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Review article

Head trauma in sport and neurodegenerative disease: an issue whose time has come?

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ABSTRACT

A number of small studies and anecdotal reports have been suggested that sports involving repeated head trauma may have long-term risks of neurodegenerative disease. There are now plausible mechanisms for these effects, and a recognition that these problems do not just occur in former boxers, but in a variety of sports involving repeated concussions, and possibly also in sports in which low-level head trauma is common. These neurodegenerative effects potentially include increased risks of impaired cognitive function and dementia, Parkinson's disease, and amyotrophic lateral sclerosis. Many would argue for taking a precautionary approach and immediately banning or restricting sports such as boxing. However, there are important public health issues in terms of how wide the net should be cast in terms of other sports, and what remedial measures could be taken? This in turn requires a major research effort involving both clinical and basic research to understand the underlying mechanisms, leading from head trauma to neurodegenerative disease and epidemiologic studies to assess the long-term consequences.

1. Introduction

The recent football World Cup in Brazil has brought renewed attention to the potential problems of neurodegenerative disease resulting from head trauma in sport (Pearce et al., 2014). For some years, a number of small studies and anecdotal reports have been suggesting that sports involving repeated head trauma may have long-term risks of neurodegenerative disease. The short-term and long-term effects of head trauma from boxing (Corsellis, 1989) have been recognized since the 1920s and have been progressively labeled as "punch-drunk syndrome," dementia pugilistica, and more recently as chronic traumatic encephalopathy (CTE) (McKee et al., 2013). The long-term effects on neurodegenerative conditions such as Parkinson's disease (PD) (Marras et al., 2014) and amyotrophic lateral sclerosis (ALS) (Armon and Nelson, 2012), as well as more general cognitive impairment (Godbolt et al., 2014) have also been recognized.

Two things have changed in recent years which have brought renewed focus on this issue. First, there are now plausible mechanisms for these effects which go from local damage at age 30 years to tangles in the brain at age 50 years, with at least some of the problems being initiated by rotational injury (Geddes et al., 1999). Furthermore, there is evidence that CSF neurofilament levels increase for several months following concussion and also after injuries not involving concussion (Neselius et al., 2013, 2014).

Second, there has been the increasing recognition that these problems do not just occur in former boxers but in a variety of sports involving repeated concussions, such as American football, ice hockey, and rugby (McKee et al., 2009). Even more disturbing has been recent evidence that they can also occur in sports such as football (soccer) in which concussion is rare, but in which low-level head trauma (e.g., from heading the ball) is common. A few reports describing features of CTE in subjects with self-injuring head banging behavior also suggest that repetitive mild traumatic brain injuries (TBIs) alone could be sufficient to trigger a CTE (Geddes et al., 1999; Hof et al., 1991; McKee et al., 2009). Thus, in the United Kingdom, the Industrial Injuries Advisory Council has recently issued a call for new evidence on neurodegenerative disease in professional sportspersons (http://iiac.independent.gov.uk/calls-addtional-research/index.shtml).

Although there is a great deal of evidence about the short-term effects of head injury, there is relatively little epidemiologic or clinical evidence on the long-term effects. Only recently,

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CTE—defined by the occurrence of repetitive mild TBIs—has been described and staged as a neuropathologic entity featuring progressive accumulation of hyperphosphorylated tau protein in specific areas of the brain (McKee et al., 2013). Phosphorylation in CTE begins perivascularly in the cerebral cortex and then gradually spreads over decades to involve widespread regions of the neocortex, the medial temporal lobe, the diencephalon, the basal ganglia, the brainstem, and the spinal cord [McKee, 2013]. Brain trauma is postulated to dissociate tau protein from microtubules in axons via a number of mechanisms, including calcium influx, glutamate-mediated excitotoxicity, and kinase activation inducing hyperphosphorylation of intracellular tau. Dissociated and hyperphoshorylated tau exert a neurotoxic effect through misfolding and aggregation. The tau isoform profile, phosphorylation, and immunoreactivity state in CTE is similar to that found in Alzheimer's disease (Jordan, 2013; McKee et al., 2009). Evidence on the association between *APOE* ε4 allele and CTE is to date not conclusive (Jordan, 2013; Jordan et al., 1997; Kutner et al., 2000). Interestingly, in the same case series, 12% of patients were also diagnosed with ALS, 11% with Alzheimer's disease, 16% with Lewy body disease, and 6% with frontotemporal degeneration, suggesting that repetitive brain trauma and hyperphosphorylated tau protein deposition may promote the accumulation of other abnormally aggregated proteins, including TAR DNA-binding protein 43, amyloid beta protein, and alpha-synuclein (McKee et al., 2013).

Animal evidence suggests that wild-type mice develop clinicopathological features of CTE after repeated head injury: neuropathologic changes appear 2 weeks after a blast exposure (Goldstein et al., 2012; Mez et al., 2013), whereas behavioral and motor deterioration is evident after repeated injuries (Mez et al., 2013; Mouzon et al., 2012). Moreover, recent evidence demonstrates how human tau transgenic mice show increased tau immunoreactivity after repetitive mild brain injury (Ojo et al., 2013).

Several studies have reported increased risks of various neurologic conditions in professional sportspersons, including ALS (Chio et al., 2005; Lehman et al., 2012), and subclinical effects such as impaired cognitive function (Guskiewicz et al., 2005; Mielke et al., 2014), and associations between head trauma and PD (Harris et al., 2013; Rugbjerg et al., 2008) and other neurologic signs, such as headache and sleep disturbances (Anon, 2013; Bryan and Clemans, 2013). However, it is not clear that research from other sports can be applied to football, because this involves relatively few concussions, but a large number of low-level head traumas.

2. Impaired cognitive function and dementia

Although the neurologic and cognitive effects of acute TBIs have been extensively studied (Belanger and Vanderploeg, 2005; Kokmen et al., 1996; Nemetz et al., 1999; Schofield et al., 1997), causal relationships between TBIs and delayed sequelae have been less studied because of the variable latency period before overt neurologic dysfunction. Neurocognitive effects of repetitive mild head injury were initially recognized in boxers for many years, with a syndrome that was distinct from the clinical and pathologic sequelae of single-incident severe TBI (Martland, 1928). The clinical syndrome of dementia pugilistica (punch-drunk syndrome) is associated with prominent tauopathy, with typical neurofibrillary tangles and neuropil threads, distributed in patches throughout the neocortex (DeKosky et al., 2010). Neuropathologic case series have demonstrated primarily tau-related pathology in the brains of individuals who suffered from a clinical syndrome encompassing dementia and movement disorders after repeated head trauma (Gavett et al., 2010). Also, examination of the brains of several professional American football players and wrestlers has revealed the pathologic underpinnings for the cognitive and neuropsychiatric decline seen in these men in later life (DeKosky et al., 2010). Although cognitive decline in longtime professional American football players has been noted for years, the first autopsy report from such a player appeared in the literature only recently (Omalu et al., 2010). In all cases, cognitive decline began years after retirement from the game.

The term CTE was introduced as a clinicopathologic construct for the neurodegeneration associated with American football and wrestling (DeKosky et al., 2010). However, there are no established clinical criteria for CTE and uncertainties remain regarding the relation between brain injury and dementia, especially when the brain injury is mild. In a subsequent neuropathologic study, brain tau deposits were detected in 5-living retired American football players, using positron emission tomography (PET) scans (Small et al., 2013). The association between head trauma and in vivo amyloid deposition and neurodegeneration among 448 cognitively normal and 141 impaired individuals was studied with PET scan and magnetic resonance imaging (MRI). No difference in any neuroimaging measure between cognitive normal subjects with and without head trauma was found. However, of 141 participants with mild cognitive impairment (MCI), participants with a head trauma had higher amyloid levels (by an average 0.36 standardized uptake value ratio units, $p = 0.002$), suggesting that head trauma may be associated with Alzheimer's disease-related neuropathology (Mielke et al., 2014). However, a smaller study found amyloid-β deposition with PET scan in 3 of 12 subjects with posttraumatic neuropsychological impairment (Kawai et al., 2013).

In another US epidemiological study, the association between previous head injury and the likelihood of developing MCI and Alzheimer's disease in a group of 2552 retired professional American football players with previous head injury exposure was investigated. Of the former players, 61% sustained at least 1 concussion during their professional American football career and 24% sustained 3 or more concussions: significant associations between recurrent concussion and clinically diagnosed MCI ($p = 0.02$) and self-reported significant memory impairments ($p = 0.001$) were detected. Retired players with 3 or more reported concussions had a 5-fold prevalence of MCI diagnosis and a 3-fold prevalence of reported significant memory problems compared with retirees without a history of concussion (Guskiewicz et al., 2005).

A long-term follow-up study carried out in former Division I sport collegiate athletes of any age reported that former American football players experienced more late-life cognitive difficulties and worse physical and mental health compared with former noncollision sport athletes and nonathletes (Hinton et al., 2011). A recent Japanese study reported that the risk of Alzheimer's disease and ALS among former professional American football players was 4 times higher than expected (Kuwahara and Sato, 2013). However, in another study, neurodegenerative disease prevalence was assessed among high school American football players in the high schools of Rochester, Minnesota, and compared with a nonfootball-playing comparison group of male students, all of them in their 60s. There was no increased risk of dementia, PD, or ALS among the 438 American football players compared with the 140 non-football-playing male classmates (Savica et al., 2012). A comprehensive review of studies published in 2011 concluded that the existing studies fail to account for all potential biopsychosocial factors, for example, gender, age, admixture of different sports, multiple comorbid medical and psychiatric conditions, and therefore, that it is not possible to draw firm conclusions on the long-term effect of concussion in sports and cognitive function later in life (Solomon et al., 2011).

A very recent study among collegiate American football players in the US reported that there was a significant inverse relationship of concussion and years of football played with hippocampal