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Neurological consequences of traumatic brain injuries in sports

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ABSTRACT

Traumatic brain injury (TBI) is common in boxing and other contact sports. The long term irreversible and progressive aftermath of TBI in boxers depicted as *punch drunk syndrome* was described almost a century ago and is now widely referred as chronic traumatic encephalopathy (CTE). The short term sequelae of acute brain injury including subdural haematoma and catastrophic brain injury may lead to death, whereas mild TBI, or concussion, causes functional disturbance and axonal injury rather than gross structural brain damage. Following concussion, symptoms such as dizziness, nausea, reduced attention, amnesia and headache tend to develop acutely but usually resolve within a week or two. Severe concussion can also lead to loss of consciousness. Despite the transient nature of the clinical symptoms, functional neuroimaging, electrophysiological, neuropsychological and neurochemical assessments indicate that the disturbance of concussion takes over a month to return to baseline and neuropathological evaluation shows that concussion-induced axonopathy may persist for years. The developing brains in children and adolescents are more susceptible to concussion than adult brain. The mechanism by which acute TBI may lead to the neurodegenerative process of CTE associated with tau hyperphosphorylation and the development of neurofibrillary tangles (NFTs) remains speculative. Focal tau-positive NFTs and neurites in close proximity to focal axonal injury and foci of microhaemorrhage and the predilection of CTE-tau pathology for perivascular and subcortical regions suggest that acute TBI-related axonal injury, loss of microvascular integrity, breach of the blood brain barrier, resulting inflammatory cascade and microglia and astrocyte activation are likely to be the basis of the mechanistic link of TBI and CTE. This article provides an overview of the acute and long-term neurological consequences of TBI in sports. Clinical, neuropathological and the possible pathophysiological mechanisms are discussed. This article is part of a Special Issue entitled 'Traumatic Brain Injury'.

Contents

Abbreviations: 3R, 3-repeat; 4R, 4-repeat; Aβ, amyloid-β; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; CSF, cerebrospinal fluid; CTE, chronic traumatic encephalopathy; FTLD, frontotemporal lobar degeneration; MND, motor neuron disease; NFL, neurofilament light polypeptide; NFT, neurofibrillary tangle; PCS, postconcussive syndrome; SIS, second impact syndrome; TBI, traumatic brain injury; TDP-43, TAR DNA binding protein.

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1. Introduction

In recent years, traumatic brain injury (TBI) and chronic traumatic encephalopathy (CTE) in contact sports participants have received intense media, medical and scientific attention. TBI is generally divided into acute and chronic (Blennow et al., 2012). Acute brain injury in sports-related trauma may lead to concussion, subconcussion, haemorrhage or other structural brain damages. The chronic consequence of TBI is CTE, a neurodegenerative condition, in which progressive clinical symptoms often begin several years after retiring from the sport with abnormal tau accumulation as the histological hallmark.

The aim of this review is to give an overview of the short and long term neurological consequences of sports-related TBI, including the characteristic clinical and neuropathological findings (Table 1). The pathophysiology of TBI and the possible mechanisms leading to progressive histological changes of CTE in later life years after the TBI has ceased are discussed.

2. Acute TBI

2.1. Catastrophic brain injuries

Common acute TBIs in sports are skull fracture, subdural and epidural haematoma and ruptured vertebral artery with subarachnoid haemorrhage (Logan et al., 2001; Miele et al., 2004). Catastrophic brain injuries refer to severe brain trauma associated with intracranial bleeding or cerebral contusions which may result in death or long term neurological sequelae. The most common cause of death in sports-related TBI is subdural haematoma especially in boxers (Guterman and Smith, 1987; Unterharnscheidt, 1995). Approximately ten deaths occur each year in boxing, most of which following knockout or technical knockout (Svinth, 2011). Most deaths are in lower weight classes in boxing. Decline in fatalities since 1983 might be related to shorter careers and fewer fights, hence, reduced exposure to repetitive TBIs (Baird et al., 2010). In the United States, there have been 133 catastrophic brain injuries registered among non-professional American football players since 1982: 90% were high school athletes and 8% were college players (Mueller and Cantu, 2009).

Table 1
Acute and chronic consequences of sports-related traumatic brain injuries (TBIs).

Acute sports-related TBIs:	Chronic sequelae of sports-related TBIs:
• Skull fracture • Subdural haematoma • Epidural haematoma • Subarachnoid haemorrhage • Intracranial haematoma • Cerebral contusion • Juvenile head trauma syndrome • Second impact syndrome • Concussion and subconcussion (or mild TBIs) • Postconcussive syndrome	• Chronic postconcussive syndrome • Chronic traumatic encephalopathy • Chronic hypopituitarism especially growth hormone deficiency (Tanriverdi et al., 2007) • Increased risk of neurodegenerative disorders including cognitive impairment, Alzheimer's disease, motor neuron disease and Parkinson's disease

2.2. Juvenile head trauma syndrome

Minor head trauma can sometimes cause severe and even fatal cerebral oedema and coma following a lucid interval. This delayed cerebral oedema, or otherwise known as the juvenile head trauma syndrome, has been described in collision sports involving children and adolescents (McQuillen et al., 1988), some of whom were found to carry the *CACNA1A* gene mutation linked with familial hemiplegic migraine (Kors et al., 2001).

2.3. Second impact syndrome

The term second impact syndrome (SIS) is a rare but widely feared complication of TBI among athletes. SIS refers to 'an athlete who has sustained an initial head injury, most often a concussion, sustains a second head injury before the symptoms associated with the first have fully cleared' (Cantu, 1998). The second head injury is typically only a minor blow to the head, but within minutes, the athlete collapses into a coma. It is postulated that severe cerebrovascular engorgement and cerebral oedema ensue following the second impact leading to brain herniation. Like juvenile head trauma syndrome, SIS is also more common in children and adolescents with a mean age of 17.9 (range: 10–24), predominantly male, and 71% occurred in American football players, usually at the high school level, 14% in boxing, and few cases were reported in karate, skiing and ice hockey (Mori et al., 2006). The relationship between SIS and juvenile head trauma is uncertain but both conditions are associated with malignant cerebral oedema after TBI. The replacement of the controversial and possibly misleading term of SIS with diffuse cerebral swelling has been proposed by some critics (McCrory, 2001).

2.4. Concussion

Concussion is the most common form of acute TBI in high-impact sports. Concussion is frequently referred as mild TBI in the literature and the two terms are used interchangeably. A concussion is defined as 'a complex pathophysiological process affecting the brain, induced by biomechanical forces either by a direct or indirect blow resulting in an impulsive force transmitted to the head.' (McCrory et al., 2013). Concussion does not cause structural injuries detectable by conventional

Table 2
Top 20 sports and recreational activities with the highest risk of head injuries requiring hospital emergency care or evaluation.[a]

1. Cycling[b] (H)
2. Football[b] (H)
3. Baseball and softball[b] (H—when batting)
4. Basketball[b]
5. Water sports[b]
6. Powered recreational vehicles[b] (H)
7. Soccer[b]
8. Skateboards and scooters[b] (H)
9. Fitness, exercise and health club
10. Winter sports (skiing (H), sledging, snowboarding (H), snowmobiling)[b]
11. Horseback riding (H)
12. Gymnastics, dance, cheerleading
13. Golf
14. Hockey (H)
15. Other ball sports
16. Trampolines[b]
17. Rugby
18. Lacrosse
19. Roller and inline skating
20. Ice skating

(H): Risk sports in which helmet or head gear use should be worn at all times. Proper fitting and safety standard approved by regulatory bodies such as the American Society for Testing and Materials (ASTM) are necessary for helmet and head gear to provide maximum protection against sports-related head injuries.

[a] Data obtained from an American Association of Neurological Surgeons (AANS) study on sports-related head injuries treated at the hospital emergency service in the United States in 2009 (http://www.aans.org/patient%20information/conditions%20and%20treatments/sports-related%20head%20injury.aspx).

[b] Top 10 sports-related head-injury categories among children aged 14 or below in the AANS study in 2009.

neuroimaging. Severe concussion can lead to loss of consciousness which may be prolonged. Acute concussion is a clinical diagnosis based on clinical evaluation of symptoms such as headache, cognitive (e.g., feeling like in a fog, reduced attention and concentration, amnesia and slowing of cognitive processing speed) and neuropsychiatric (e.g., emotional lability, irritability) changes and sleep disturbance, which reflect functional disturbance (Hall and Chapman, 2005).

If an athlete shows any clinical symptoms, on-field or sideline evaluation is required. Neuropsychiatric testing is an important aid in the overall assessment of concussion and contributes to the return-to-play decision (Walker and Tesco, 2013). Rest for 24–48 h is thought to be of benefit in the acute symptomatic period although further research to evaluate the benefit of long-term rest is required (McCrory et al., 2013). Low-level rehabilitation or exercise programme may be beneficial after a month if symptoms persist (Gagnon et al., 2009; Leddy et al., 2010). About 80–90% of concussions resolve in 7–10 days but the recovery time for children and adolescents is longer (McCrory et al., 2005).

In boxing, a 'knockout' is associated with concussion and loss of consciousness by definition. Due to the nature of the sport, concussion occurs more frequently in professional boxing than in amateur boxing or other contact sports (Koh et al., 2003). Concussion is reported in other martial arts including karate (Stricevic et al., 1983), taekwondo (Koh et al., 2003) and kickboxing (Gartland et al., 2001; Zazryn et al., 2003) but is an area in need of more research to highlight the potential magnitude of the TBI-related risks in view of their global popularity. Of the 2328 competitors in a Korean taekwondo tournament, the incidence of head blows and concussions was 226 with a higher propensity for younger participants, likely related to less competition experience, and those who lacked blocking skills (Koh and Cassidy, 2004). In soccer, heading, a manoeuvre using the head to advance or redirect the ball, or collisions with another player, the goalpost or the ground are the common causes of concussion.

2.5. Postconcussive syndrome

Postconcussive syndrome (PCS) is a clinical entity referred to as the presence of persistent neurological symptoms lasting for more than 3 months and is observed in 40–80% of individuals exposed to mild TBI (Hall and Chapman, 2005). About 10–15% of individuals experience persistent symptoms after 1 year (Roe et al., 2009; Williams et al., 2010). Neuropsychological tests reveal that cognitive impairment often persists beyond the subjectively symptomatic time in boxers following mild TBI or a knockout. Cognitive function is measurably impaired for days following a knockout in amateur boxers (Bleiberg et al., 2004). The seemingly mild head injury causing these subtle subjective and objective neuropsychiatric deficits is sometimes referred to as subconcussion (Guskiewicz et al., 2007b). Inappropriate management of concussion and subconcussion may put the athlete at risk of developing SIS and/or chronic PCS (CPCS) with persistent neurological symptoms, most commonly, headache, dizziness, impaired attention, poor memory, executive dysfunction, irritability and depression. CPCS is a clinical entity of chronic TBI, which is probably distinct from CTE, and the onset of neurological symptoms begins rapidly after the head trauma and persists but rarely progresses. The pathological substrate of CPCS is yet to be established as is its precise relation to CTE regarding its molecular pathology (Harmon et al., 2013; Kelly and Rosenberg, 1998).

3. Pathophysiology of sports-related TBI

3.1. Biophysical mechanisms in risk sports

Rapid acceleration and deceleration forces on the brain, either linear or rotational, are the primary mechanism in which concussion and subconcussion occur. Rotational acceleration such as blows to the head by hook punches in boxing results in concussion more frequently than linear acceleration caused by straight head blows and head contacts in other sports such as American football (Ohhashi et al., 2002) (Table 2). When subjected to rapid acceleration, deceleration and rotational forces, the brain and all its components including neurons, glial cells and blood vessels are stretched, which may disrupt their normal

Table 3
Differentiating histological features between CTE and Alzheimer's disease (Geddes et al., 1999; Hof et al., 1992; Ling et al., 2014; McKee et al., 2013).

	CTE	Alzheimer's disease
Tau isoforms	Mixed 3R and 4R	Mixed 3R and 4R
Distribution of astrocytic tangles and NFTs	–Patchy and irregular –Absence of neuritic plaques –Predilection for perivascular regions, in depths of cerebral sulci –NFTs are predominant in the superficial cortical layers (layer II and upper third of layer III) and periventricular regions –Early involvements of the frontal and temporal cortices	–Neuritic and mature plaques rather than astrocytic tangles –NFTs are predominant in the deep cortical layers –Early involvements of the hippocampal formation and limbic region
Aβ pathology	Rare; if present, likely to be age- or Alzheimer-related	Abundant amyloid deposition and plaques
Tau pathology in locus coeruleus	Early	Early
Ghost tangles	Frequently observed	Frequently observed
TDP-43 inclusions	Frequently observed	Occasionally observed

functions. Axons that span long distances from the cell bodies are particularly susceptible to stretching, which may lead to diffuse axonal injury, a basis for the symptoms experienced in concussion (McKee et al., 2014) (Fig. 1).

3.2. Neurobiology and neurometabolic cascade

A neurometabolic cascade of concussion sets into motion immediately following the biomechanical injury to the brain, with rapid release of neurotransmitters, efflux of K^+ and influx of Na^+, causing an increase in intra-axonal calcium concentrations, which activates protease calpain and triggers calpain-mediated proteolysis of the cytoskeletal proteins, a process that can potentially lead to irreversible axonal pathology (Blennow et al., 2012; McKee et al., 2014) (Fig. 1). An increase in intra-axonal calcium also stimulates glutamate release and glutamate-mediated activation of *N*-methyl-D-aspartate receptors causing depolarization of neurons (Spain et al., 2010). To restore the ionic balance, glucose consumption is increased, which depletes the energy stores, leading to events of impaired oxidative metabolism, glycolysis with lactate production resulting in acidosis and cerebral oedema (Barkhoudarian et al., 2011). Progressive microtubule disassembly is evident at the time of acute TBI impairing axonal transport. Axonal swellings occur and axons become disconnected at the location of the injury, which most commonly occur in the deep gyri at the grey and white matter interface (Barkhoudarian et al., 2011). Diffusion tensor imaging has found a correlation between white matter abnormalities after mild TBI and the severity of postconcussive cognitive problems (Bazarian et al., 2007).

3.3. Functional abnormalities following TBI

Despite the transient nature of clinical symptoms which usually resolve within 7–10 days, magnetic resonance spectroscopy, electrophysiological data and neuropsychological assessments indicate that the functional disturbance takes 30–45 days to return to baseline level (Brooks et al., 2000; Iverson et al., 2004). Functional MRI studies have shown alterations in brain activation patterns in individuals with persistent symptoms after TBI despite normal neurocognitive task performance (Chen et al., 2008; Gosselin et al., 2011; Lovell et al., 2007). Reallocation of neurocognitive resources as a compensatory mechanism and recruitment of brain regions outside the normal cognitive network is thought to enable the maintenance of a normal level of neuropsychiatric performance (Smits et al., 2009). Neuropathological analyses show axonopathy may persist for years after TBI (Johnson et al., 2013).

Children and adolescents experience prolonged recovery rates after TBI compared to adults (Field et al., 2003) and poorer outcome (Giza et al., 2005). The reasons for the greater susceptibility of the developing brain to TBI than adult brain are possibly due to the differences in the degree of myelination, volume ratio of brain to water, elastic properties and blood–brain barrier integrity (Anderson et al., 2000). To educate and raise awareness of the risk of contact sports in children is a public health responsibility to enable parents to make informed decision.

4. Biomarkers

4.1. Cerebrospinal fluid

Several cerebrospinal fluid (CSF) biomarkers of TBI have been established (Zetterberg et al., 2013). The levels of total tau protein and neurofilament light polypeptide (NFL) are raised reaching peak levels 4–10 days after TBI (Neselius et al., 2012; Zetterberg et al., 2006). Tau protein is highly expressed in thin, non-myelinated axons of cortical interneurons and NFL is found in large-calibre myelinated axons which project into deep brain layers and the spinal cord. The distinct regional distribution of tau and NFL is likely to indicate the components of the brain being affected by injury with raised CSF total tau protein representing axonal damage in grey matter neurons and raised CSF NFL signifying long myelinated axonal damage in white matter (Zetterberg et al., 2013).

Total tau protein levels in ventricular CSF correlate with lesion size and clinical outcome in patients with TBI (Franz et al., 2003; Ost et al., 2006; Zemlan et al., 2002). Total tau protein levels are elevated in lumbar CSF in boxers 4–10 days after a bout and in boxers who have not been knockout (Neselius et al., 2012; Zetterberg et al., 2006). The level of total tau protein levels normalize within the 8–12 weeks providing the boxers have not been subjected to further bouts (Neselius et al., 2012; Zetterberg et al., 2006).

Levels of NFL in lumbar CSF from amateur boxers with mild TBI after a bout are also raised (Neselius et al., 2012; Zetterberg et al., 2006). The raised level of NFL is of a larger magnitude than that of total tau protein, suggesting NFL in lumbar CSF is probably the most sensitive biomarker of axonal injury, representing the susceptibility of long myelinated axons to mild TBI (Zetterberg et al., 2013). NFL levels in lumbar CSF correlate with amateur boxers' exposure to head trauma, including number of blows to the head (Neselius et al., 2012; Zetterberg et al., 2006).

S100-B and glial fibrillary acidic proteins represent astroglial injury and have been shown to increase following TBI but to a lesser degree than NFL and total tau protein (Neselius et al., 2012; Zetterberg et al., 2006).

4.2. Blood

Blood biomarkers have been studied but no reliable markers of TBI have been established owing to various difficulties including proteolytic degradation of potential markers, clearance from blood via the liver or kidney, binding to carrier proteins and interference of lysis of red blood cells (Zetterberg et al., 2013). Levels of total tau and S100-B in the blood are increased in professional ice-hockey players following concussion and returned to pre-concussion baseline levels during rehabilitation, suggesting acute axonal and astroglial injury associated with the concussion. Future validation of these potential blood biomarkers of TBI is required (Shahim et al., 2014).

5. Pathology of acute TBI

5.1. Microscopic findings

Neuropathological findings in the literature on individuals who died of acute mild TBI are rare and have been compiled either as isolated case reports or small case series only (Blumbergs et al., 1994; Oppenheimer, 1968). Oppenheimer described microglial clusters that had appeared in less than 24 h after TBI (Oppenheimer, 1968). In some cases, petechial haemorrhage was observed, a result of stretching of the microvascular structures. Myelin destruction and numerous axonal retraction bulbs were found in variable regions likely to have been subjected to the most acceleration and deceleration forces. In cases with survival times of 6 weeks or more after TBI, the appearance of 'glial stars' was observed, which is now known as astrocytic tangles, one of the characteristic histological features of CTE along with neurofibrillary tangles (NFTs). Importantly, Oppenheimer concluded that '*permanent damage, in the form of microscopic destructive foci, can be inflicted on the brain by what are regarded as trivial head injuries*' (Oppenheimer, 1968). We now know that repeated TBI can potentially lead to irreversible and progressive neurodegeneration of CTE.

5.2. APP and Aβ

Blumbergs et al. performed immunohistochemistry with antibody to amyloid precursor protein (APP), a marker of fast axonal transport, in 5 postmortem cases with mild TBI and demonstrated APP-immunoreactive multifocal axonal injury in the fornix, a region which forms the major hippocampal projection pathways involved in memory

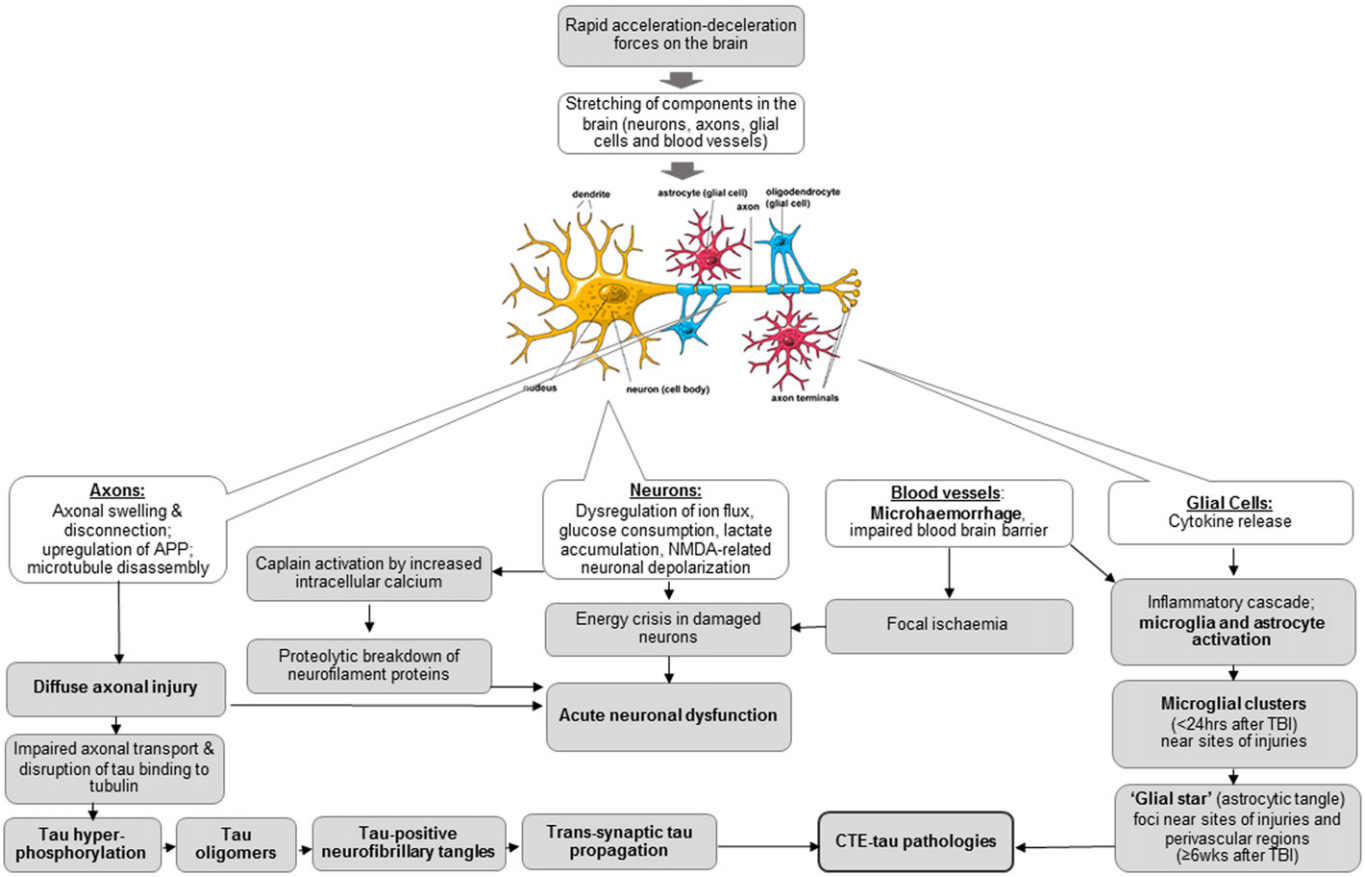

Fig. 1. Schematic illustration of the proposed cascade of events triggered by acute TBIs and its possible mechanistic links with the development of CTE pathology (Blennow et al., 2012; Lucke-Wold et al., 2014; Morales et al., 2009).

function (Blumbergs et al., 1994). APP is cleaved to amyloid-β (Aβ) peptides, a key component in the pathophysiology in Alzheimer's disease. Nevertheless, multiple studies using various techniques demonstrate the absence of Aβ pathology in most cases of acute TBI and CTE, particularly in young individuals and in early stages (Geddes et al., 1999; Hof et al., 1992; McKee et al., 2013); those with positive Aβ pathology most likely represent co-incidental age-related changes in older individuals (Tokuda et al., 1991).

5.3. Mechanistic link between TBI and CTE

The mechanism by which acute TBI leads to tau hyperphosphorylation and the development of neurofibrillary tangles (NFTs) in CTE remains speculative (Fig. 1). A histological report of 6 athletes who died within 6 months of a reported concussion revealed focal tau-positive NFTs and neurites in close proximity to focal axonal injury and foci of microhaemorrhage (McKee et al., 2014). It is also well recognised that NFTs in CTE have a predilection for perivascular and subcortical areas near reactive astrocytes and microglia (Geddes et al., 1999; Hof et al., 1992). It is possible that acute TBI leads to axonal injury, loss of microvascular integrity and breach of the blood brain barrier, triggering an inflammatory cascade and microglia and astrocyte activation, which form the basis of a mechanistic link with the subsequent development of CTE-tau pathology (Lucke-Wold et al., 2014) (Fig. 1).

6. CTE

6.1. Historical aspects

The concept that exposure to TBI can lead to neurodegenerative changes was first introduced in 1926 in a presentation at the annual meeting of the American Neurological Association by Osnato and Giliberti, neurologists from New York (Osnato and Giliberti, 1927). In 1928, a New Jersey pathologist, Harrison Martland, described 'punch drunk syndrome' in retired boxers who developed chronic motor and neuropsychiatric symptoms (Martland, 1928). In 1937, Millspaugh introduced the term 'dementia pugilistica' describing the potential long-term aftermath of repetitive TBI from professional and amateur boxing supported by neuropathological findings (Millspaugh, 1937). In 1949, the eminent British neurologist, Macdonald Critchley coined the term CTE (Critchley, 1949), which has become the prevailing term used in modern day literature in recognition that this potential long-term neurological consequence of repetitive TBI also occurs in other contact sports, such as American football, wrestling, rugby, ice hockey, steeplechase horse racing and basketball (Foster et al., 1976; Geddes et al., 1999; Hof et al., 1992; McKee et al., 2013, 2014; Omalu et al., 2005, 2006, 2010) as well as in war veterans and in people who have been repeatedly battered (Geddes et al., 1999; McKee and Robinson, 2014; McKee et al., 2013). In particular, the post-mortem case reports of American football players have attracted significant media attention in recent years (Omalu et al., 2005, 2006).

6.2. Epidemiology

1969, Roberts reported a prevalence of CTE of 17% among retired boxers in the UK. Risk factors for CTE include high number of bouts (>20 bouts), older age at retirement from boxing, longer length of boxing career (>10 years) (McCrory, 2011; Roberts, 1969) and possibly positive apolipoprotein e4 allele (Jordan et al., 1997; Kutner et al., 2000).

Epidemiological data in non-boxing sports is scant (McCrea et al., 2003; Pellman et al., 2004). Gavett et al. estimated a lifetime prevalence of CTE of 3.7% among National Football League athletes but this figure would require validation in large scale longitudinal study in view of

the potential selection bias of the propensity for performing post-mortem in more symptomatic athletes (Gavett et al., 2011).

The risk of CTE from heading the ball in soccer is increasingly recognised. Early CTE changes were reported in an amateur soccer player (Geddes et al., 1999). Soccer players who head the ball more than 1800 times per year were found to have microstructural abnormalities in the temporo-occipital white matter on diffusion tensor imaging correlating with poorer memory scores (Lipton et al., 2013). In a human experimental study of controlled headings in soccer, no changes in CSF biomarkers for neuronal or astroglial injury were seen (Zetterberg et al., 2007). This may indicate that the ball-to-head contact may not be the primary problem, but instead heading may represent a risk situation for other head injuries, for instance, head-to-head contact accidents. Enforcers in ice hockey have high overall exposure to repetitive TBI and the profile of the linear and rotational head impacts differs from those in American football players (Wilcox et al., 2014).

Exposure to single bout of moderate to severe TBI have been shown to attribute to an increased risk of dementia in later life but this concept remains controversial due to potential recall bias (Smith et al., 2013).

On the other hand, repetitive TBI is now firmly linked with dementia with a 'dose-response' relationship (Guskiewicz et al., 2005; Lye and Shores, 2000), particularly in individuals with greater severity of TBI (Plassman et al., 2000) and history of loss of consciousness (Guo et al., 2000). Onset of dementia is accelerated in individuals with a history of TBI-related loss of consciousness for more than five minutes (Nemetz et al., 1999; Schofield et al., 1997). Epidemiological studies have also linked sports-related TBI to mood disorders (Guskiewicz et al., 2007a) and suicide (Roberts, 1969).

Nevertheless, not all boxers develop dementia or have CTE-tau pathology in post-mortem despite exposure to repetitive TBI (Stern et al., 2011). A study found 68 out of 85 (80%) participants with histories of repetitive e head injury had CTE pathology (McKee et al., 2013). It is possible that some individuals may be resilient to the development of CTE following TBI and potential protective factors such as genetic (Zhou et al., 2008), sex, age or environmental interplay (Cottler et al., 2011; Okawa et al., 2003; Ramage et al., 2005) await to be investigated.

6.3. Clinical features

Martland in his monograph on *the punch drunk syndrome* described unsteadiness of gait, mental confusion, slowing of muscular movements and, occasionally, hesitancy in speech, tremors of the hands and

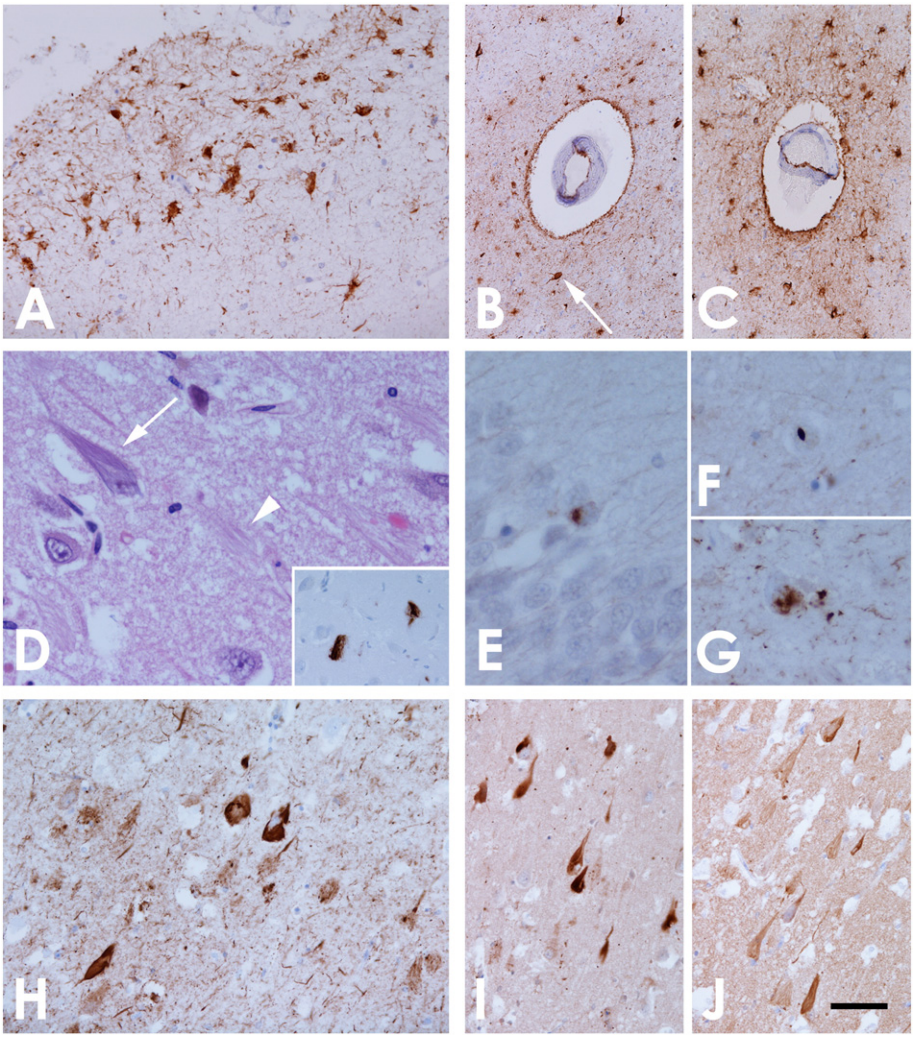

Fig. 2. Chronic traumatic encephalopathy (CTE) pathology. Tau immunohistochemistry demonstrates subpial astrocytic tangles in the depth of sulci of the frontal cortex (A), perivascular astrocytic tangles (B–C). Neurofibrillary tangles (NFTs) are occasionally observed in the perivascular region (white arrow, B). Marked neuronal loss with ghost tangles (arrowhead) and NFTs (arrow) in the CA1 hippocampal subregion on H&E (D) and amyloid-β deposition on the ghost tangles can be observed (inset in D). TDP-43 immunohistochemistry shows occasional neuronal cytoplasmic inclusions (NCIs) in the dentate fascia of the hippocampus (E) and a neuronal intranuclear inclusion (NII) (F), NCIs and threads (G) are demonstrated. Extensive tau-immunoreactive NFTs and neuropil threads (NTs, H) in the hippocampal formation. These NFTs and NTs are characteristically immunoreactive for 3-repeat (I) and 4-repeat tau antibodies (J). A, B, C, H: tau immunohistochemistry (AT8), D: H&E, inset in D: Aβ immunohistochemistry, E–G: TDP-43 immunohistochemistry, I: 3-repeat, and J: 4-repeat tau immunohistochemistry. Bar in J = 50 μm in A, H–J, = 100 μm in B and = 25 μm in D–G.

nodding of the head (Martland, 1928). Behavioural disturbances are usually the earliest findings in CTE and may include depression, mood swings, apathy, impulsivity, aggression and suicidality (Corsellis et al., 1973; Critchley, 1949; Jordan, 2013; McKee et al., 2013; Roberts, 1969). Cognitive deficits include attention and concentration impairment, memory problems, executive dysfunction and eventually dementia. Common motor symptoms are parkinsonism, tremor, dysarthria, coordination difficulties and ataxia, reflect extrapyramidal and pyramidal system and cerebellum involvements. Headache is another prominent feature but may represent comorbid CPCS. Research and clinical diagnostic criteria have been proposed but their accuracies in predicting underlying CTE pathological changes will require validation (Jordan, 2013; Montenigro et al., 2014; Victoroff, 2013). In 2014, a large cohort of pathologically confirmed CTE delineated CTE into two clinical phenotypic presentations: one with predominant mood and behavioural symptoms in younger individuals in the third decade and another with cognitive impairment presenting in the fifth decade (Stern et al., 2013). The majority of cases (86%) with mood and behavioural changes at presentation gradually developed cognitive and memory impairment prior to death. It should be noted that environmental influences such as alcohol, opioid and performance-enhancing drugs may attribute to the mood and behavioural symptoms especially in the younger subgroup leading to potential bias in the delineation of clinical phenotypes.

6.4. Neuropathological findings

The macroscopic features of CTE include diffuse brain atrophy, ventricular dilatation, cavum septum pellucidum with or without fenestrations, cerebellar scarring and depigmentation and degeneration of the substantia nigra. Marked atrophy of the medial temporal lobe, thalamus, hypothalamus and mammillary bodies becomes evident in advanced CTE.

The histological hallmarks are extensive NFTs composed of mixed 3-repeat (3R) and 4-repeat (4R) tau isoforms (Fig. 2). NFTs and astrocytic tangles in CTE are most abundant in the frontal and temporal cortices, often patchy and irregular, with predilection for perivascular regions, in the depths of cerebral sulci and in the superficial cortical layers and periventricular regions (Geddes et al., 1999; Hof et al., 1992). NFTs are abundant in the limbic regions, diencephalon and brainstem. Although both are mixed 3R and 4R tauopathies, CTE is distinctive from Alzheimer's disease by the lack of or relatively few Aβ deposition especially in younger individuals and in early stage of CTE. Astrocytic tau pathology in CTE is predominantly 4R tau and is more widely distributed than those observed in ageing and Alzheimer's disease (Table 3). Tau pathology in locus coeruleus is an early finding in CTE and can be abundant even in individuals under the age 30.

Ghost tangles, representing residual NFTs lying in the neuropil following neuronal death, are frequently observed in the limbic region and temporal neocortex, especially in the CA1 hippocampal subregion, and are visible in sections stained with H&E and Bielschowsky's silver impregnation (Ling et al., 2014). In the presence of ghost tangles, secondary Aβ deposition on extracellular protein aggregates is an accompanying feature.

TAR DNA binding protein (TDP-43) inclusions are the hallmark of amyotrophic lateral sclerosis (ALS) and a subtype of frontotemporal lobar degeneration (FTLD-TDP) and can be observed in a number of other neurodegenerative diseases (Neumann et al., 2006). TDP-43 is a RNA binding protein that regulates gene expression. TDP-43 pathology is found in the majority of CTE cases across all disease stages (McKee et al., 2013). In stage IV CTE cases, severe and extensive TDP-43 immunoreactive intraneuonal and glial inclusions in the cortex, white matter, diencephalon, basal ganglia and brainstem are observed (McKee et al., 2013).

6.5. Pathological diagnostic criteria

In the seminal clinicopathological series of 15 boxers, Corsellis et al. proposed four major criteria for CTE (Corsellis et al., 1973): 1. Abnormalities of the septum pellucidum (i.e., cavum, fenestrations), 2. Cerebellar scarring on the inferior surface of the lateral lobes (especially the tonsillar regions), 3. Degeneration of the substantia nigra (pallor) and 4. Widespread NFTs containing hyperphosphorylated tau in the cerebral cortex and brainstem. Two recent and competing neuropathological criteria have since been proposed (McKee et al., 2013; Omalu et al., 2011): Omalu et al. identified four phenotypes of CTE and McKee et al. classified CTE into four pathological stages. The McKee et al. (McKee et al., 2013) staging system indicates that NFTs and astrocytic tangles in the sulcal depths and subpial regions in the superior and dorsolateral frontal lobes frontal cortices are the earliest features, concurring with one of the four features delineated by Corsellis et al. (Corsellis et al., 1973), whereas the other 3 features represent more advanced disease stages. McKee et al. proposes that NFT pathology becomes more extensive over decades of the disease progression, initially involving superior and dorsolateral frontal lobes, the pathology eventually affects most regions of the cerebral cortex are involved, as well as the diencephalon, basal ganglia, brainstem and spinal cord, in association with marked axonal loss of subcortical white matter tract (McKee et al., 2013).

6.6. Clinicopathological correlations

The progression from multifocal stage (stage II) to widespread disease (stage III) is likely to represent an exponential increase in tau accumulation through mechanisms of protein templating and other modes of interneuronal spreading (McKee et al., 2014; Morales et al., 2009). Asymptomatic CTE can be observed in 11% of all pathologically confirmed CTE cases with the majority in early stage of disease (stage I) (McKee et al., 2013). Clinically, stage II and III disease correlate with the onset of intrusive neuropsychiatric symptoms including depression and death due to suicide, alcohol or drug overdose. Stage IV is associated with overt dementia. The degree of tau and TDP-43 pathologies, neuronal loss and cerebral atrophy increase with longer survival and all of which in combination attributes to the relentlessly progressive clinical symptoms (McKee et al., 2014).

The early and predominant involvement of tau pathology in the superior and dorsolateral frontal lobes in American football players corresponds to the more vulnerable regions subjected to the acceleration–deceleration force of the TBC due to high frequency of head collisions to the top-front of the head, a finding that is also confirmed by functional MRI data (Guskiewicz et al., 2007b).

6.7. Co-morbid neurodegenerative diseases

A third of CTE cases have comorbid neurodegenerative diseases (McKee et al., 2013, 2014). Of the 103 path confirmed CTE cases, co-existing Lewy body diseases was found in 12 (12%), motor neuron disease in 13 (13%), Alzheimer's disease in 15 (15%) and frontotemporal lobar degeneration in 6 (6%). We reported the case of a retired boxer with concomitant CTE and PSP pathologies (Ling et al., 2014). It is plausible that either the CTE-tau pathology or the repetitive TBI and the resulting axonal injury increase the risk of another neurodegenerative processes (Blennow et al., 2012; Morales et al., 2009).

Some data suggests trauma and athletic exposure are risk factors for developing ALS (Chen et al., 2007; Chio et al., 2005, 2009). American football players who played professionally for more than 5 seasons show four times higher risk of mortality from ALS than age- and gender-matched controls. The incidence of ALS and mortality are unusually high among professional soccer players in Italy (Chio et al., 2005, 2009).

In McKee et al. series, 13% of CTE also had motor neuron disease (CTE-MND) (McKee et al., 2013). Among the CTE-MND cases, those

with predominant motor symptoms including motor weakness, atrophy, fasciculations have milder CTE at death (stages II–III), probably due to shortened life span, whereas those who present with cognitive symptoms die with advanced CTE (stage III and IV). Behavioural changes and cognitive impairment usually develop several years after the onset of motor symptoms. All CTE-MND cases show distinct TDP-43 pathology in the brain and spinal cord (McKee et al., 2014).

7. Conclusion

Increasing data supportive of the link of repetitive TBI with axonal injury and long term neurodegenerative consequence has had significant implications in sports which have already lead to changes in the rule and management of many popular sports. Understandably, resistance and refusal to accept the risk of TBI exist due to potential enormous financial repercussions, major change in the rule of the sports and even the possibilities of banning some high risk contact sports entirely or among children who are more susceptible to damage than adults.

Many unknowns related to the field will require clarification, including the risk of a single bout of TBI, other risk and protective factors, clinical diagnostic criteria, CSF, blood and radiological biomarkers, the precise pathophysiological cascade of events from TBI to CTE and potential therapeutic strategies. Prospective longitudinal studies along with clinicopathological evaluation would be the key in providing more information on the acute and long-term consequences of TBI in sport.

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