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The Pathophysiology of Sports Concussion

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Abstract During concussion, the brain is exposed to rapid acceleration, deceleration, and rotational forces, resulting in the stretching and distortion of neural structures. This produces in an injury of transient neurological dysfunction, as evidenced by the clinical symptomatology. It is now evident that recurrent head trauma is also associated with the development of some chronic neurodegenerative disorders. Despite increased awareness of concussion over the past decade, large voids remain in our understanding of its pathophysiology. Prospective longitudinal studies are needed to better understand the underlying biological mechanism of acute concussive injury as it relates to chronic neuropathology.

Keywords Concussion · Neural structures · Head injury · Pathophysiology · Chronic neuropathology

Introduction

The 2012 Zurich consensus statement on concussion in sports defines concussion as a brain injury produced by biomechanical forces resulting in a rapid onset complex pathophysiological process affecting the brain. These injuries are associated most commonly with a direct blow to the face, head, neck, or body that in turn initiates an "impulsive force" to be transmitted to the head [1]. This coup-contrecoup injury exposes the brain to rapid acceleration, deceleration, and rotational forces instigating stretching and distortion injuries to components such as neuronal cell bodies, axons, dendrites, glial cells, and blood vessels. Axons are most vulnerable to these stretch injuries and may sustain injury even without the occurrence of neuronal death [2]. After concussion occurs, a complex neurophysiological cascade is initiated resulting in the disruption of axonal and membrane function, including ionic flux with widespread neurotransmitter release, cerebral blood flow (CBF) alterations, and synaptic dysfunction [3, 4]. This results in an injury of transient neurological dysfunction, as evidenced by the clinical syndrome of concussion. It is also now evident that recurrent head trauma may be associated with the development of some chronic neurodegenerative disorders.

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Basic Science Pathophysiology

Ionic Flux and Glutamate Release

In a 2011 review of the post-concussive neurometabolic cascade, Barkhoudarian et al. illustrate that during concussive injury, shearing forces damage the neuronal membrane producing an efflux of potassium into the extracellular space and initiating a widespread release of glutamate. This in turn binds to *N*-methyl-D-aspartate (NMDA) and D-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) ionic channels instigating further depolarization and influx of calcium ions. Depolarization results in an extensive "spreading depression" of neurons and ATP-dependent Na+/K+ pumps become activated, which require high levels of glucose metabolism. Post-injury, the Na+/K+ pump quickly diminishes intracellular energy stores and neurons are forced to use glycolysis.

Concomitantly, oxidative metabolism is further disturbed due to mitochondrial dysfunction and an upsurge in lactate production which contributes to localized acidosis, cerebral edema, and an increase in membrane permeability [4].

Energy Crisis

In an animal model of fluid percussion injuries in rats, hypermetabolism occurs in conjunction with reduced cerebral blood flow (CBF) creating a discrepancy between glucose supply and demand, creating a cellular energy crisis [2]. After experimental fluid percussion injury in rats, CBF may be decreased by as much as 50 % of normal [5]. This "metabolic mismatch" of decreased CBF and increased glucose requirements is theorized to be a potential cause of ongoing vulnerability and increased likelihood of recurrent injury. A second injury occurring during this phase of increased susceptibility will bring about metabolic changes in glucose comparable to those occurring with the initial insult. Several TBI studies indicate decreased CBF in adult and pediatric populations is consistently correlated with inferior patient outcomes. Maugans et al. observed that despite documented improvement on computerized neurocognitive exams, decreased CBF was noted on magnetic resonance phase contrast angiography in 36 % of participants at 30 days post-injury. While the precise pathophysiologic mechanism of decreased CBF is unknown, possibilities include interruption of cerebral autoregulation, vasospasm, or disturbance of regional perfusion [6–8]. After the initial timeframe of hyperglycolysis and "metabolic uncoupling," glucose ratios become hypometabolic lasting roughly 7–10 days in adult animals but may vary by age and in younger animals with studies indicating a shorter period of impairment [9••].

Altered Neurotransmission and Inflammation

In previous reviews of neuro-metabolic changes following concussion, Giza and Hovda have described alterations in ligand-gated excitatory and inhibitory neurotransmission balance during in vivo experimental TBI, including changes in glutamatergic *N*-methly-D-aspartate (NMDA), adrenergic and cholinergic systems, and γ-aminobutyric acid (GABA) [5,9]. Changes in glutamate *N*-methly-D-aspartate (NMDA) receptor function and makeup have been noted in research following TBI in both the developed and immature brain. These same changes noted in rat pups indicate functional consequences including impeding normal memory, electrophysiology, and plasticity found in a developing brain. NMDA receptor changes also trigger functional alteration in calcium flux patterns, phosphorylation/activation of downstream signal transduction, and immediate gene activation in adult rats. Furthermore, the excitatory-inhibitory balance post-concussion can be altered by changes in inhibitory neurotransmission and receptors of GABA. This is theorized to cause post-concussion susceptibility for the development of anxiety or post-traumatic stress disorder due to the decreased levels in the amygdala [9••].

In the past, inflammation was usually overlooked in mild TBI; however, more recent studies indicate inflammatory changes also occur with mild TBI. It has been noted in rats that a widespread upregulation of cytokine and inflammatory genes occur after TBI. One theory suggests glutamate release paired with the activation of immune receptors most likely increases oxidative stress and the possibility of cell injury. This is termed "immunoexcitotoxicity" [9••].

Mechanism of Injury

Multiple mechanisms of injury may result in concussion. These include direct head impacts from colliding with another player, falls to the ground, or being struck by inanimate objects. Forces applied to the body may similarly induce head/neck acceleration sufficient to result in concussive injury. Studies have sought to determine whether specific mechanism of injury and impact to certain regions of the body predispose to concussive injury. Among football, soccer, and ice hockey, blows to the temporal side of the head were the most probable area to be struck resulting in concussion [10]. It is conceivable that the origin of temporal blows may arise from an athlete's "blind spot," thus, rendering the individual unable to anticipate the impending collision. A 2010 study suggested that head impact severity is lessened in contact sport athletes when collisions are anticipated [11]. The failure to adequately contract cervical musculature prior to contact likely enhances the degree of head/neck acceleration following impact. This underscores the need to provide contact sport players with the necessary technical skills to heighten their awareness of imminent collisions to mitigate the severity of head impacts.

It is also possible that the temporal region is inherently more vulnerable to concussions than other focal areas of the head. Biomechanical models have suggested that direct impacts to the side of the head result in more shear stress to areas of the brain relative to frontal or occipital impacts [10]. If this finding is replicated in future studies, helmet manufacturers should consider research and development in ways to further attenuate forces delivered directly to this region of the head.

Despite direct head impact being the most likely etiology of concussion, other mechanisms provide adequate force to result in injury. Concussion can result from high-speed acceleration-deceleration head motions that do not require a direct blow to the head. A study in ice hockey, for example, reported concussive impacts were more likely to occur from contact with another object or body part other than the head [10]. Identifying the precise mechanism of injury, however, can prove challenging in the context of sport. At times,

determining the specific object or body part responsible for the concussive force is difficult in the presence of multiple impacts on a single play. For example, some ice hockey players in the matter of one sequence are sometimes struck directly in the head and then checked into the boards or ice. It may be prudent to formally investigate these types of double head contacts in the context of concussive injury to gather as much accurate information as possible [10].

Studies have also sought to determine the role of gender in concussion pathophysiology. The increased rate of concussion in female athletes relative to males within similar sports is thought partially due to anatomic and biomechanical differences. Females are known to have lower isometric neck strength, neck mass, and head mass, when compared to their male counterparts [12, 13]. Females display greater head and neck acceleration/deceleration when an external force is applied to the upper body. These findings may explain why females have less inherent ability to tolerate comparable forces to the head and neck region. Routine cervical resistance training has subsequently gained favor as a potential means of attenuating the acceleration forces that cause concussions in high-risk sports such as football, soccer, ice hockey, boxing, and lacrosse.

Mechanism of injury is also thought to play a role in the duration of recovery from concussion. Studies indicate that athletes recover in the range of 1 week to 3 months post-injury [14, 15]. The significant variability in recovery time thought due to multiple risk factors such as age, prior concussive injury, and pre-morbid medical conditions. Despite presenting with similar symptoms and normal neuroimaging, it is possible that mechanism of injury (motor vehicle accident [MVA] vs. sports-related impact) may influence the severity of injury. Specifically, MVA patients sustaining concussion have shown a significantly longer recovery time when compared to similar age-matched athletes following sports-related concussion. Recovery time, measured via computerized neuropsychological testing, found that soccer and football players had a median recovery of 35 and 32 days, respectively. On the contrary, MVA subjects experienced a median recovery time of 97 days. Particular areas of prolonged impairment were noted in both memory as well as visual processing within the MVA cohort [16•]. While return to play pressures likely influence recovery and symptom reporting, data has also suggested that more pronounced cognitive dysfunction likely exists in the MVA population, subsequently lengthening recovery times [16•]. The reasons behind this discrepancy remain unclear; however, the authors suspect that external forces applied to the brain during MVA-related concussion likely result in more pronounced axonal shearing, potentially predisposing individuals to longer recovery trajectories. Larger studies are needed to further explore these variables that differentiate patient populations and their clinical course.

Most head impacts sustained in sports do not result in the clinical syndrome of concussion; however, repetitive subconcussive hits may produce structural and functional brain changes. White matter abnormalities on diffusion tensor imaging have been discovered in professional soccer players and collegiate hockey players with no documented history of concussion. Relative to swimmers of similar age, male professional soccer players have shown decreased white matter integrity, similar to the axonal degeneration observed in individuals with mild traumatic brain injury (mTBI) [17]. Repetitive subconcussive head impacts in collegiate football players have been associated with functional defects in the blood-brain barrier, loss of white matter integrity, and neurocognitive impairment in a dose-dependent manner [18]. These findings are worrisome, especially for adolescents and teens who sustain similar head impact exposures in youth sports. Very little research has focused on the acute or long-term sequelae of subconcussive head trauma. The proposals of "hit counts" and other objective measures to track head impact exposures over the course of seasons and careers could potentially provide the metrics needed to evaluate cumulative risk exposure [19].

Similar Mechanism to Migraine

Previous research raises the possibility of a common molecular pathophysiological cause of migraines and post-traumatic headache [20–22]. Fluid percussion injury in rats, a model used to study traumatic brain injury, is noted to cause a widespread ionic flux. Cortical spreading depression was originally described in the context of migraine and referred to significant neurophysiological changes within the central nervous system [23]. Extracellular potassium and intracellular sodium, calcium, and chloride are increased in the brain after mTBI and migraine. Furthermore, both mTBI and migraines appear to result from an excess release of excitatory amino acids and opioids, such as glutamate and beta-endorphins, respectively [20, 24].

Mild head trauma can activate trigeminal nociception, similar to that seen in migraine. This, in turn, results in the sequential activation of second- and third-order neurons within the brain stem, hypothalamus, and thalamus, leading to cortical spreading depression. The upper cervical sensory nerve roots that converge on the trigeminal nucleus caudalis may also contribute to the activation process, as inciting trauma results in forced flexion and extension of the cervical spine [25].

An additional intriguing connection between concussion and migraine has been suggested within the pedigree of a family with the CACNA1A gene mutation implicated in familial hemiplegic migraine. Kors et al. have reported delayed cerebral edema and coma following trivial head trauma in carriers of this ion channelopathy [26]. This suggests a potential genetic predisposition for symptomatic neurological

impairment with associated head trauma. With increasing numbers of ion channelopathies being discovered, it is possible that genetic factors such as these may belie the "glass jaw" phenomenon whereby some athletes are more prone to the syndrome of concussion as well as further catastrophic neurological injury [9••].

Acute to Chronic Transformation

Approximately 90 % of adults experience clinical recovery from concussion within 7–21 days, while up to 10 % progress to post-concussion syndrome, a symptom complex that includes persistent dizziness, fatigue, irritability, anxiety, insomnia, loss of concentration, memory impairment, and noise sensitivity [27]. Prolonged recovery courses are more common in the pediatric population, with 15 % still reporting post-concussion symptoms 90 days after injury [28]. Neurocognitive dysfunction is concurrent with persistent post-concussive symptoms, as adolescents perform below average on measures of memory, verbal ability, and executive function [29].

Axonal dysfunction is thought to contribute to ongoing cognitive challenges through delayed conduction, damage to cerebral networks, and deficits in neurotransmission [9••]. Recent evidence has focused on the potential of persistent axonal degeneration following even a single mTBI [30]. The mechanism of chronic axonal damage may especially worrisome in the context of recurrent head trauma, particularly in athletes who sustain a recurrent head injury before symptoms associated with the first have fully cleared, immature myelination in youth, or those with underlying genetic predispositions [9••]. What remains uncertain, however, is the confluence of factors dictating the specific threshold of injury.

The immature brain is more susceptible to neurological impairment after concussion, and evidence confirms that children and adolescents have slower rates of recovery than adults [31, 32]. Many factors potentially influence recovery from concussion, including age, history of prior concussion, and preexisting comorbidities [33]. Youth with a history of one or more concussions within the 12 months prior to sustaining a new injury experience poorer recovery outcomes, suggesting a period of vulnerability in which previously injured youths are at higher risk of a refractory recovery course [28]. Multiple studies also suggest that post-traumatic migraine characteristics following concussion are associated with cognitive impairments and prolonged symptoms, further highlighting the considerable overlap of typical post-concussive symptoms and those commonly described in migraine [34, 35••]. With regard to persistent post-traumatic headache (formerly chronic post-traumatic headache), there is legitimate concern that duration of symptoms may impact the efficacy of future treatment attempts. For this reason, some have proposed an earlier and more aggressive treatment paradigm with regard to post-traumatic headache [36].

Despite recent advances in neuroimaging and our understanding of concussion, long-term cognitive outcomes remain poorly understood. It should be stressed, however, that numerous causes of neurocognitive impairment have been reported, including primary headache disorders, psychiatric comorbidities, and even urinary urgency [37–39]. It would, therefore, be erroneous to conclude that cognitive dysfunction is unique to mTBI [40]. Regardless, a high index of suspicion is imperative when evaluating those individuals exhibiting cognitive difficulties in the context of recent head trauma.

Biomarkers

According to the National Institutes of Health, biomarkers are defined as a characteristic that can be objectively evaluated and measured as a reliable indicator of a normal biological process, pathogenic process, or pharmacologic response to an intervention. A strong biomarker candidate for concussion should be able to detect either injury to structural changes of cellular elements, leakage of specific brain-related proteins into peripheral circulation and cerebral spinal fluid, or a subtle change in neurological function [41]. Researchers hope to ultimately detect concussion on a cellular level by measuring specific proteins released during axonal injury. Biomarkers could potentially provide practitioners an objective means to detect cerebral dysfunction at onset, recognize the window of vulnerability post-concussion, aid in return-to-play decision making, and possibly identify those individuals at risk of long-term cognitive problems [42].

Tau

Tau is a microtubule associated with proteins located in CSF axons. Tau elevates in serum samples within 6 h of sustaining mild TBI [43]. Currently, Tau is considered one of the most promising biomarkers being studied. Tau levels in both blood and CSF have been noted to increase in boxers after a match; furthermore, it was noted CSF tau levels correlate with both the number and severity of head impacts [44•]. In a study of professional ice hockey, Shahim et al. noted the highest serum levels of Tau were measured 1 h post-concussion. It was also documented that Tau sampling at 1 h post-concussion could predict the number of days it took for concussion symptoms to resolve and player be safely cleared for competition. This is clinically relevant as it may be possible to predict the severity of the concussion using the Tau level at 1 h post-concussion [44•, 45•]. Tau serum levels, however, are not considered useful in predicting the need for head CT in patients after mTBI. Overall, the reliability of this biomarker is yet to be established in several studies and further research is needed [45•, 46].

S-100 Calcium-Binding Protein β

S-100 calcium-binding protein β (S-100β) found in astrocytes and some neuronal cells is a promising biomarker as detecting this protein in the serum is a good indicator of damage to the blood-brain barrier (BBB) [42, 43]. Shahim et al. recently completed a study of concussion in professional Swedish ice hockey players in which an immediate increase in S-100β levels was noted post-concussion [45•]. Levels peaked during the first hour after concussion and declined in the first 12 h post-concussion. The same study, documented a significant association between the concentration of S-100β 1 hour after injury and the time to resolution of post-concussion symptoms. Previous research of S-100β was noted to correlate with Glasglow Coma Scale scores and consistently parallel radiologic findings indicating it can be used to predict the need for CT imaging [45•]. S-100β testing is already available in the market in Europe and is now used as an official part of the decision guidelines to determine who should receive a CT scan post-injury under the 2013 Scandinavian guidelines for head injury management with low levels of S-100β indicating no scan is needed [42]. A possible limitation of S-100β is a documented increase in levels even after controlled games not involving concussion leaving researchers to determine if concentrations of S-100β are consistently higher in concussed players versus a lower elevation noted in controlled games with no concussion. Research has also indicated S-100β may have questionable value in pediatric patients [45•, 46].

Neuron-Specific Enolase

Neuron-specific enolase (NSE) is a glycolytic enzyme specific to the cytoplasm of neurons [43]. The presence of NSE in serum has been shown to be a reliable indicator of neuronal cell death. However, data is limited in its usefulness in mTBI [46]. In the study performed by Shahim et al., NSE did not increase significantly post-concussion and levels were noted to be elevated even after games in which players did not experience concussion when compared to baseline blood concentrations. NSE levels were not prognostic in determining severity of concussion and no correlation between NSE levels and recovery time after a concussion was noted [44•, 45•]. An additional limitation is that NSE concentrations may vary between the internal jugular and peripheral blood depending on the timing of the blood draw. Comparative changes were noted when samples were drawn after the initial primary injury during which markers were released into the blood at the moment of mechanical disruption versus those samples taken after secondary injury involving active destruction of the cerebral tissue [47]. Concerns for rapid degradation of NSE in the CSF and blood have also been noted in past research [48].

Glial Fibrillary Acidic Protein

Glial fibrillary acidic protein (GFAP) is a protein found in glial cells and represents a major part of the astroglial skeleton. Finding this marker in the blood or CSF suggests astrocyte damage and possible disruption of the BBB making it a highly specific marker for CNS pathology [43]. Elevated GFAP levels 3 h post-injury reliably suggest the need for CT imaging. Alternate studies of GFAP demonstrated a high predictive value for MRI indicating that low-serum GFAP values predict normal MRI. Research has noted when compared to S-100β, GFAP appears to be a more sensitive biomarker as it was found to be reliable in predicting the need for MRI and also was shown to have prognostic value in patient outcomes. Limitations of GFAP include a high potential for undetectable levels of GFAP in patients experiencing mTBI and unknown reliability in pediatric patients [44•, 46].

Ubiquitin C-terminal Hydrolase

Ubiquitin C-terminal hydrolase (UCH-L1) is a cytoplasmic protein found specifically in neurons and is an indicator of neuronal loss and disruption of the BBB when found in serum [43]. UCH-L1 is more frequently associated with severe TBI, and levels are directly related to the significance of the injury. A recent study noted the serum levels of UCH-L1 were significantly higher in CT-positive patients making this a likely predictor of both intracranial lesion and severity of injury. Increased concentration correlates with lower GCS score and need for neurosurgical intervention. A limitation of this biomarker is the suggestion that increased serum levels may not associate with subconcussive hits or mTBI, most likely making it useful only in more severe injuries. Very little research has been completed in the pediatric population [44•, 46].

Neuroimaging

Concussion currently remains a clinical diagnosis as neuroimaging techniques have not been shown to be useful as diagnostic tools [44•]. Neuroimaging has proven unsuccessful in the past because the rotational and shearing injuries associated with concussion is not evident on conventional imaging such as computed tomography (CT) scans or T1- or T2-weighted magnetic response (MR) imaging [49]. Two promising imaging techniques being researched include diffusion tensor imaging (DTI) and functional MRI (fMRI) [44•, 49].

DTI is an advanced MRI imaging technique used to quantify microstructural variations in white matter by mapping in vivo configurations of water diffusion using scalar maps of fractional anisotrophy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). Evidence from animal models of both acute and subacute brain injuries

suggest DTI can identify the primary axotomy and secondary demyelination associated with complex mild-to-severe TBI [49]. Findings are controversial as research has demonstrated both increased and decreased FA after similar injuries. It is unknown if this is due to the "great spatial heterogeneity" of the different areas of the brain researched or if it is possibly related to the lack of consistency in the timing of imaging post-injury. FA may have some predictive value and may correlate with patient outcomes depending on the direction and degree of FA changes. It is currently undecided if FA can fully realize white matter tract changes or if other modalities would be superior. While this initial research is promising, very little has been completed in the area of pediatric neuroimaging and more data in this population is gravely needed [6, 44•].

Significant alterations in patterns of brain activation have been detected using fMRI in individuals with ongoing post-concussive symptoms. fMRI detects changes in various physiological correlates of neuronal brain activation such as cerebral blood flow, blood oxygenation, and cerebral blood volume instead of imaging brain activity. The most majority of research is based on blood oxygenation changes and the signal contrast has been termed blood oxygen level dependent, which is an indirect measure of brain activity. The premise behind this imaging techniques is that when a particular cerebral area is active, it will experience a local increase in oxygen-rich blood leading to a greater proportion of oxygen-rich blood in the vein and deoxygenated blood in the surrounding the brain tissue causing an increased signal [41]. Axonal damage has been related to cognitive impairment post-concussion in both adult and pediatric patient populations. fMRI is able to detect abnormal activation of neural circuits associated with cognitive deficits post-concussion. A recent study used fMRI both prior to and after performance of cognitive tasks to establish patterns of hyperactivity in the post-concussive brain even 1 week after injury. This hyperactivity correlates with prolonged recovery in post-concussive athletes. Abnormal hyperactive brain patterns have been noted to remain for months after neurocognitive testing has normalized. This lingering hyperactivity is theorized to be the result of a compensatory mechanism of functional re-distribution of neurocognitive resources during recovery [2, 4, 6].

Chronic Traumatic Encephalopathy and Other Neurodegenerative Disorders

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with recurrent head trauma, including concussive and subconcussive injuries. It is thought to result in executive dysfunction, memory impairment, depression, apathy, poor impulse control, and eventually dementia. Since the description of CTE by Omalu et al. in a former professional football player, further cases of contact sports athletes have shown gross and microscopic pathology attributed to repeated exposure to concussive blows [50–52]. The disease has gained widespread public attention and has now been described post-mortem in former hockey, baseball, rugby, and soccer players [53]. In these cases, tau protein deposition was proposed as the pathological hallmark of the condition now known as CTE; however, tau deposition is a nonspecific marker of brain inflammation in response to many different stimuli, not all of which are traumatic [53]. Interestingly, McKee et al. have reported findings consistent with CTE in the brains of approximately 80–100 % of the former football players studied. This substantially high rate has led some to question a possible selection bias in the samples studied [54••]. To date, the baseline rate of CTE in amateur and professional athletes is still unknown, and it remains uncertain how head trauma itself initiates disease pathology, acts to accelerate an underlying predisposition, or both.

More convincing evidence for the chronic sequelae of recurrent/cumulative head trauma has long been reported in the pathological studies of combat sport athletes, such as boxers [55]. The syndrome of dementia pugilistica or the "punch drunk" syndrome was first described in the medical literature by Martland in 1928, when he described a 38-year-old retired boxer with advanced parkinsonism, ataxia, behavioral changes, and pyramidal tract dysfunction [56]. The clinical spectrum of dementia pugilistica is now known to be synonymous with the clinical phenotype of modern day CTE. The findings are typically delayed in onset and occur after an extended exposure to the sport, usually after a boxer retires or late in the boxer's career. Due to this delayed onset in clinical symptomatology, chronic neurologic dysfunction remains the most difficult safety challenge in combat sports. The true incidence and prevalence of chronic neurologic impairment in modern-day boxing remains unknown. The prevalence was approximately 17 % among former professional boxers who were licensed by the British Board of Control from 1929 to 1955, with further increases seen as exposure to head trauma accumulated [57]. Despite this knowledge base within the professional boxing ranks, strong objective evidence of chronic neurologic pathology associated with amateur boxers remains elusive [58].

The neurodegenerative pathophysiology of CTE is complex, and the neurological sequelae are poorly understood. Areas of the cerebral cortex and limbic system appear most affected, with typical findings characterized by neurofibrillary tangles of TAR DNA-binding protein and phosphorylated tau [59–61]. NFT pathology in CTE is concentrated near the bottom of sulci, distinguishing it from Alzheimer's disease pathology that is located primarily within the cerebral and entorhinal cortices [62]. Post-mortem brain analysis also points to substantial brain atrophy, notably in the frontal cortex and medial temporal lobe in structures such as the thalamus, hypothalamus, and mammillary glands [44•, 59].

Lehman et al. recently reported on the neurodegenerative causes of death among retired National Football League players. Although the overall mortality of the studied population was lower than predicted, the neurodegenerative mortality was found to be three times greater than that of the general US population. Specifically, the rates of AD and amyotrophic lateral sclerosis were four times higher [63].

Despite the resurgence of interest in the long-term effects of sports concussion, it should be stressed that no empirical data yet exists regarding a dose-dependent threshold of developing chronic neurological sequelae after head trauma (i.e., how much head trauma is too much?). Furthermore, no level I evidence has demonstrated a causal link between concussion in sports and the development of CTE later in life. Some have suggested a divergence of media accounts of sports-related concussion in relation to the existing scientific and medical findings [64]. Andrikopoulos raised the question of whether individuals were creating a "concussion crisis" regarding CTE in a recent JAMA Neurology issue [65]. The most recent version of the International Concussion in Sport consensus statement concluded, "It was further agreed that a cause-and-effect relationship has not yet been demonstrated between CTE and concussions or exposure to contact sports. At present, the interpretation of causation in the modern CTE case studies should proceed cautiously [1]." Prospective longitudinal studies are necessary to clarify the underlying biological mechanism of acute concussive injury and its influence in the evolution to chronic neuropathology.

Summary

While our understanding of concussion pathophysiology has improved significantly in the past decade, the diagnosis remains an imperfect art. Large voids remain in our understanding of the pathophysiology and clinical presentation of concussion. In the absence of rapid and inexpensive diagnostic measures, it remains a clinical diagnosis that is subject to tremendous variability among clinicians. There is clearly a great need for further research exploring the diagnosis, treatment, and long-term ramifications of this injury. This evolving field of neuroscience will ultimately provide the opportunity to offer far more effective treatment options to our athletic and non-athletic patients alike.

Compliance with Ethics Guidelines

Conflict of Interest Tad Seifert and Victoria Shipman each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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