The Current Status of Research on Chronic Traumatic Encephalopathy

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Key words
- Chronic traumatic encephalopathy
- Concussion
- Mild traumatic brain injury
- Tauopathy
- Traumatic encephalopathy syndrome

Abbreviations and Acronyms
AD: Alzheimer disease
ApoE: Apolipoprotein
ADHD: Attention-deficit/hyperactivity disorder
ALS: Amyotrophic lateral sclerosis
CTE: Chronic traumatic encephalopathy
DTI: Diffusion tensor imaging
FTD: Frontotemporal dementia
MRI: Magnetic resonance imaging
NFL: National Football League
NFT: Neurofibrillary tangles
PED: Performance-enhancing drug
p-tau: Phosphorylated tau
TBI: Traumatic brain injury
TDP-43: Transactive response DNA binding protein 43 kDa
TES: Traumatic encephalopathy syndrome

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Chronic traumatic encephalopathy (CTE) evolved from the term dementia pugilistica describing the dementia found in many boxers to its current use in describing the dementia and depression sometimes found in athletes subjected to multiple concussions or subconcussive blows to the head. Concurrently, the neuropathology evolved to specify a unique type of tauopathy found in perivascular spaces at the depth of sulci and other features not typically seen in neurodegenerative tauopathies. Four stages of CTE have been proposed, with 4 corresponding clinical syndromes of traumatic encephalopathy syndrome. However, it remains unclear whether this is a syndrome unique to repetitive head trauma, especially in contact sports, because the epidemiology has been difficult to establish. In particular, research to date has had a denominator problem in not establishing the total number of potential cases at risk for developing CTE.

The current review examines the evidence to date for these syndromes and contributing or complicating factors affecting the neuropathology, neuroimaging, and clinical presentations associated with them.

INTRODUCTION

A dramatic increase in the discussion of concussions and brain disease in contact sport athletes occurred in the last decade, both in the popular press and in the scientific literature. Chronic traumatic encephalopathy (CTE) is implicated as a neurodegenerative condition resulting from the repetitive head trauma often sustained by participation in contact sports such as football and boxing. The first description of a disorder predating the term CTE dates back to 1928, when a "punch drunk" syndrome in 23 boxers was described by Martland.[1] The term then evolved to "traumatic encephalopathy" in 1934,[2] "dementia pugilistica" in 1937,[3] and chronic traumatic encephalopathy by Critchley in 1949.[4] This original description of CTE was characterized by cerebellar or extrapyramidal disorders with dysarthria and motor deficits and was sometimes accompanied by dementia. Roberts et al.[5] reported in 1990 that 17% of 224 retired boxers had CTE. Jordan[6] reviewed the literature on boxers to 2000 and reported clinical phenomenon of cerebellar and extrapyramidal signs along with cognitive and behavioral problems. He noted that it was unclear whether the signs and symptoms observed were indicative of a neurodegenerative disorder or a neurologic disorder exacerbated by aging. Other instances of CTE had been reported in nonboxers, including patients with repeated head banging or battery.[7,8]

CTE is believed to result from multiple concussions or repetitive head trauma, which are more prevalent in athletes in contact sports. Coupled with substantial media attention surrounding sport-related concussions, the research focus is dominated by investigations of CTE in deceased football players. Renewed interest in CTE began when Omalu et al.[9-11] reported finding evidence of CTE in 3 retired football players. McKee[12] reported similar findings in 3 new individuals when reviewing the world literature on CTE including 1 football player, followed by numerous reports and case studies of evidence of CTE in athletes, veterans, and others exposed to repetitive head trauma.[8,12-17]

The neurobehavioral changes associated with CTE reportedly involve a wide spectrum of diseases, such as depression severe enough to lead to suicide, substance abuse, emotional instability, aggressiveness, poor impulse control, irritability, and advanced dementia.[16,17] Similar to other neurodegenerative disorders, the cognitive difficulties seen in patients with CTE typically have a gradual, progressive course and can include significant memory impairment, executive dysfunction, language difficulties, and motor disturbances. The onset of behavioral and cognitive symptoms is generally years after exposure to repetitive trauma and often presents in midlife (e.g., after retirement from sports).[16,17] However, neuropathologic changes can be seen at a microscopic level in patients with a single

traumatic brain injury (TBI) or as early as adolescence (i.e., in high-school football players) in some case reports.[18]

Just as the demographics of CTE evolved from boxers to football players and other contact sport athletes, the observed pathologic features have also expanded from gross morphologic changes such as cavum septi pellucidi to specific locations involving phosphorylated tau (p-tau) and from clinical phenomena with extrapyramidal signs and parkinsonian-like dementia to a broad spectrum of neurobehavioral disorders. The various definitional shifts since the first description of CTE raise important questions about our current understanding of CTE that remain unanswered: is the modern description of CTE a new, distinct disorder or is modern CTE merely a variant of the same essential pathologic process initially described in the classic CTE of boxers? Or is CTE a variant or comorbidity of other unrelated more essential neurodegenerative conditions such as frontotemporal dementia (FTD) and Alzheimer disease (AD) to which individuals with exposure to trauma may have increased susceptibility?

Some of the challenges in studying CTE include the fact that there seems to be great variability in the clinical presentation of CTE across studies, as well as signs and symptoms that overlap with other neurodegenerative conditions. Second, there is considerable heterogeneity in the histopathologic changes cited for CTE with 4 stages and 4 phenotypes[8,18] associated with histopathologic findings. Third, as most studies acknowledge, many of the brains examined for CTE were donated explicitly because of the presence of neurobehavioral symptoms before death, resulting in a pronounced selection bias. Related to these problems and perhaps more importantly with respect to the public's perception of the disease and how CTE may influence policy, the current literature based on case studies suffers from a denominator problem. That is, there is still an absence of sufficient epidemiologic evidence of CTE from a broad, randomly sampled population of retired athletes with and without concussions or subconcussive blows. The current review explores these issues in more detail to present the evidence of CTE as a unique neuropathologic disorder accompanied by distinctive clinical presentations with a presumptive cause of concussions or multiple subconcussive blows to the head.

PATHOPHYSIOLOGY OF HEAD INJURY

Despite the advances made in the neuropathologic findings of CTE, mechanistic information correlating particular clinical features with anatomic abnormalities is still missing. It is feasible that the motor symptoms previously seen in boxers with CTE are reflective of injuries to the pyramidal tracts, extrapyramidal system, or cerebellum. However, the injury mechanisms behind the other cognitive and behavioral manifestations of CTE are less clear. For example, Stern et al.[16] described some apparent clinical presentations of CTE in their study of athletes and attempted to differentiate them from symptoms seen in other dementias. However, these investigators did not relate how the clinical features may be correlated with the presence and degree of tauopathy, whereas this association is established in other dementias, such as FTD and Alzheimer. The impact of p-tau depositions in scattered perivascular spaces on depression and cognitive deficits is also unclear. For example, some studies show that depression[19,20] and word-finding difficulty lateralize to injury to the left hemisphere, and a predominance of p-tau in the left hemisphere would be expected to relate to associated deficits in these domains. However, lateralization is discussed in CTE, further obscuring the mechanism causing depression and language deficits.

Similarly, little is known about the pathophysiology of concussions and the anatomic correlates of its clinical features. Our knowledge on why concussions cause loss of consciousness, photosensitivity, headaches, fatigue, poor concentration, and other symptoms is limited.[21] Thus, to understand the mechanisms that contribute to the clinical features of CTE, a more thorough comprehension of the physiology of concussions is needed. Moreover, studies are mixed on whether concussions and mild TBI are distinct clinical entities, rather than milder forms of moderate to severe TBI.[21,22] Animal models help clarify some physiologic processes in the acute stages but still do not paint a full picture.[23-28]

NEUROPATHOLOGY OF CTE

There is substantial diversity in the clinical history and presentation of those patients who are assigned a pathologic diagnosis of CTE, and many clinical symptoms may overlap with those of other neurodegenerative diseases. Studies suggest that CTE is a neuropathologically distinct entity from disorders such as AD, Parkinson disease, FTD, sporadic amyotrophic lateral sclerosis (ALS), and other neurodegenerative diseases. Even so, considerable heterogeneity exists across individual cases of CTE.

The initial neuropathology described CTE in boxers. In 1973, Corsellis et al.[29] examined 15 boxers with dementia pugilistica and described the neuropathologic substrate of CTE as involving 1) neurofibrillary tangles (NFTs) in the absence of plaques, particularly involving the medial temporal lobe and brainstem tegmentum, 2) neuronal loss in the substantia nigra, occasionally with NFTs, 3) scarring of the cerebellar tonsils, and 4) cavum septi pellucidi.[29]

Considering that β-amyloid deposition has variably been considered a distinguishing feature of CTE relative to AD, several studies have sought to further characterize β-amyloid in CTE cases. The cases initially examined by Corsellis et al.[29] were later re-examined by Roberts et al.[5] for β-amyloid. This study showed extensive, diffuse-type β-amyloid plaques that had not been observed previously using less sensitive techniques. McKee et al.[12] found β-amyloid deposition, an essential feature of AD, in 40%–45% of CTE cases.[12] Further efforts to characterize β-amyloid deposition in CTE cases by Stein et al.[30] found β-amyloid deposition in 52% of patients with CTE. Importantly, this study distinguished between the diffuse plaques observed with immunohistochemical staining (seen in 52% patients) versus neuritic plaques as assessed by silver staining (36% of patients), the plaques which are also quantified to assess the CERAD (Consortium to Establish A Registry for Alzheimer's Disease) or C score for neuritic plaques in AD cases. The