

Chronic Traumatic Encephalopathy Among Athletes

By Elaine He

Author Bio

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Abstract

Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative disorder caused by the repetitive occurrence of mild Traumatic Brain Injuries (mTBI), commonly known as concussions, which remains a public health issue found most prevalent in high contact sports, specifically, American football. Typically, the severity of CTE is classified with McKee's staging scheme, which is mainly based on the degeneration and accumulation of p-tau neurofibrillary tangles in different parts of the brain. This refers to the unwound and clumped together tau proteins that are highly associated with CTE. The severity of the symptoms of stage I-IV can range from light headaches to a severe loss in motor and neural function. The underlying mechanisms and definitive biomarkers of CTE are still under debate, therefore, it cannot be diagnosed in vivo. Furthermore, external factors such as gender, age, and genetics (the presence of the ApoE4 allele) can affect both the severity and an individual's sensitivity to head trauma. However, interest in this topic has only recently begun to grow exponentially, and knowledge of CTE is still relatively preliminary. It has been shown to have overlapping biomarkers and symptoms with other neurodegenerative diseases such as Alzheimer's disease or Parkinson's disease. Treatment of this issue so far has solely been preventative, as the development of medical therapies cannot proceed until CTE can be diagnosed in vivo. The implication of education and stricter rules protecting athletes have been at the forefront of these measures.

Introduction

As head injuries become more normalised in high contact sports, a seemingly minor concussion every so often can quickly lead to more serious problems. Chronic Traumatic Encephalopathy (CTE) is a progressive tauopathy, or an abnormal amount of tau proteins in the brain that is associated with neurodegenerative disorders, caused by repetitive mild traumatic brain injuries, or concussions. It has been associated with aggression, depression, and the decline of many other cognitive functions among other symptoms. Additionally, CTE leads to a decrease in brain weight caused by a decline in the size of the cerebral cortex, temporal lobes, thalamus, brain stem, and other key regions of the brain (McKee et al., 2015).

Most commonly found in American football players and boxers- in addition to other high contact sports athletes e.g. soccer, wrestling, or rugby- concussions remain a prevalent problem in many professional leagues. Notably, the National Football League (NFL) raises concerns about concussions in many youth leagues. Additionally, CTE is also found in military personnel, with a significant number of combat injuries being head injuries (McKee et al., 2013).

Currently, the only way to definitively diagnose CTE is through autopsy, therefore, it is difficult to diagnose the disorder when an individual is still alive. Although there is no clear consensus on a specific diagnosis of CTE or the amount of trauma needed to cause it, the severity of symptoms correlated with it is defined by the density and regional distribution of p-tau, classified into four stages (I-IV) in McKee's staging scheme (McKee et al., 2015). Symptoms usually show 8-10 years after experiencing repeated head injuries and primarily progress with age, with older people tending to have higher CTE stages. The symptoms of stage I (mild) CTE are similar to those of concussions, including headaches or a loss of concentration and attention, but could also be asymptomatic. Similarly, stage II can also occasionally be asymptomatic, but additional symptoms included explosivity, short-term memory loss, and depression. In stage III, more cognitive impairments are found, such as apathy, memory loss, and executive dysfunction. Lastly, stage IV, the most severe stage,

includes problems with motor functioning, aggression, word-finding difficulty, and has a strong association with dementia. CTE is often associated with other neurodegenerative disorders such as Alzheimer's, Motor Neuron Disease, or Parkinson's Disease. Similar to Alzheimer's Disease, where the ApoE4 allele has been associated with an increased risk of developing the disease, this allele is also speculated to affect the development of CTE (McKee et al., 2015).

Despite the recent growth in interest and research of CTE, much is still unknown about it. Given the importance of sports to human health and the prevalence of mild traumatic brain injuries in many of these popular activities, it is critical to identify the symptoms of a concussion and validate a set of criteria and underlying mechanisms for CTE, allowing the development and implementation of future preventative and recovery methods into different programs. In the following sections, an overview of the development and factors that affect both mTBI and CTE will be presented, followed by the prevalence of CTE in athletics. Based on empirical research, it is evident that CTE remains a major public health issue, primarily in high contact sports of all levels.

Development of Mild Traumatic Brain Injury (mTBI)

Given the millions of sports-related concussions estimated annually just in the United States, mild traumatic brain injuries, more commonly known as concussions, have been a major cause of concern for many athletes. It is one of the most common neurological disorders, accounting for around 90% of brain injuries (Saulle & Greenwald, 2012). Impact or a strong jolt to the head or shoulders, most common in sports like American football or boxing, if severe enough, can shift the brain to hit against the skull. This causes the stretching of axons along with a distortion in cellular membranes that cause the release of chemicals such as potassium and glutamate, and a depletion of intracellular energy stores which worsens the brain's metabolic dysfunction (McKee et al., 2013). mTBI is commonly defined as mild based on the Glasgow Coma Score, which categorises brain trauma as mild, moderate, and severe. Headaches, nausea, confusion, imbalance, and dizziness are some of the most common acute symptoms of concussions, which can be paired with a loss of consciousness, all

of which usually stop after a period of 1-6 weeks. However, during this period of metabolic dysfunction, an individual has a significantly higher vulnerability to a second concussion, which takes much longer to recover from as well as poses a long-term risk (Giza & Hovda 2001). Additionally, post-concussive syndrome (PCS) occasionally occurs, when symptoms of the concussion remain after three months since the injury, and usually lasts up to a year, though it could extend beyond this time frame in rare cases. In addition to the symptoms of concussions, many have also experienced emotional, cognitive, behavioural, and physical problems.

Concussion rates are generally highest in youth sports, besides the NFL, as the skulls and brains of minors are still developing during these years. Additionally, children with a history of concussion(s) generally have an increased risk of a slower recovery and longer symptoms after the injury, and this has been shown to have adverse effects on a student's academic performance, which emphasises the importance of adequate safety measures (Moser, 2002; Graham et al., 2001). Although these symptoms can be alleviated without medical intervention or long-term effects, the repeated or overlapping occurrence of the injury can lead to long-term consequences, namely, Chronic Traumatic Encephalopathy (Saulle & Greenwald, 2012).

Development of CTE

In contrast to the relatively straightforward timeline of mTBI, the development of CTE is not as direct, as in PCS does not directly lead to CTE. Given the axonal damage caused by repeated injuries, there are many shifts in the balance of the brain: membrane permeability, ionic shifts, and other chemical imbalances keep the brain in a prolonged state of hyperactivity that can lead to long-term neuron damage (McKee et al., 2013). Symptoms of CTE can be correlated with the specific part of the brain that is injured for example, damage to part of the hippocampal circuitry is associated with emotional, behavioural, or memory disturbances to the individual (McKee et al., 2012).

It is important to note that there is not yet a consensus on the exact mechanism of CTE. Typically, the emergence of CTE symptoms varies

based on the individual and does not surface until later in life. In fact, some individuals were reported to be asymptomatic many years into retirement while others experienced symptoms only 4 years after they left their sport, while the youngest known individual with CTE was only 17 (McKee et al., 2013). The progression of symptoms follows a continuous decline in cognitive, emotional, and motor functions. Although at first, individuals affected may only experience concussion-like symptoms- poor concentration and attention, dizziness, headaches, disorientation, and memory problems, it can quickly progress to unstable behaviour in the form of outbursts and irritability, and speech issues. At this stage, a correlation between CTE and severe depression, suicide, and mood disorders, and the worsening of cognitive functions have been reported in previous research (Saulle & Greenwald, 2012). This proves to be devastating to the individuals affected as they often experience poor decision-making that can affect the people around them, such as divorce, relationship issues, abuse, drug addiction, paranoia, and bankruptcy to name a few. Finally, it can lead to a further loss in cognitive-motor functions where symptoms can resemble that of Parkinson's, Alzheimer's, dementia, and other neurodegenerative disorders (Mez et al., 2017).

The progression of CTE is captured by McKee's staging scheme, defined by stages I-IV, where stage I is the mildest stage and stage IV is the most severe (McKee et al., 2015). In accordance with the progression of CTE, corresponding pathological change can also be seen in the accumulation of p-tau neurofibrillary tangles(NFT) and the deterioration and change occurring within the brain. In stage I, abnormalities in p-tau are found in parts of the cerebral cortex but are minor, and the changes are still microscopic. These changes are associated with concussion-like symptoms. In stage II, there can be short-term memory loss and some emotional instability. There are more points of p-tau NFT in the cerebral sulci, and macroscopic changes begin to appear along with clusters of reactive microglia and axonal swelling. Stage III begins to show more macroscopic changes such as the reduction of brain weight and the enlargement of the third and lateral ventricles. The presence of NFT becomes more widespread, found in a majority of the key areas of the brain for example, the hippocampus, amygdala, frontal pole, and on occasion in the cerebellum and spinal cord grey matter. Finally, in stage IV,

the degeneration of the brain is readily apparent. Compared to the average 1,300-1,400 g brains, a brain weighing 1,000 g or less is not considered rare. There is atrophy, or a decrease of size, specifically in the frontal and temporal lobes, anterior thalamus, medial temporal lobes, white matter, and corpus callosum, to name a few. Additionally, p-tau is heavily distributed throughout the majority of the brain and a significant diminish in myelinated nerve fibres.

Currently, there is no definitive way to diagnose CTE, as it can only be diagnosed through autopsy. Due to its overlap in symptoms with other diseases, it is difficult to find specific biomarkers that can aid in making a diagnosis. However, there are speculations of different technologies and measurements to help define it, with advancements in neuroimaging, specifically diffusion tensor imaging (DTI) being one of the forefront technologies that many have hopes of using to detect changes associated with CTE (Saulle & Greenwald, 2012). DTI studies have shown to be sensitive enough to assess axonal structure and damage, and show changes in occult white matter that cannot be seen in other types of scans. Finally, several biomarkers have been proposed to diagnose CTE such as levels of change in glutamate, myoinositol, and tau levels among others.

p-tau and its Relevance to CTE

The presence of tau protein has been suggested to serve as a biomarker for neurodegenerative disorders, specifically Alzheimer's disease. However, because of the overlap between CTE and Alzheimer's, phosphorylated tau (p-tau) neurofibrillary tangles (NFT) inside brain cells have been used to track the progression of CTE. This occurs when the tau becomes hypophosphorylated and begins to unbind itself and disintegrate, clumping together to form these tangles. However, research has indicated that following traumatic brain injuries, the iron from bleeding is correlated to the formation of NTFs but are more associated with multiple mTBIs rather than one severe injury, overlapping the causes of CTE (Yoshiyama et. al, 2005).

CTE and mild TBI in the Context of Athletics

The majority of CTE cases have been

reported in contact sports, notably, American football. One of the main figures in CTE research, Dr. McKee, is responsible for the development of the staging scheme (I-IV) of CTE and conducted one of the largest CTE studies in regards to football players, with 202 subjects (McKee, 2014, as cited in Mez et al., 2017). Out of these subjects, 87% (177 subjects) were diagnosed with CTE, and out of the 111 NFL players among the subjects, over 99% (110) were diagnosed. Out of these 110 subjects, 86% had severe CTE, with many of these individuals holding positions with significant helmet-to-helmet contact. In a smaller study of 34 NFL players, 89% of them had stage III or IV CTE with the mean development age of this disorder being 54. Another study showed a correspondence of CTE alongside neuropathological diseases such as Amyotrophic Lateral Sclerosis.

Furthermore, statistics about concussions in youth sports are still incomplete. Many of these studies do not include individuals below high school age and are more focused on football rather than other high school sports myoinositol. Out of the 700,000 (Gessel, 2017) concussions that occurred in United States high school athletics, 13.2 % were recurrent. It is important to note that many of these injuries go unreported. For a variety of reasons, a student may continue to play longer with a mTBI, greatly increasing their risk of recurrent concussions and long-term impairment that is often associated with CTE (Saulle & Greenwaldd 2012).

Internal and External Risk Factors among Different Populations in Concussions and CTE

Genetics have also been thought to be a factor in the development and severity of CTE, specifically, the presence of the ApoE4 allele (Saulle & Greenwald, 2012). In Alzheimer's Disease, the allele has been shown to increase the risk of developing the disorder. Given the overlap with CTE and Alzheimer's Disease, studies have shown that ApoE4 also has a role in the development of CTE, with many of the individuals with this allele having worse problems with head trauma (Saulle & Greenwald, 2012). Many studies have found a correlation with the allele and severe chronic impairment. Specifically, studies done by McKee & Omalu (2009) reported the presence of ApoE4 in the majority of the CTE cases studied (50%

and 70%) in each of their experiments. Furthermore, a study 2000 done by Kutner et al. found that older age and the presence of the genotype scored lower on cognitive tests than those without ApoE4.

Generally, females have a higher rate of concussions than males, even though males sustain more concussions as shown in a 2003 study. This study collected data from the NCAA Injury Surveillance System (ISS) over the period of three years, and concluded that out of 14,592 injured, 471 female athletes sustained concussion compared to 402 male athletes (Alosco et al., 2003). Additionally, on a high school level, the rates of concussions in girls' soccer (6.2%) were slightly higher than boys' soccer (5.7%). However, it is unclear as to why exactly this is the case. It is speculated that the higher rates can be attributed to females having weaker neck muscles than male athletes, or their smaller size, in the context of a greater ball-to-head size ratio (Covassin et al., 2003).

Finally, age, military involvement, lengths of years of playing, and the presence of the ApoE4 allele is speculated to affect the risk for the development of CTE. Soldiers are often exposed to head injuries in combat and exposed to certain toxins that can increase their risk of injuries (Saulle & Greenwald 2012). Given the higher risk nature of concussions in children due to their developing brains, it is a possibility that an injury can lead to a domino-like effect on destructive events through later years. However, this is not definitive, and conversely, the higher brain plasticity present in younger people could allow a better recovery than in adults. Years of athletic participation is also a risk factor for many athletes, with longer careers generally correlating to more severe CTE, presumably due to the positive correlation between the number of injuries and playing time (Lindsley 2017).

CTE vs Other Diseases

There is difficulty in defining CTE to create a clinical diagnosis due to the fact that its symptoms overlap with other diseases, which all may be traced back to head trauma such as Alzheimer's disease, Parkinson's disease, and frontotemporal dementia (FTD) (Tartaglia et al., 2014). There is a strong overlap in the clinical and pathological features that define many of these diseases, and the presence of CET in an individual is often found alongside these other

neurodegenerative diseases.

Treatment and Possible Future Research

Due to the somewhat preliminary stages of research on CTE, despite the significant growth of interest on this topic, treatment is still limited to preventative measures. However, in many sports such as American football and boxing, high contact is a part of what makes up the sport. Therefore, these measures need to be implemented within the practice of the sport. From stricter policies that penalise athletes from acting on overly aggressive or reckless plays to coaches educating both themselves and their players on the detrimental effects of mTBI, many suggest a change to these programs from an administrative level.

Another preventative measure entails an improvement of protective equipment. Studies have proven that newer helmets in American football were more protective and better at absorbing force than helmets in 1970, and the addition of more fitted, effective protective gear lowered the impact of an individual's body; Additionally, there has recently been an interest in neck strength and its correlation to injury strength[CITATION]. Cognitive rehabilitation therapy (CRT) and other medical therapies are continuing to be developed to limit damage after injury and aid in recovery. However, much of these developments will heavily benefit from a definitive pathological definition and diagnostic criteria of CTE, which is something only future research can help clarify.

Summary

Chronic Traumatic Encephalopathy (CTE), a progressive tauopathy caused by repetitive mTBIs, or concussions, has been associated with aggression, depression, and the decline of many other cognitive functions among many other symptoms. Its prevalence in high contact sports that many view as an essential part of childhood and culture, specifically American football, is a cause of concern to many of these athletes. CTE is defined into 4 stages by a framework developed by Dr. McKee. Dr. McKee's studies show that 99% of NFL participants have CTE, with the majority of them having stage III-IV CTE. These stages are often associated with other neurodegenerative diseases such as Alzheimer's, Parkinson's, Motor Neuron Disease, and FDT.

However, due to the absence of definitive biomarkers and the underlying mechanisms of CTE, it currently can only be confirmed with an autopsy and not be diagnosed when a patient is alive. Despite the relatively preliminary knowledge of CTE, existing research has revealed risk factors such as age, gender, occupation, and the presence of the ApoE genotype, which increased the severity of the symptoms of concussions and hindered cognitive function in many football players. The identification and validation of a criteria and underlying mechanisms for CTE is essential to the development and implication of future preventative and recovery methods into different programs.

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