteins, such as neurofilament proteins [22, 23].

Diffusion tensor imaging (DTI) is a valuable tool in diagnosing, prognosing, and managing mild TBI. DTI provides information about the microstructure and fiber tract integrity of white matter. Other techniques that may be valuable in evaluating mild TBI include alterations in brain activation through BOLD signals, resting state functional connectivity, magnetic resonance spectroscopy, and SPECT imaging.

Blast injury is becoming an increasingly important form of TBI in civilian and military populations, with the majority of injuries associated with blast exposure. Individuals exposed to blast injury are susceptible to acute and long-term neuropsychiatric and cognitive consequences. Some military veterans with a history of blast exposure show neuropathological changes of chronic traumatic encephalopathy (CTE) during autopsy, while single-blast exposure in wild-type laboratory mice produces neuropathological changes of axonal injury, neuroinflammation, microvascular injury, and abnormal tau pathology, as well as neurobehavioral abnormalities. A post-mortem series of military veterans with documented histories of blast exposure showed focal neuropathological changes of CTE, including cortical foci of perivascular tau pathology, disseminated microgliosis and astrocytosis, myelinated axonopathy, and focal neurodegeneration, very similar to mild CTE pathology found in the brains of athletes with a history of repetitive concussive injury [4]. Also, the clinical symptoms experienced by veterans with blast injury include progressive affective lability, irritability, distractibility, executive dysfunction, memory disturbances, and cognitive deficits [4].

4. Microtubule disorganization

Microtubule disorganization may be a direct effect of dynamic axon stretching, leading to immediate breakage and buckling of microtubules post-injury, which triggers progressive microtubule disassembly [24]. This results in the accumulation of organelles that are transported in the axon, and axonal swelling known as axonal retraction balls, leading to eventual disconnection and axotomy [20, 21]. Neuronal damage with axonal bulbs and swellings is most commonly found in the cortical sulci at the interface between gray and white matter [25]. DTI studies have shown that the extent of DAI after mild TBI is related to post-concussion cognitive problems [26].

5. The role of microglia

Microglia plays an essential role in the immune system in the brain and mediates the inflammatory response after TBI. Studies in animal models of TBI have shown that activated microglia migrate rapidly toward damaged tissue, forming extended cytoplasmic processes that create a potential barrier between healthy and injured tissues, indicating that microglial activation is a response to axonal damage [27, 28]. This microglial response is associated with the upregulation of both pro- and anti-inflammatory genes, chemokines, and other inflammatory mediators [29]. However, it is still not clear whether modulation of this inflammatory response to brain trauma may have any therapeutic effects. While pharmacological reduction of microglial activation might reduce inflammation and improve neuronal survival, microglial activation might stimulate axonal regeneration after injury [30].

6. Dendritic and spinal changes

After TBI, dendritic and synaptic sprouting occurs, leading to increased dendritic arborization and synaptogenesis as part of a regenerative response [31]. Transcription factors c-Jun and ATF-3 have been implicated in axonal regeneration after DAI [32]. Structural proteins, including growth-associated protein GAP-43, have also been associated with neurite sprouting of disconnected damaged axons after the acute phase of TBI [33].

7. TDP-43 deposition

TAR DNA-binding protein 43 (TDP-43) may also play a role in mild TBI and CTE pathogenesis. TDP-43 accumulation is a feature of several neurodegenerative diseases, including CTE, AD, and dementia with Lewy bodies. Recent studies have shown that TDP-43 accumulations occur in boxers and American football players with CTE after repeated brain trauma in several gray matter structures, including the brainstem, basal ganglia cortical areas, and subcortical white matter. TDP-43 accumulation after TBI may be part of a physiological injury response, and animal experiments suggest that axonal damage results in an upregulation of TDP-43 expression [34–36].

8. The role of tau protein

Tau protein, characterized by a molecular weight ranging between 48 and 67 kDa, serves as a crucial structural component within the axonal cytoskeleton of both the central nervous system (CNS) and peripheral nervous system (PNS) [37, 38]. This microtubule-associated protein is predominantly found in unmyelinated cortical axons, contributing significantly to their structural integrity [39, 40]. Although the expression of tau is mainly observed in the brain, it is also present in extracranial tissues, such as the liver, kidneys, and testis [41]. Historically, research investigating TBI biomarkers has primarily concentrated on total tau (T-tau). However, recent studies have expanded their focus to include phosphorylated tau (P-tau) and cleaved tau (C-tau) as well. Following a TBI, there is a noticeable increase in tau levels within cerebrospinal fluid (CSF) and plasma [42]. Elevated concentrations of tau protein in

CSF have been identified in patients who have experienced TBI, with admission CSF tau levels displaying a correlation with the patients' long-term outcomes [43, 44]. A study analyzing CSF samples from Olympic boxers within one to six days following their bouts revealed a significant increase in tau levels in the boxers' CSF, as compared to healthy control samples [45]. Moreover, higher concentrations of CSF tau were observed in Olympic boxers post-bout, though this was not necessarily linked to the number of head impacts received [46]. Similar findings were reported in a study involving college football players where no correlation was observed between the number of mild TBIs or concussions and tau concentrations. Increased plasma tau levels were also noted following training sessions [47].

In chronic neurodegenerative disorders, such as Alzheimer's disease (AD), CSF T-tau concentrations exhibit a weak correlation with plasma T-tau concentrations [48]. In contrast, a stronger correlation more likely exists in cases of acute TBI, contingent upon injury severity and the subsequent release of T-tau from neurons into both CSF and plasma. Notably, the elevation of tau levels post-TBI tends to persist longer in CSF (weeks) compared to blood (days) [49]. Given the typically low concentrations of tau protein in peripheral blood during both healthy and diseased states, accurate measurement through conventional immunoassays has proven challenging. The advent of ultrasensitive Single molecule array (Simoa) technology has facilitated the precise quantification of T-tau in both plasma and serum [50]. Multiple studies have documented elevated plasma T-tau concentrations in relation to TBI [51], with tau levels generally peaking between 12 and 24 hours after the injury and occasionally persisting at high levels.

The previous studies suggested that tau levels increases following TBI may exhibit both acute and chronic trajectories. While the initial increase in tau levels is indicative of acute neuronal damage, a secondary increase may be associated with chronic neurodegenerative processes and secondary pathologies [52]. Notably, blood tau concentrations have been observed to rise with age [53], and recent findings have reported distinct temporal profiles and substantially higher T-tau levels in female athletes with concussions, as compared to their male counterparts [54]. Furthermore, significant correlations have been found between serum tau concentrations and neurological outcomes in patients who have experienced resuscitated cardiac arrest [55].

In studies involving professional ice hockey players with concussions, plasma T-tau concentrations were elevated one hour post-injury compared to pre-season levels, and accurately predicted return-to-play (RTP) time [56]. Additionally, a study focusing on concussed athletes found that plasma T-tau concentrations six hours after injury correlated significantly with RTP time [57]. Elevated plasma tau levels have also been reported in military personnel exposed to blast injuries within the prior 18 months [50], with higher exosomal tau concentrations being associated with chronic symptoms in military personnel after mild TBI [58]. In a study encompassing TBIs of varying severity, plasma T-tau concentrations successfully differentiated mild TBI cases from controls when samples were collected within 24 hours of injury [59]. Serum tau levels have similarly been identified as significant outcome predictors following TBI [60]. Recent research has demonstrated that acute plasma P-tau concentrations and the P-tau/T-tau ratio outperform T-tau concentrations in predicting TBI outcomes [61]. However, plasma T-tau concentrations upon admission were unable to distinguish between incomplete and complete recovery in cases of single and uncomplicated mild TBIs [62]. Conflicting results have been reported concerning the utilization of C-tau as a fluid biomarker for the acute biochemical diagnosis of mild TBI [62, 63].

9. Second impact syndrome and juvenile head trauma syndrome

The second impact syndrome (SIS) and juvenile head trauma syndrome are conditions that affect children and young adults who have suffered minor brain trauma. Juvenile head trauma syndrome refers to the catastrophic or fatal cerebral edema and coma that can result from a single injury in this population. SIS occurs when an athlete experiences a mild head injury or concussion, then suffers a second head injury before the symptoms associated with the first injury have resolved, producing rapid cerebral swelling. SIS typically affects young athletes, particularly males, ranging in age from 10 to 24 years, with a mean age of 17.9 years. Most athletes reported to have SIS were American football players, usually at the high school level, but it has also been reported in association with boxing, karate, skiing, and ice hockey. SIS is thought to result from an abrupt post-traumatic loss of cerebral blood flow auto-regulation and catecholamine release that create a rapid increase in intracranial blood volume and catastrophic cerebral edema. In two-thirds of cases, a thin, acute subdural hematoma has been found on neuroimaging or at autopsy, which may reflect the hyperemic state, in the absence of other major hematomas or space-occupying lesions. The relationship of SIS with juvenile head trauma syndrome or with malignant cerebral edema after mild TBI is uncertain, and both may be manifestations of the same underlying pathophysiology [64].

10. The inflammatory response in mild TBI

The inflammatory response is a multifaceted process that involves the activation of various cell types, including microglia and astrocytes, and the release of a multitude of pro-inflammatory and anti-inflammatory mediators [65]. Numerous studies have demonstrated that the inflammatory response is activated early after mild TBI and can persist for several weeks or even months. Inflammatory biomarkers, such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), have been proposed as potential indicators of mild TBI [20, 66, 67]. These biomarkers are elevated in individuals with mild TBI, and their levels have been linked to the severity and outcome of the injury [68]. Inflammation is characterized by the activation of immune cells and the release of inflammatory mediators, such as cytokines and chemokines [69]. In the context of concussion, inflammation has been proposed as a potential contributor to the pathophysiology of the injury and the persistence of symptoms in some individuals [70]. Several studies have investigated the levels of inflammatory biomarkers in individuals with concussions. Some studies have found elevated levels of cytokines, such as IL-6 and TNF-α, in the serum or CSF of individuals affected by concussion events, while others have not observed significant differences in inflammatory biomarker levels between individuals with trauma and controls [71–73].

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