Post-Concussion Syndrome and Chronic Traumatic Encephalopathy

Subjects: Anatomy & Morphology

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Traumatic brain injury is a significant public health issue and represents the main contributor to death and disability globally among all trauma-related injuries. Martial arts practitioners, military veterans, athletes, victims of physical abuse, and epileptic patients could be affected by the consequences of repetitive mild head injuries (RMHI) that do not resume only to short-termed traumatic brain injuries (TBI) effects but also to more complex and time-extended outcomes, such as post-concussive syndrome (PCS) and chronic traumatic encephalopathy (CTE).

Keywords: post-concussion syndrome ; chronic traumatic encephalopathy ; neuropathology

1. Introduction

Traumatic brain injury (TBI) is a significant global public health issue and represents the main contributor to death and disability among all trauma-related injuries [1]. Sixty-nine million patients are estimated to suffer a traumatic brain injury each year worldwide [2].

Non-recurring concussions and mild brain injuries due to TBI usually do not impose chronic consequences on the brain tissues of the patients [3]. The effects of such traumatism are usually short-termed, and the symptoms alleviate over some weeks or months. In this way, the post-concussive syndrome (PCS) following a mild traumatic brain injury could exhibit mild symptoms that last no more than four weeks [4]. However, in some cases, persistent PCS symptomatology could predict subsequent brain damage or risk for further comorbid conditions [5][6]. Thus, repetitive brain injuries are linked to increased risk of later-life cognitive impairment and neurodegenerative disorders, including Chronic Traumatic Encephalopathy [7].

2. Clinical Diagnosis and Definition

2.1. Concussion, TBI, and RMHI

Traumatic brain injuries can cause loss of consciousness, post-traumatic amnesia, disorientation and confusion, and new-onset neurological symptoms such as post-traumatic epilepsy, anosmia, or hemiparesis. These symptoms present immediately after the occurrence of the TBI, or immediately after the recovery of consciousness and may persist past the acute post-injury period [8]. The clinical entity defined by the persistent neurological symptoms following a TBI is post-concussion syndrome (PCS).

The pathophysiology of concussion is not clearly understood. It is believed that stretching and disruption of neuronal and axonal cell membranes occur after a head injury, leading to neurometabolic cascade activation preceding neuronal and axonal injury and death and potentially to neuroinflammation and microglia activation [9][10]. Considering these aspects, many classifications systems were proposed. However, only a few are still widely used, possibly due to the fact that most of the classification and diagnostic criteria for concussion consequences and TBI are instead based on clinical observations and symptomatology. Cantu et al. 2006 thoroughly described most of these classification systems and provided evidence on their grounds and use direction [11].

There are different classification systems for TBIs, based on severity, pathoanatomic type, outcome, and prognosis [7]. Generally, TBIs were classified as mild, moderate, or severe by using the Glasgow Coma Scale (GCS). A TBI with a GCS score of 13–15 is defined as mild TBI, between 9–12 as moderate and 3–8 as severe [12]. An important parameter of the severity of TBI is post- or peri-traumatic amnesia. Post-traumatic amnesia (PTA) of 1–24 h indicates a moderately severe TBI; however, more recent classifications of moderate TBI require post-traumatic amnesia extending beyond 24 h [13][14].

A widely acceptable TBI classification system is the Mayo System which divided TBIs as possible, probable-moderate, and definite moderate-severe [14]. A TBI is classified as probable mild if there is loss of consciousness below 30 min, post-traumatic amnesia for less than 24 h, and there is a depressed, basilar, or linear skull fracture, but with intact dura matter. A TBI is classified as possible if the patient develops blurred vision, confusion, headache, or nausea, and as definite moderate-severe if there is loss of consciousness lasting 30 min or more, post-traumatic amnesia of 24 h or more, or worst full Glasgow Coma Scale score below 13, or if there is death due to this TBI. The Mayo Classification System also requires that all other causes of impaired consciousness should be excluded. If there is additional evidence of brain hematoma, haemorrhage, contusions, or ruptured dura mater, the TBI is classified as moderate-severe [15].

Repetitive mild head injuries (RMHI) can be observed in athletes, military veterans, martial arts practitioners, victims of physical abuse, and epileptic patients. The effects of traumatic brain injury (TBI) or RMHI in later life are not well understood. However, recent studies suggested that even mild head injuries could increase the risk of later-life cognitive impairment and neurodegenerative disease [16]. Even less severe traumatic brain injuries have been linked with an increased risk of dementia and reduced age of onset for Alzheimer's disease (AD) [16]. Furthermore, it was demonstrated that repeated TBIs could increase the risk for neurodegenerative processes, such as the development of Chronic Traumatic Encephalopathy (CTE) [17][18][19][20][21][22][23][24][25][26][27][28]. In this way, it was shown that the neuropathological hallmark of CTE is the deposition of p-tau immunoreactive pre-tangles and thread-like neurites at the depths of cerebral sulci, and neurofibrillary tangles in the superficial layers I and II [29], which are also some of the most important features of initial neurodegeneration processes [30][31]. However, CTE could only be diagnosed post-mortem, and although different diagnostic criteria can be used for clinical and research purposes, their specificity and sensitivity are unclear [32][33][34].

A possible link between TBI/RMHI and CTE or early dementia has widespread implications for predisposed individuals in which TBI/RMHI are prone to occur more often or repeatedly. Neurodegeneration was not the only risk associated with the RMHI occurrence, as some recent studies showed that depression, anxiety, post-traumatic stress disorder, sleep disorders, as well as cardiovascular disorders, metabolic syndromes, chronic pain, musculoskeletal fragility, and other heterotypic disorders were also associated with the subsequent long-term consequences of traumatic brain injuries [35][36][37][38][39].

2.2. Post-Concussion Syndrome

Post-concussion syndrome (PCS) is a sequela of minor brain injury. Although about 29–90% of patients may experience PCS after a head injury [23][24][25][26][27][28], its etiology is unclear. Despite that no universally accepted definition of PCS exists, it is generally accepted as the development of at least three of the following symptoms: headache, fatigue, irritability, dizziness, and balance issues, affected sleep, poor memory and concentration, and increased sensitivity to light and noise. The symptoms occur shortly after a head impact and could persist for weeks or months. When the symptoms persist for more than six months or one year, the condition is defined as persistent PCS. PCS is usually characterized by the absence of objective findings and inconsistencies in presentation [31].

The ICD-10 diagnostic criteria for PCS include a history of traumatic brain injury and the presence of three or more of the following: headache, dizziness, fatigue, irritability, insomnia, concentration or memory disturbance, and intolerance to stress, alcohol, and emotion [40][41].

2.3. Chronic Traumatic Encephalopathy

Chronic Traumatic Encephalopathy (CTE) was initially introduced as "punch drunk" or dementia pugilistica in the early 1900s. It was first described in boxing, where many retired boxers developed dementia at a higher incidence than the general population [17][20][42][43].

The definition of CTE is mainly based on neuropathological changes, and the term traumatic encephalopathy syndrome (TES) refers to the clinical syndrome associated with exposure to repetitive head impacts.

Traumatic encephalopathy syndrome and CTE do not include the acute or post-acute manifestations of a concussion or post-concussion syndrome.

TES/CTE is classified into probable, possible, and improbable, based on clinical presentation and the pathologic changes [44]. Jordan et al. (2013) proposed that definite TES should include neurologic signs and symptoms in keeping with CTE, including behavioural or cognitive disturbance and motor symptoms [44]. Pathologic confirmation of tau deposition in brain autopsy could also be considered definitory [32]. Probable TES is described as two or more of the following: cognitive and/or behavioural impairment, cerebellar dysfunction, pyramidal tract disease, or extrapyramidal disease. Thus, Jordan

et al. (2013), as well as Reams et al. (2016), suggested that the diagnosis could be supported by abnormal neuroimaging findings on positron emission tomography, single-emission tomography, structural magnetic resonance imaging, or diffusion-tensor imaging [33][44].

There are multiple clinical diagnostic criteria for TES/CTE for clinically probable and possible TES [32][33][34]. The former requires a history of head trauma exposure, the persistence of symptoms for longer than two years, lack of another diagnosis to otherwise explain the signs and symptoms, and the presence of at least two symptoms, such as speech, mood, or behavioural disturbance, and three signs including ataxia, memory loss, and dysarthria [34].

Based on the clinical presentation, TES/CTE can be further classified into behavioural or mood variant, cognitive variant, mixed variant, or dementia variant, and based on the progression, into progressive type, stable type, unknown or inconsistent type [33].

3. Clinical Biomarkers

3.1. Neuroimaging

Severe traumatic brain injury can result in diffuse white matter injury, focal contusions, or hemorrhages that can be seen on conventional MRI or CT. Several studies on the white matter integrity using diffusion tensor imaging (DTI) support the assertion that repetitive asymptomatic head trauma concussion and mild traumatic brain injuries result in damage to cortical and subcortical microstructures despite observable findings on conventional MRI being absent [45][46].

Herweh et al. (2016) performed a DTI study on 31 amateur boxers and 31 control individuals, and they reported significantly reduced fractional anisotropy (FA) in the boxers group [47]. The neurite orientation dispersion and density imaging (NODDI) is a DTI technique that can show changes of axons and dendrites and can also provide information on neurite density and orientation [48]. Using NODDI in athletes following a sport-related concussion, Churchill et al., 2019 found that decreases in fractional anisotropy and increases in axial and radial diffusivity were associated with reduced intraneuritic water volume [49]. They also reported a positive correlation between the severity of symptoms and changes in fractional diffusivity axial and radial diffusivity [50].

Abnormalities in functional MRI (fMRI) in patients with mild TBIs have been reported in multiple studies [51][52][53][54]. Repetitive head injury is related to acute and long-term changes, while irregularities in the default mode network and other white matter changes have been described [51][52][53].

MRS measures human brain metabolism in vivo. Alosco et al. (2019) on an MRS study in 77 symptomatic retired NFL players, reported a positive correlation between behavioural/mood symptoms and neurochemicals related to neuroinflammation [55]. They described a positive correlation between accumulative head impacts and lower parietal white matter creatine levels.

SWI is sensitive to venous blood and can detect hemorrhage or microbleeds in traumatic brain injuries. Studies in patients with a history of mild TBIs have shown a correlation between SWI findings and cognitive outcome [56].

FDG-PET. 2-deoxy-2-(18F) fluorodeoxyglucose can provide in vivo evidence of the severity and distribution of brain changes presumably representing altered synaptic activity. Former boxers with a history of repetitive brain injury revealed hypometabolism in multiple brain regions, including posterior cingulate, bilateral frontal lobes, parieto-occipital cortex, and cerebellum. The findings were very inconsistent between studies [57][58].

Aβ-PET and Tau-PET. Although Aβ deposition is a common co-pathology in advanced CTE cases [59], it occurs at an accelerated rate and predominantly affects the depths of cortical sulci [60]. Many tracers, including FDDNP, flortaucipir, and FTP, have been developed to detect tau deposition in CTE; however, the sensitivity and specificity of most of them remain low; thus, their use is limited [48][61][62][63][64].

3.2. Fluid Biomarkers

Although the pathophysiology and the underlying mechanisms of PCS and the other discussed concussion, TBI, and RMHI are not yet clearly understood. Neuroimaging could offer viable diagnostic solutions; fluid biomarkers could still be a good alternative, considering that molecular biomarkers also have predictive value and could show many pathological molecular features which occur before other visible/detectable symptoms. In this way, fluid biomarkers could be of crucial interest in the context of predicting the neurodegeneration processes to which predisposing risk repetitive brain injuries are contributed.

Thus, recent studies on the relevant body fluids dynamics during and following head injuries showed that several molecules occurring in blood, cerebrospinal fluid (CSF), saliva, and even urine recorded specific changes of suggestive diagnostic value. In this way, altered plasma tau concentrations are reported to be related to the persistent post-concussion syndrome in military personnel with a history of TBIs [65], there might be an association between tau or axonal injury and PCS. Additional recent studies on professional athletes with PCS and matched controls showed increased NFL concentration, astroglia activation, and Aβ peptide dysmetabolism in the brain [66][67][68], however further studies are required. A recent meta-analysis showed significantly increased serum light neurofilament chain (NFL) levels in all patients with a history of concussion compared to controls. That sports-related concussion was specifically associated with higher levels of NFL, marking the potential of NfL levels as a biomarker in mild TBI and head impacts [69].

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