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Article type : Review-Symposium

Head trauma in sports – clinical characteristics, epidemiology and biomarkers

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Abstract

Traumatic brain injury (TBI) is clinically divided into a spectrum of severities, with mild TBI being the least severe form and a frequent occurrence in contact sports, such as ice hockey, American football, rugby, horse riding and boxing. Mild TBI is caused by blunt non-penetrating head trauma that causes movement of the brain and stretching and tearing of axons, with diffuse axonal injury being a central pathogenic mechanism. Mild TBI is in principle synonymous with concussion; both have similar criteria in which the most important elements are acute alteration or loss of consciousness and/or post-traumatic amnesia following head trauma and no apparent brain changes on standard

neuroimaging. Symptoms in mild TBI are highly variable and there are no validated imaging or fluid biomarkers to determine whether or not a patient with a normal computerized tomography scan of the brain has neuronal damage. Mild TBI typically resolves within a few weeks but 10-15% of concussion patients develop post-concussive syndrome. Repetitive mild TBI, which is frequent in contact sports, is a risk factor for a complicated recovery process. This overview paper discusses the relationships between repetitive head impacts in contact sports, mild TBI and chronic neurological symptoms. What are these conditions, how common are they, how are they linked and can they be objectified using imaging or fluid-based biomarkers? It gives an update on the current state of research on these questions with a specific focus on clinical characteristics, epidemiology and biomarkers.

Key words: head trauma; traumatic brain injury; clinical characteristics; epidemiology; biomarkers

Introduction

Traumatic brain injury (TBI) affects people of all ages and is recognized as a major cause of death and disability worldwide. TBI can be categorized into mild, moderate and severe, largely based on clinical rating scales that include items such as loss of consciousness (including duration), amnesia and neurological symptoms [1]. While moderate and severe TBIs mainly are a neurosurgical and intensive care problem, at least in the acute phase, the focus of this overview paper is mild TBI, which constitutes the majority of all TBIs [2, 3]. Mild TBI (Box 1) is common in some types of sports, where the exposure can be extreme (*e.g.*, in boxing where repetitive head impacts [RHI] is an inherent part of the game).

Mild TBI is typically caused by blunt non-penetrating head impact resulting in transient symptoms without any structural abnormalities on a routine computerized tomography (CT) scan of the brain [2]. Even if CT is part of the diagnosis, many cases with mild TBI evaluated in the emergency department and most cases of sports concussion do not undergo structural brain imaging. Further, it has been reported that 28% of mild TBI patients with normal CT have lesions on a magnetic resonance imaging (MRI) scan done within two weeks after the trauma, with lesions (contusions and/or multiple foci of haemorrhagic axonal injury) being associated with worse outcome [4]. Symptoms in mild TBI are highly variable, and may, except for loss of consciousness (which is not a mandatory sign), include physical (*e.g.*, nausea and vomiting, dizziness, headache), cognitive (*e.g.*,

poor concentration and memory problems), and behavioural (*e.g.*, irritability, and emotional lability) symptoms [5].

Most patients who exhibit post-concussion symptoms following mild TBI (sports-related or not) show symptom resolution within one to 12 weeks [6]. However, a subgroup have persisting symptoms, known as post-concussive syndrome (PCS) [6]. PCS is poorly defined since symptoms are even more variable than in mild TBI, which also makes its exact prevalence difficult to estimate; 10-15% is probably a reasonable inference [6]. Additionally, symptoms that may be seen in PCS, such as headache, fatigue, sleep disturbances and anxiety, are common in everyday life in healthy people, especially in persons with pre-existing psychiatric conditions such as anxiety and depression. Symptoms are also influenced by both personality and psychological and demographic factors [6], such as social status, gender, ethnicity and alcohol use, that also may affect the rate of recovery after mild TBI [7]. There is also a growing body of literature on the role of genetic variation in determining various outcomes following TBI. Some, but not all, studies suggest a weak association of Alzheimer-associated apolipoprotein E (*APOE*) genotypes with worse clinical outcome [8]. Regarding non-*APOE* single nucleotide polymorphisms, a recent meta-analysis concluded that no firm data exist [9].

Recently, a long-term consequence of RHI with mild TBIs, a chronic neurodegenerative disorder called chronic traumatic encephalopathy (CTE) that mostly has been reported in contact sport athletes and military veterans, has gotten massive attention in media and research, as well as in the society at large. The condition is not new; ever since Martland described a disease he called “punch drunk syndrome” in retired boxers in 1928 [10], it has been known that RHI may cause chronic and progressive neurological disorders. Millspaugh replaced this term in 1937 when he coined the more generally known name *dementia pugilistica* [11]. In 1949, Critchley introduced the broader term “chronic traumatic encephalopathy” (CTE) for the same condition [12].

The start of modern CTE research was in 1973, when Corsellis presented the neuropathological findings in retired professional boxers with severe symptoms [13]. The key finding was widespread neurofibrillary tangles in several brain regions, but a set of other neuropathological findings were common, including cavum septum pellucidum, scarring of the cerebellum and cerebral hemispheres, and degeneration of the substantia nigra [13]. After the identification of amyloid β (Aβ) as the main component of plaques in Alzheimer’s disease (AD) and antibodies became available, these brains were re-examined and it became evident that most boxers with *dementia pugilistica* (or CTE) also had widespread diffuse Aβ plaques in their brains [14]. In 2005, the first case report on CTE in a former American football player was published [15], and after that CTE pathology has been

identified in several other contact sports, such as ice hockey and rugby, and also in soldiers exposed to explosive blasts [16]. At present, CTE is a neuropathological diagnosis requiring *post mortem* examination, since there are no established clinical criteria and no biomarkers to support the diagnosis *ante mortem*.

Since RHI in sports is such a common event and since athletes in some sports are extremely exposed, a group of researchers convened to scrutinize the existing literature to come up with a conclusion regarding if there are reasons to worry about the future incidence of PCS and CTE, not only in professional athletes, but also in the large group of people who take part in these types of sports as they grow up or as a leisure activity in adulthood. Can we improve the diagnosis of mild TBI upon a head impact to reduce the risk of new injuries before the brain has healed properly? And can we develop biomarkers and clinical cohorts through which we can learn more about how strong the association of RHI with CTE is and if there are objective signs of vulnerability that could guide secondary prevention?

What are the clinical characteristics of repetitive head trauma and suspected CTE?

Certain segments of the population are exposed to RHI including those participating in sports, serving in the military, or vulnerable in civilian life (*e.g.*, domestic abuse). While some of these head impacts will result in transient neurological dysfunction (*i.e.*, concussion), most of the blows are subconcussive in nature, and some might not have any impact on the gross structural or functional integrity of the brain parenchyma. The cumulative exposure to RHI may result in several possible neurological outcomes: (i) none, that is, there is no appreciable neurological signs or symptoms (ii) static neurological deficits that do not progress, and (iii) a neurodegenerative process such as CTE [17].

The symptoms and signs associated with CTE pathology have been generally categorized into four domains: cognitive, behavioural, mood, and motor function. The cognitive deficits most commonly seen are in the spheres of memory, attention, executive function and psychomotor speed. Behavioural symptoms can include explosivity, impulsivity, aggression/rage, and disinhibition [18]. Mood disorders often involve features of depression, anxiety, irritability, and hopelessness; while motoric signs consist of dysarthria, ataxia, parkinsonism, spasticity, or some combination of these [18]. In addition, motor neuron disease has been reported in a subset of cases (11%) with CTE and the predominant presentation being motor weakness, atrophy, and fasciculations, along with cognitive and behavioural symptoms [19].

The concept that there are two distinct presentations of CTE has been raised in the literature and described as “classic” and “modern” forms. The classic form is derived from older studies of boxers and highlights primarily motoric features such as dysarthria, difficulty with gait, and other parkinsonian signs, with little progression of cognitive impairment. On the other hand, the modern cases (seen primarily in football players) show mood, behavioural, and cognitive symptoms, with scant motor findings [20]. The differences between these two presentations are most likely due to the lack of attention paid to the behavioural and cognitive symptoms in the older literature on boxers, along with the sport-specific type and volume of head impacts and their differential mechanical effects on regional brain tissue.

Attempts have been made to create clinical criteria for the diagnosis of CTE. A more recent proposal for research diagnostic criteria employs the term traumatic encephalopathy syndrome to acknowledge that CTE is currently a neuropathologically defined entity and that there may be other long term consequences of RHI (such as chronic axonal injury and astrocytosis without the classic tau pathology of CTE) [21-23]. The clinical diagnosis of CTE, specifically, will likely depend on identification of accurate biomarkers for the disease. While imaging techniques such as positron emission tomography (PET) imaging of tau pathology and various fluid biomarkers are being explored, none has yet been validated against pathological diagnosis (please see below for an in depth discussion of each biomarker modality).

How common is mild TBI?

A recent meta-analysis determined that the annual international incidence rate of mild TBI is 224 per 100,000 [24], with estimates ranging from 100 to 300 per 100,000 [3]. The incidence of sports-related concussion, often included under the category of mild TBIs, ranges from 0.17 to 0.99 per 1000 athlete exposures but vary greatly depending on the sport [25-27]. It is very likely that these reports underestimate the true incidence, as mild TBIs are often not diagnosed or treated and thus remain undocumented [28-30]. Furthermore, there are currently no consensus criteria for mild TBI [31-33]. Although the World Health Organization Collaborating Center Task Force on Mild Traumatic Injury has recommended an operationalized definition of mild TBI [34], the application of this definition can differ across data sources, surveillance systems and studies [33].

While prior studies have linked moderate and severe TBI with increased dementia risk [35-37], evidence is evolving for the association between mild TBI and dementia. A 2014 review by the International Collaboration on Mild Traumatic Brain Injury Prognosis found that there was insufficient data to support mild TBI as a risk factor for dementia [38]; however, several recent population-based studies have examined the association between mild TBI, determined mostly by electronic medical records, and dementia and reported a 1.2- to 3.3-fold increase in risk of dementia even after adjusting for demographics, as well as key medical and psychiatric comorbidities [39-43]. Data from a US cohort of older veterans found that even mild TBI without loss of consciousness was associated with an increased risk of dementia [42]. In general, these investigations have observed a small but significant increase in risk of dementia with mild TBI and support a dose response effect with increasing TBI severity [40-43]. Future research, based on biomarker-based diagnoses, are warranted to examined whether TBI specifically increases the risk of AD pathology (*i.e.*, plaques and tangles) or whether TBI lowers the reserve capacity of the brain, *i.e.*, the threshold for age-related AD-type pathology to result in clinical dementia.

There is heightened awareness regarding the effects of RHI that may cause repetitive mild TBIs or concussions, particularly in sports, and risk of CTE [44]. Some epidemiologic studies have reported an increased risk of dementia with multiple TBIs [41, 43], and a consensus panel has outlined criteria for the neuropathological diagnosis of CTE [16]. However, previous work on CTE has primarily been based on retrospectively collected data in selective populations, and the relationship between repetitive TBIs, CTE pathology, and clinical symptoms requires further investigation [45]. While increasing evidence supports an association between mild TBI and risk of dementia, additional longitudinal studies are needed to understand the mechanisms of this association and to track the clinical course of mild TBI, especially repetitive mild TBIs.

What can we learn from EU registries regarding the association of head trauma in sports with neurological and/or psychiatric problems, as well as potential CTE?

Although the amount of research on epidemiology of TBI is on increase, valid and comparable epidemiological data on national or international level are still limited [46, 47]. Two recent studies have looked into the patterns TBI in European countries, using microlevel data provided by Eurostat [48, 49].

One of the studies analysed data from 25 countries and produced age-standardized hospital discharge rates (HDR) and mortality rates due to TBI. HDRs have varied quite substantially between the analysed countries, ranging from 81 to 643.5; mortality rates ranged from 3.6 to 21.8 per 100,000 people. Pooled age-standardized rates were estimated: 287.2 for HDR and 11.7 for mortality rates. The pooled rates were extrapolated to the population of the 28 countries of the European Union (EU) and the whole of Europe. These extrapolations suggest that in the EU, about 57,000 people die and around 1.45 million are admitted to the hospital as a consequence of a TBI. In the whole Europe (48 countries), the number of deaths is estimated at about 82,000 and the number of hospital discharges at about 2.1 million, annually. Falls were identified as the predominant cause of fatal TBI, followed by traffic-related injuries [48].

The second study estimated the years of lost life (YLLs) due to TBI in Europe. This study found that, on average, 259.1 YLLs could be attributed annually to TBI per 100,000 people in the analysed countries. One TBI death was associated on average with 24.3 YLLs. Extrapolated, these rates suggest that about 1.32 million YLLs could be attributed to TBI in the EU [49].

At this point, it is not possible to directly link these TBI data to head trauma in sports with neurological and/or psychiatric problems, or potential CTE. Additionally, the data on mild TBI is limited. However, the pooled rates provided in these studies used together with rates of the occurrence of these health problems in patients with head trauma could provide grounds for a first assessment of the problem on the level of individual countries and Europe as a whole.

What biomarker candidates show promising results for mild TBI and CTE?

Biomarker definition

A biomarker is an objective measure of a biological or pathological process that can be used to evaluate disease risk or prognosis, to guide clinical diagnosis and/or to monitor therapeutic interventions. Fluid biomarkers have the potential to help to define: (i) the severity of TBI; (ii) adaptive and recovery processes following TBI; (iii) the transition between a normal injury/recovery pattern and a progressive CTE process; and (iv) intervention outcomes. As pointed out above, validated biomarkers for mild TBI may help dissecting the cause-and-effect relationships between RHI, mild TBI, PCS and CTE. Candidate biomarkers for TBI-related processes are summarized in Figure 1 and discussed in detail below.

Structural MRI

Structural MRI may offer important insights after TBI, and in particular sports-related brain injuries. While CT is the most commonly used imaging modality in the acute phase of all TBIs, and particularly useful in the detection of lesions that require neurosurgical intervention, it is poor at detection of traumatic axonal injury. This lack of sensitivity for microstructural injury may explain, at least in part, why CT is not predictive of outcomes after mild TBI. The distribution and extent of such lesions, detected using structural MRI with conventional sequences (including FLAIR, T1-weighted, T2-weighted, and gradient echo [GE]- or susceptibility-weighted imaging [SWI]), have been shown to improve prediction of outcome in both mild [4] and severe TBI [50]. SWI is more sensitive for the detection of microhaemorrhages than GE, and a higher number detected may be associated with an unfavourable outcome [51]. The ability of structural MRI to detect key prognosis-defining lesions, as may be found in the brainstem, is of particular importance [52].

Diffusion tensor imaging (DTI) is one of the most commonly used advanced structural MRI sequences in TBI. This technique characterizes the diffusion of water molecules in tissue environments, which are influenced by the microstructural organization of tissues and their constituent cells and can provide unique insights into pathophysiology. In the acute phase after injury, DTI may be used to characterize cytotoxic and vasogenic oedema around contusions, providing insights into a potentially reversible “traumatic penumbra” that may targeted in future clinical trials [53]. In addition to better insight into lesions that may be seen, DTI may identify lesions not detectable on CT or more conventional MRI sequences, and may be the only abnormality found in mild TBI [54, 55]. Dynamic structural changes after TBI can also be detected using DTI and have been found to correlate with changes in behaviour [56]. Knowledge of such changes are important to provide insights into late pathophysiology, and provide a framework that allows MRI to be used as an imaging biomarker for therapy response.

Functional MRI

The most commonly used functional MRI (fMRI) method is Blood-Oxygen-Level-Dependent (BOLD) signal imaging, which is considered an indirect measure of neuronal activity. Two main classes of BOLD imaging are task- and task-free (resting state) fMRI. Task fMRI typically involves the alteration between two or more functional states, for example intense visual stimulation mixed with periods of no or simple visual stimulation. In resting-state fMRI, the BOLD signal may be measured over 10 minutes when a participant is passively observing a fixation cross. Image analyses can reveal

networks of distributed regions in which slow-wave fluctuations in the BOLD signal are synchronized. Many studies converge on about a dozen of resting-state networks, including visual, auditory, sensory-motor, attention and default-mode networks.

The potential of task and resting-state fMRI have been considered in a number of clinical contexts, although several issues remain, such as reproducibility and lack of standards for pre- and post-processing of images [57]. fMRI has been used in studies of TBI at acute as well as chronic stages, and a meta-analysis provided evidence for reduced frontal activity after mild TBI [58]. An fMRI correlate of fatigue after mild TBI has been revealed by monitoring activity changes within a single extended fMRI session [59]. MRI sessions can also be repeated within the same participant, for example to prospectively acquire pre-injury measures of neuronal functioning in athletes at risk for TBI and to monitor recovery over time. In a study of concussed high-school football athletes, a working-memory task fMRI design revealed hypo-activation in several regions, including frontal cortex, at the acute stage, followed by increased activity at 7 weeks [60]. At this later stage, the athletes showed no signs of cognitive deficits, but elevated frontal fMRI activity could still reflect compensatory operations that may contribute to fatigue. Thus, fMRI can provide unique information, not readily apparent from behavioural testing.

Amyloid and tau PET

Hyperphosphorylated tau protein in neurofibrillary tangles and Aβ aggregates have been reported in both AD and CTE and provide promising targets for new diagnostics as they are identifiable using molecular imaging techniques such as PET. This approach could dramatically improve the ability to identify patients developing progressive post-traumatic neurodegeneration, potentially allowing characteristic features of CTE and other types of post-traumatic dementia to be identified in vivo.

The localization of fibrillar Aβ pathology *in vivo* is possible using amyloid PET tracers such as ^{11}C-Pittsburgh compound-B (^{11}C-PIB). Increased ^{11}C-PIB is seen in patients with AD [61] in a pattern consistent with the neuropathology of this condition [62]. Following TBI, ^{11}C-PIB binding is increased in cortical grey matter and striatum in the first year after injury [63] and remains increased in the chronic phase many years after injury [64]. The distribution of ^{11}C-PIB binding in TBI and AD shows similarities but also differences. In AD, early deposition of Aβ is often seen in the posterior cingulate cortex [65] and this region also shows increased ^{11}C-PIB following TBI. However, increased ^{11}C-PIB binding is also seen after TBI in regions not typically affected by AD, including the cerebellum,

suggesting that Aβ pathology may be produced by a different mechanism in TBI, *e.g.*, TBI-related injury to Purkinje cells.

Major advances have been made recently in the development of PET tracers binding to hyperphosphorylated tau. These hold great promise for the diagnosis of tauopathies and may be useful in TBI. For example, flortaucipir ([^{18}F]AV-1451, [^{18}F]T807) demonstrates potent and specific non-displaceable binding to tau neurofibrillary tangles in *post mortem* human brain tissue in AD [66-68]. Flortaucipir is selective for tau and does not significantly bind to Aβ, α-synuclein or transactive response DNA-binding protein 43 (TDP-43) [66]. The pattern of binding is in keeping with the clinical phenotype [69], cognitive profile [69] and estimated Braak & Braak staging of AD [70]. However, in non-AD tauopathies, the utility of this ligand is less clear [68]. In TBI, one case of an American football player exposed to repetitive TBI and manifesting progressive neuropsychiatric symptoms has been reported to exhibit increased flortaucipir-binding [71]. Current studies exploring flortaucipir and other PET ligands in various post-traumatic cohorts should clarify whether tau PET has the potential to become a clinically useful diagnostic test.

Fluid biomarkers

Biomarker fluids of relevance to TBI include cerebrospinal fluid (CSF; a fluid that is in direct contact with the extracellular space of the brain and can reflect biochemical changes in the central nervous system), serum and plasma. There has been some discussion on TBI biomarkers in urine and saliva, but the data so far on this topic are only preliminary. The most vulnerable part of neurons in TBI are the axons. Biomarkers for axonal injury include neurofilaments (the best studied is the light subunit of neurofilament; NfL) and tau. These proteins can be measured in both CSF and blood. Tau concentrations in ventricular CSF correlate with lesion size and outcome in severe TBI, so that high levels indicate worse injury [72]. Studies in mild TBI show elevated CSF concentrations of both tau and NfL but the magnitude of the rise is larger for NfL than for tau [73], suggesting that blows to the head impact long, myelinated (NfL-rich) axons in the white matter more than short, non-myelinated (tau-rich) axons in the cortex, which is in agreement with experimental, as well as neuroimaging and neuropathological studies [72]. Biomarker studies in CSF also show that TBI is followed by an inflammatory acute phase response within the central nervous system, which is reflected in the CSF as increased concentrations of pro-inflammatory proteins, such as IL-6, IL-8 and IL-10 [74, 75]. Studies on mild TBI are lacking. Candidate blood biomarkers for TBI include the neuronal injury markers neuron-specific enolase (NSE) and UCHL1, the astroglial injury markers S100B and glial

fibrillary acidic protein (GFAP), the axonal injury markers tau and NfL [76]. Standard enzyme-linked immunosorbent assays for tau and NfL were recently transferred onto the Single molecule array (Simoa) platform, which allows for the ultrasensitive measurement of these two proteins in the blood [77]. Plasma tau concentrations correlate poorly with CSF concentrations [78, 79], but in acute brain injury a rise in plasma T-tau concentration already during the first hours post-injury is predictive of outcome [80, 81]. In sports-related concussion, plasma T-tau concentration at 1 hour post-injury predicts return-to-play time with high accuracy [81]. It is not clear if these rapid tau changes represent axonal injury or release of pre-existing interstitial fluid tau into the blood across an injured blood-brain barrier (the latter seems more likely from a pathophysiological standpoint). Serum NfL correlates strongly with CSF NfL, is increased in active professional fighters [82], in ice hockey players with post-concussive syndrome [83] and in retired fighters who have neurological symptoms [82]. The marker increases over time in American football athletes over the course of a season, suggesting that it may be sensitive to repetitive subconcussive head impacts [84]. It appears to be a slower biomarker than tau, reaching a maximum several days post-injury [83, 85] and may therefore be more useful as a return-to-play test to determine which players had a head impact that was complicated by neuronal injury than an acute injury test.

Regarding the association of TBI with CTE, there are currently no validated fluid biomarkers for the disease, but AD-type tau pathology may be detected using CSF total and phosphorylated tau [86]. The best fluid biomarker for Aβ pathology (>90% accurate) is the CSF Aβ42/Aβ40 ratio, which appears to be working reasonably well in plasma as well [87]. Recently, an intriguing interaction of greater RHI and increased microglial activation, as reflected by increased CSF levels of the soluble form of the triggering receptor expressed on myeloid cells 2 (sTREM2), with higher CSF total tau concentrations was reported in a sample of former professional American football players [88]. These data, if replicated, suggest that RHI may induce microglial activation that in turn may help promoting tau pathology of potential relevance to the development of CTE. Validated fluid biomarkers for other CTE-related pathologies, including TDP-43 inclusions, are currently lacking.

Metabolomics

Metabolites are small molecules (*e.g.*, carbohydrates, amino acids, lipids and organic acids) that are produced by the metabolic processes of an organism. Metabolomics is a fairly new area in biomedicine, which analyses these substances as potential biomarkers of on-going metabolic processes. Metabolite biomarkers have some special advantages in brain research over the more conventional protein biomarkers [89]: as small molecules they are less dependent on the blood-brain-barrier, they usually react more quickly on (patho)physiological phenomena, and they can describe simultaneously an array of concomitant processes. As shortcomings, they are usually not organ-specific; they are influenced by external factors, such as diet, exercise and medications, and their origin may be difficult to ascertain.

Due to the vast complexity of TBI, metabolomics certainly has great potential to reveal clinically useful biomarkers, possibly in combination with other types of biomarkers, such as proteins and microRNAs. Because of the novelty of this field, human studies are still few. However, in pilot studies, metabolites have been shown to correlate with both the initial severity and outcome of TBI, and they seem to add predictive value beyond a combination of known clinical predictors [90]. Metabolites have also been able to separate mild TBI patients from patients with acute orthopaedic injuries [91] and predict CT abnormalities in patients with acute TBI [92]. In animal studies, lesions of different brain regions produced different metabolite profiles [93], which is an exciting finding that awaits replication in human studies. Using metabolomics to study associations between TBI and long-term neurodegeneration is in its very infancy; there is only one experimental study that suggests that this approach could reveal something about the potential mechanisms [94].

Summary and future perspectives

There is consensus that sports-related RHI and mild TBIs are a potential concern for public health but the precise risk and if there is a certain dose of RHI or mild TBI that should be avoided is not known. Researchers discussed if the neurological consequences are caused by a few relatively severe injuries or more subtle but repetitive head blows that may cause subconcussive small brain injuries that accumulate over time and eventually cause symptoms; no consensus was reached and the topic is thus in need of more research. In any case, sports athletes are undoubtedly people at increased risk. Data suggest that RHI (irrespective of precise cause but commonly seen in athletes and military personnel) increases the risk of chronic neurological symptoms that may translate into frank CTE, which is a *post mortem* diagnosis that is presently hard to ascertain based on clinical criteria.

Imaging and fluid-based biomarkers will be essential parts of such criteria. They will also probably be useful to define how common neuronal injury in sports athletes is and if subgroups at particularly high risk of chronic symptoms can be detected. Acute mild injuries could potentially be discerned with the help of biomarkers and so called return-to-play tests have the potential to identify people with incomplete recovery or a complicated recovery process, where it would make sense to avoid getting new injuries. Biomarkers will hopefully also be useful to evaluate novel treatment strategies aimed at reducing the extent of neuronal injury in TBI. The main challenge in research on the epidemiology of TBI is uncertainties regarding how the diagnosis was made. The main challenge in TBI biomarker research is to validate optimal panels for different clinical needs, taking into account also the time factor, since TBI is a very dynamic injury. Combining different biomarker modalities with novel statistical analysis tools will probably an important part of future TBI research.

Conflict of interest statements

Charles Bernick: CB reports research funding from UFC, Top Rank Promotions, Haymon Boxing and Bellator/Spike TV.

Kaj Blennow: KB has served at scientific advisory boards for Roche Diagnostics, Fujirebio Europe, IBL International, Eli Lilly and Alzheon and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg.

Gunilla Johansson: Reports no disclosures.

Marek Majdan: Reports no disclosures.

Virginia Newcombe: Reports no disclosures.

Lars Nyberg: Reports no disclosures.

Olli Tenovuo: Reports no disclosures.

Bengt Winblad: Reports no disclosures.

Kristine Yaffe: KY serves on DSMBs for Takeda, Eli Lilly, and an NIH sponsored study and is a member of the Beeson Scholars in Aging Scientific Advisory Board and a Senate member of the German Center for Neurodegenerative Diseases.

Henrik Zetterberg: HZ has served at scientific advisory boards for Roche Diagnostics, Wave, Samumed and CogRx and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg.

Acknowledgements

The conference was sponsored by Stiftelsen för Gamla Tjänarinnor.

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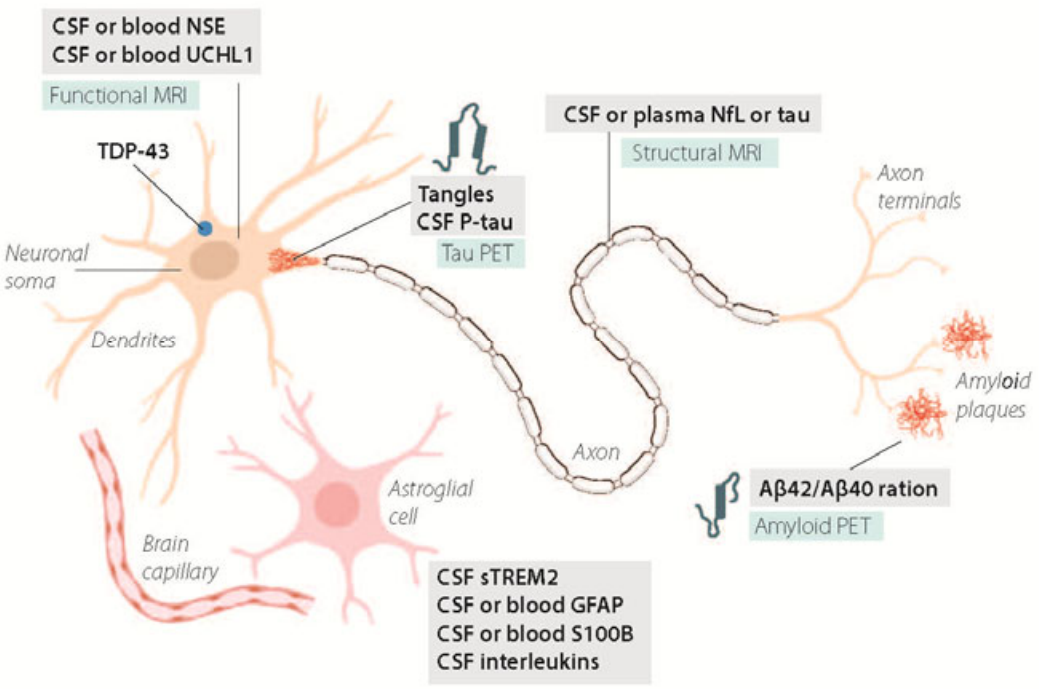
Figure legend

A schematic of TBI-related pathologies in the central nervous system, including candidate biomarkers that can be measured using imaging- or fluid-based techniques. Abbreviations: TDP-43, transactive response DNA-binding protein 43; NSE, neuron-specific enolase; UCHL1, ubiquitin C‑terminal hydrolase‑L1; P-tau, phosphorylated tau; PET, positron emission tomography; NfL, neurofilament light; MRI, magnetic resonance imaging; sTREM2, soluble triggering receptor expressed on myeloid cells 2; GFAP, glial fibrillary acidic protein; Aβ, amyloid β.



Box 1: Criteria for mild traumatic brain injury*

- Alteration of consciousness: Momentary up to 24 hours
- Loss of consciousness: 0-30 minutes
- Posttraumatic amnesia: 0-1 day
- Glasgow Coma Scale§: 13-15 (best score in first 24 hours)
- Structural imaging: Normal

*Definition by Department of Veterans Affairs/Department of Defense Evidence Based Practice (2009)

§The Glasgow Coma Scale consists of subscale scores for behaviours (such as eye opening and verbal and motor responses to questions and painful stimuli), with a higher total score indicating a higher level of consciousness of the patient. For example, the total score for the best eye opening, verbal response and motor response ranges from 3 to 15, with a sum score of 3 indicating total unresponsiveness and 15 indicating the best response (totally conscious).