Chronic Traumatic Encephalopathy: A Neurodegenerative Disease Caused by Brain Injury
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Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease induced by repeated blows to the head. Clinically, it is characterized by cognitive decline, mood disorders, and parkinsonism. Pathologically, it is a tauopathy characterized by neurofibrillary tangles and glial tau inclusions that preferentially involve the cortical sulci, medial temporal lobe, diencephalon, and brainstem. Originally described in boxers and termed dementia pugilistica, it has now been shown to occur in a variety of sports, most notably American football (Figure 1A).

In fact, former National Football League (NFL) players over 50 years-old are five times more likely to have dementia than the national average for men in that age group.1 Of those former NFL players who have died and donated their brains to research, the percentage of players who have pathologically confirmed CTE is remarkably high (>90%). While many players had a history of repeated concussions, some did not, suggesting that repeated subconcussive blows to the head may also induce this disease. Moreover, players from multiple other sports are also at risk, including hockey, soccer, and basketball, as are soldiers that suffer brain trauma from improvised explosive devices in Iraq and Afghanistan.

Neuropathologically, CTE is characterized by cerebral and medial temporal lobe atrophy, ventriculomegaly, and cavum and fenestrated septum pellucidum. Microscopically, there are numerous tau-positive neurofibrillary tangles throughout the neocortex (Figure 1B), thalamus, brainstem, and occasionally, spinal cord. The tau pathology, including both NFTs and tau-positive astrocytes, is often perivascular and preferentially affects the superficial cortex as well as the depths of sulci where mechanical stresses are greatest after traumatic injury.2 The majority of cases are not associated with beta-amyloid deposition, and the distribution of abnormal tau is distinct from that seen in Alzheimer disease.3 Recently, CTE has been described in athletes who subsequently developed amyotrophic lateral sclerosis (ALS), suggesting a link between trauma and motor neuron disease.4

There are no known, clear-cut genetic risk factors for CTE. However, a potential candidate may be the e4 allele of apolipoprotein E (APOE), a well-known risk factor for Alzheimer disease. In fact, an analysis of all CTE cases in the literature verified by autopsy showed that APOE e4 was overrepresented as compared to the prevalence in the general population among the 10 cases where APOE status was known.3 Additionally, several studies have demonstrated worse clinical outcomes in e4 carriers following a traumatic brain injury or concussion.5,7,8 Furthermore, mouse models of concussion support a role for the e4 allele in predicting a poor outcome.9 However, most human studies have been small and one larger study did not show a robust difference of APOE e4 carriers following brain injury.10

Currently, there is no treatment for CTE. Management involves the prevention of head trauma and improved recognition and treatment of concussion. Concussion itself is defined as a transient disturbance of neurological function following a mild traumatic injury,11 and can manifest as a variety of physical, emotional, and cognitive symptoms. These symptoms can be monitored with a checklist such as the Sports Concussion Assessment Tool (SCAT2).11 In addition, computerized tests can measure reaction times to tease out subtle cognitive deficits—an outcome aided greatly by comparing to a baseline test. Most sports-related concussion symptoms resolve within 7–10 days. However, biochemical abnormalities such as lowered N-acetylaspartate levels measured by magnetic resonance spectroscopy can persist for 15–30 days for a single concussion and up to 45 days for two successive concussions.12 Although no prospective data exist, the current recommendation is to refrain from...
physical and mental activity until symptoms resolve and then to gradually reintroduce activity. This includes a period of "cognitive rest," which involves a quiet environment devoid of concentration-dependent activities such as schoolwork, text messaging, and video games.\textsuperscript{11}

Across the country new rules are being implemented to reduce and manage concussion.\textsuperscript{13,14,15} In addition to the risk of subsequent development of CTE, there are other acute risks from concussion. First, a history of concussion increases the likelihood of suffering subsequent ones and increases the time required to recover.\textsuperscript{16} Second, the brains of children and young adults under the age of 24 are still developing and exhibit a greater susceptibility to concussion and its sequelae. In particular, they are at risk for second impact syndrome, which is catastrophic cerebral edema and vascular dysregulation that occurs in the setting of a second concussion days to weeks after a first. Second impact syndrome carries a markedly high morbidity and mortality.\textsuperscript{17,18,19}

Clearly, the consequences of mild traumatic brain injury are serious and include not only the acute risks of neurologic sequelae and second-impact syndrome, but also the long-term risk of developing CTE. The precise threshold of force and number of hits required to induce these disorders is likely specific to each individual and dependent on a host of genetic factors yet to be determined. Research needs to focus on better understanding the pathophysiology of this disease as well as defining and reducing the risks, so that well-informed decisions can be made to protect our athletes while best maintaining the integrity of our sports.

References


Figure 1: Chronic traumatic encephalopathy in American football. A) A pending tackle in college football. B) Immunohistochemistry for tau of a former NFL player with chronic traumatic encephalopathy shows the abnormal accumulation of tau within neurons and astrocytes that is most severe within the hippocampus (*) and at the depths of sulci (arrows).

Photo courtesy of Duane Stein; tau immunostaining courtesy of Ann McKee, MD.