

Long-term Consequences of Repetitive Brain Trauma: Chronic Traumatic Encephalopathy

Robert A. Stern, PhD, David O. Riley, BS, Daniel H. Daneshvar, MA, Christopher J. Nowinski, BA, Robert C. Cantu, MD, Ann C. McKee, MD

Abstract: Chronic traumatic encephalopathy (CTE) has been linked to participation in contact sports such as boxing and American football. CTE results in a progressive decline of memory and cognition, as well as depression, suicidal behavior, poor impulse control, aggressiveness, parkinsonism, and, eventually, dementia. In some individuals, it is associated with motor neuron disease, referred to as chronic traumatic encephalomyelopathy, which appears clinically similar to amyotrophic lateral sclerosis. Results of neuropathologic research has shown that CTE may be more common in former contact sports athletes than previously believed. It is believed that repetitive brain trauma, with or possibly without symptomatic concussion, is responsible for neurodegenerative changes highlighted by accumulations of hyperphosphorylated tau and TDP-43 proteins. Given the millions of youth, high school, collegiate, and professional athletes participating in contact sports that involve repetitive brain trauma, as well as military personnel exposed to repeated brain trauma from blast and other injuries in the military, CTE represents an important public health issue. Focused and intensive study of the risk factors and in vivo diagnosis of CTE will potentially allow for methods to prevent and treat these diseases. Research also will provide policy makers with the scientific knowledge to make appropriate guidelines regarding the prevention and treatment of brain trauma in all levels of athletic involvement as well as the military theater.

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INTRODUCTION

There has been increased attention given to the recognition, diagnosis, and management of sports-related concussion. Participants in popular sports such as American football, hockey, wrestling, rugby, soccer, and lacrosse all risk exposure to brain injury that range from asymptomatic subconcussive blows to symptomatic concussion to more moderate or severe traumatic brain injury (TBI). In addition, military service and many other activities, including, but not limited to, downhill skiing, martial arts, horse riding, parachuting, and other adventure sports have been associated with TBI [1-3]. An estimated 1.6-3.8 million sports- and recreation-related concussions occur in the United States each year, although the true figure is unknown because most concussions are not recognized and reported [4-6]. In addition to symptomatic concussions, players in collision sports such as American football may experience many more subconcussive impacts throughout a season and career. Athletes at certain positions (eg, linemen) may sustain up to 1400 impacts per season, and high school players who play both offense and defense potentially sustain closer to 2000 impacts [7-10].

A mild TBI (mTBI) or concussion is a brain injury that results from a force transmitted to the head that leads to a collision between the brain and skull or to a strain on the tissue and vasculature of the brain [11,12]. This injury can lead to a variety of physical, psychosocial, and cognitive symptoms, and, when these deficits do not resolve, can result in postconcussion syndrome (PCS) [13]. Common symptoms include fatigue, dizziness, headache, light and noise sensitivity, mental fogging, depression, irritability, and impairments of executive functioning and concentration. Because a concussion and its symptoms result from temporary, reversible cytoskeletal and metabolic derangements that involve shifts in ion

R.A.S. Center for the Study of Traumatic Encephalopathy, Boston University School of Medicine, Boston University, 72 East Concord St, 7380, Boston, MA 02118; Department of Neurology and Neurosurgery; Alzheimer's Disease Center Clinical Core, Boston University School of Medicine, Boston, MA. Address correspondence to: R.A.S.; e-mail: bobstern@bu.edu

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D.O.R. Center for the Study of Traumatic Encephalopathy, Department of Neurology, Boston University School of Medicine, Boston, MA

Disclosure: nothing to disclose

D.H.D. Department of Neurology, Boston University School of Medicine, Boston, MA

Disclosure: nothing to disclose

C.J.N. Center for the Study of Traumatic Encephalopathy, Boston University School of Medicine, Boston, MA, Sports Legacy Institute, Waltham, MA

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R.C.C. Center for the Study of Traumatic Encephalopathy, and the Department of Neurosurgery, Boston University School of Medicine, Boston, MA; Sports Legacy Institute, Waltham, MA; Neurosurgery Service, and the Department of Surgery, Emerson Hospital, Concord, MA; and Sports Medicine, Emerson Hospital, Concord, MA

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A.C.M. Center for the Study of Traumatic Encephalopathy; Neurology and Pathology, Boston University School of Medicine, Boston, MA

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channels and energy imbalance, the majority of deficits associated with a concussive injury resolve within a matter of days, weeks, or months [13-16]. In some instances, PCS may persist for months or years after the initial injury. However, it is believed that no more than 15% of individuals with a history of mTBI still experience symptoms 1 year after injury [13,17,18].

To date, the resulting progressive tauopathy, known as chronic traumatic encephalopathy (CTE), has only been found in individuals with a history of repetitive brain trauma [3,7]. Despite the recent increase in attention on the long-term effects of repetitive brain trauma, including CTE, it has been known for some time that contact sports may be associated with neurodegenerative disease. In 1928, Martland [19] described a symptom spectrum in boxers, which he termed "punch drunk," that appeared to result from the repeated blows experienced in the sport, particularly in slugging boxers who took significant head punishment as part of their fighting style. In 1937, Millsbaugh [20] introduced the term dementia pugilistica to describe the syndrome characterized by motor deficits and mental confusion in boxers. By 1973, a neuropathologic report, by Corsellis et al [21], of dementia pugilistica in 15 boxers concluded that, although similar to other neurodegenerative diseases, dementia pugilistica is a neuropathologically distinct disorder.

After its initial description, evidence emerged that the clinical symptoms and neuropathology associated with dementia pugilistica were not solely limited to the boxing population. As a result, the term CTE surfaced in the 1960s and is now the term used to describe the neurologic deterioration that results from repetitive brain trauma [3,22]. Recent research results have demonstrated neuropathologic evidence of CTE in participants of many sports outside of boxing, including American football, professional hockey, and professional wrestling. CTE also has been found in those with a history of repetitive brain trauma aside from athletics, including a victim of physical abuse, a person who is a self-injurer, a person with epilepsy, and a circus clown [3,7,23-28].

Although CTE is associated with a history of repetitive brain trauma, the exact relationship between the acute traumatic injury and CTE is unclear. It has been hypothesized that a neurodegenerative cascade is triggered by repetitive axonal stretching and deformation induced by trauma, particularly in individuals with previous unresolved concussive and/or subconcussive injuries [14,29]. It also is unknown whether CTE is more likely to occur after extended exposure to repetitive brain trauma or whether a single traumatic injury can initiate this neurodegenerative cascade in susceptible individuals. Given the current understanding of CTE, it seems likely that trauma type and frequency play a role in CTE development [30]. An athlete's specific sport, level of competition (eg, professional versus collegiate), position, and playing career duration may all confer different degrees

of CTE risk [30]. Other factors, such as age, gender, and genetic predisposition, may contribute to CTE's development in susceptible individuals, although these variables require further investigation [3].

To date, there has been no randomized neuropathologic study of CTE, and, as a result, there is a selection bias in the reported cases. Fourteen of the 15 professional American football players examined neuropathologically at the Veterans Affairs Center for the Study of Traumatic Encephalopathy (VA CSTE) Brain Bank have been diagnosed with CTE. This is a biased sample, which overrepresents the actual incidence of CTE in professional American football players, because families are more likely to consider neuropathologic examination if they suspect that their loved one has symptoms related to CTE or another neurodegenerative disease. Future research, perhaps in vivo studies that use biologic markers of disease and new clinical diagnostic criteria for CTE, will lead to improved understanding of the incidence, prevalence, and risk factors for CTE.

In the sections below, we will provide (1) an overview of the neuropathologic findings of CTE (including gross and microscopic pathology) and a related variant, chronic traumatic encephalomyelopathy that is associated with motor neuron disease; (2) descriptions of the early and later clinical presentations and course of CTE; and (3) a description of the possible risk factors for CTE, in addition to the necessary repetitive brain trauma.

GROSS NEUROPATHOLOGY

The gross changes of CTE are typically observed in late-stage disease (Table 1). Advanced cases of CTE demonstrate generalized atrophy, most prominent in the frontal and medial temporal lobes; enlargement of the lateral and third ventricles; cavum septum pellucidum; and septal fenestrations (Figure 1). There also may be thinning of the hypothalamic

Table 1. Gross neuropathology of chronic traumatic encephalopathy

Overall
Decrease in brain mass
Cavum septum pellucidum
Septal fenestrations
Ventricles
Enlarged lateral ventricles
Enlarged third ventricle
Atrophy
Generalized atrophy, particularly of the frontal and temporal lobes
Atrophy of the medial temporal lobes
Mammillary body atrophy
Thalamic atrophy
Pallor
Locus coeruleus
Substantia nigra

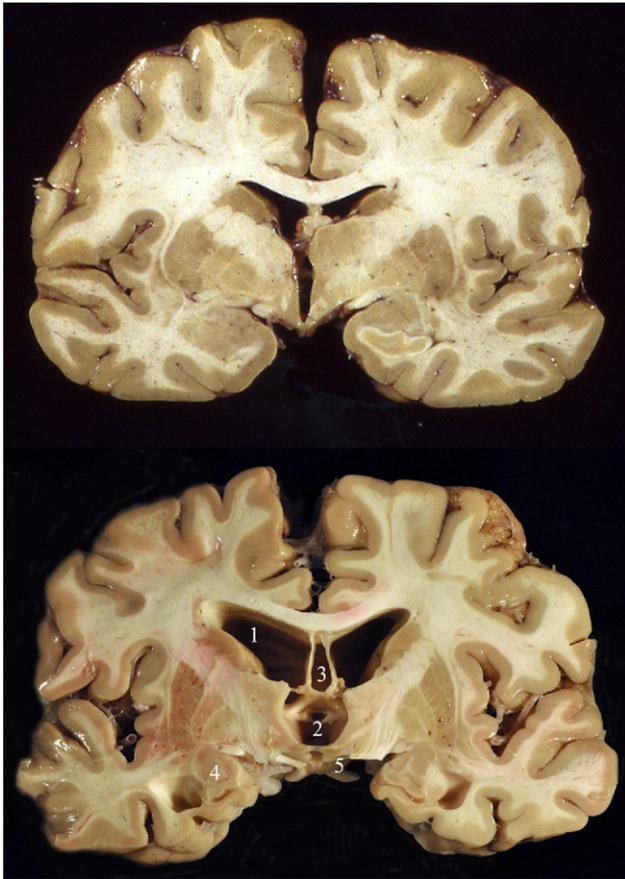


Figure 1. Gross pathology of chronic traumatic encephalopathy (CTE). The coronal section of normal brain (top), showing the expected size and relationship of the cerebral cortex and ventricles. The brain from a retired professional football player (bottom), showing the characteristic gross pathology of CTE with severe dilatation of ventricles II (1) and III (2), cavum septum pellucidum (3), marked atrophy of the medial temporal lobe structures (4), and shrinkage of the mammillary bodies (5).

floor, shrinkage of the mammillary bodies, and atrophy of the hippocampus, entorhinal cortex, and amygdala [3,7].

MICROSCOPIC NEUROPATHOLOGY: GENERAL DESCRIPTION

CTE is characterized by a unique pattern of microscopic changes (Table 2). There are extensive tau-immunoreactive neurofibrillary tangles (NFT), neuropil neurites (NT), and glial tangles (GT) in the frontal and temporal cortices (Figure 2). Unlike Alzheimer disease (AD) or many other tauopathies, the tau immunoreactive abnormalities tend to cluster at the depths of sulci, around small blood vessels, and in superficial cortical layers [3,7]. In advanced cases, there are tau-immunoreactive inclusions in the limbic and paralimbic regions, diencephalon, brainstem, and subcortical white

matter. The specific soluble and insoluble tau isoforms found in CTE are indistinguishable from those found in AD, and the ratio of tau isoforms with 4 versus 3 microtubule binding repeats is approximately 1 in both diseases [31]. Importantly, these changes seen in CTE usually occur in the relative absence of beta-amyloid (A β) deposits [3,7].

In addition to the widespread tau immunoreactivity, the majority of CTE cases also are marked by TDP-43 proteinopathy. The TDP-43 inclusions can be widespread and are typically found in the brainstem; basal ganglia; diencephalon; medial temporal lobe; frontal, temporal, and insular cortices; and subcortical white matter. In a subset of individuals with CTE, abundant TDP-43 immunoreactive inclusions and neurites are found in the anterior horns of the spinal cord and motor cortex, combined with corticospinal-tract degeneration, loss of anterior horn cells of the spinal cord, and ventral root atrophy. These individuals develop a progressive motor neuron disease that appears very similar to amyotrophic lateral sclerosis (ALS) and is characterized by profound weakness, muscular atrophy, spasticity, and fasciculations [32]. The fact that an ALS-like condition is found in some individuals with CTE suggests that some forms of clinical ALS may be associated with TBI [33,34].

Table 2. Microscopic neuropathology of chronic traumatic encephalopathy

Neurofibrillary tangles, frequent
Olfactory bulb
Dorsolateral frontal cortex
Orbital frontal cortex
Subcallosal frontal cortex
Insular cortex
Superior and/or middle temporal gyri
Inferior temporal gyrus
Entorhinal cortex
Hippocampus
Amygdala
Mammillary bodies
Substantia nigra
Locus coeruleus
Neurofibrillary tangles, common
Hypothalamus
Substantia innominata
Medulla
Thalamus
Neurofibrillary tangles, rare
Cingulate gyrus
Inferior parietal cortex
Occipital lobe
β -Amyloid deposits
Diffuse plaques in 45%
Sparse neuritic plaques
White matter
Loss of myelinated fibers
Perivascular macrophages
Cribriform state

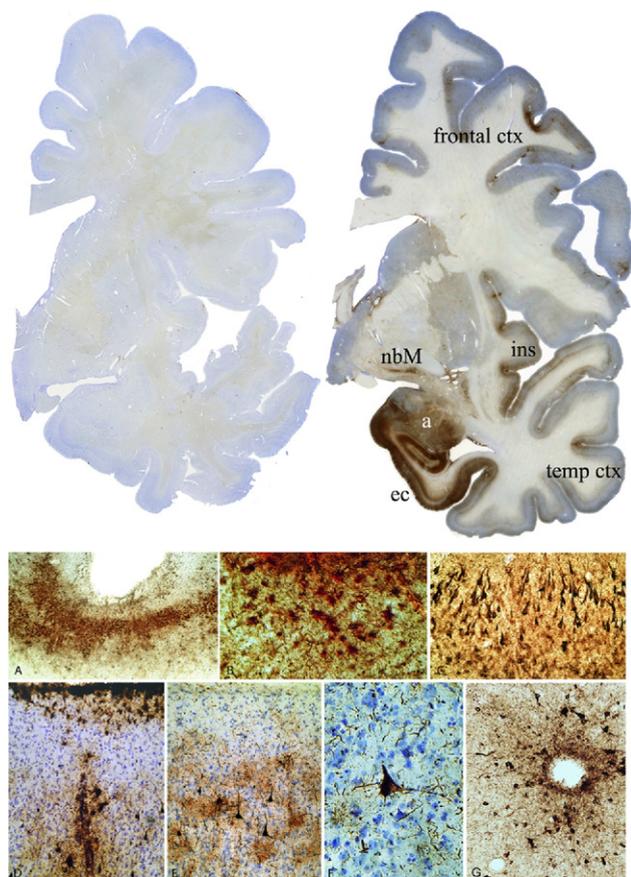


Figure 2. Microscopic pathology of chronic traumatic encephalopathy (CTE). **Top panel:** Phosphorylated tau (AT8) immunostained coronal hemisections of a normal brain (left) and a brain from a retired professional football player with CTE (right). The brain with CTE, showing severe neurofibrillary degeneration of the amygdala (a), entorhinal cortex (ec), temporal cortex, insular cortex (ins), nucleus basalis of Meynert (nbM), and frontal cortex. The cortical changes are most severe at the depths of the sulci. **Lower panels:** (A) Tau neurofibrillary tangles (NFT) are often prominent at depths of the sulci (AT8 immunostain, original magnification $\times 60$). (B) Subpial tau immunoreactive tangles are found in both neurons and astrocytes (double immunostained section for GFAP (red) and AT8 (brown), showing colocalization of tau and GFAP; original magnification $\times 350$). (C) Extremely dense NFTs are found in the medial temporal lobe structures, including CA1 of the hippocampus, shown here. Senile plaques are absent (AT8 immunostain, original magnification $\times 150$). (D) NFTs and astrocytic tangles tend to be centered around small blood vessels and in subpial patches (AT8 immunostain, original magnification $\times 150$). (E) NFTs characteristically involve cortical layers II and III (AT8 immunostain, original magnification $\times 150$). (F) NFT in a Betz cell of primary motor cortex (AT8 immunostain, original magnification $\times 350$). (G) Perivascular tau immunoreactive NFTs are a characteristic feature of CTE (original magnification $\times 150$).

CLINICAL PRESENTATION

To date, we have found more than 50 neuropathologic-confirmed cases of CTE, with patients ranging in age from teens to their 80s, and occurring in individuals who have played contact sports as well as military personnel exposed to blast injuries. During diagnosis, the neuropathologist (A.C.M.) remained blinded to the patient's clinical history (eg, medical, behavioral, cognitive, brain trauma exposure) until after the neuropathologic examination was completed and the pathologic diagnosis was made. This clinical history was obtained from semistructured interviews with next of kin and by review of medical records by the neuropsychologist (R.A.S.) who remained blinded to the neuropathologic results until after all aspects of the clinical history were completed. The results of this experience, along with our previously published review of the literature of CTE and/or dementia pugilistica as of 2009, resulted in a surprisingly consistent description of the clinical course and presentation of CTE [3].

It is important to note that the clinical presentation of CTE is distinct from the long-term sequelae of a concussion or from PCS. CTE is not the accumulation of symptoms from the earlier injuries. Rather, the symptoms of CTE, like other neurodegenerative diseases, results from the progressive decline in functioning of neurons or of the progressive neuronal death. That is, when there is sufficient disruption of normal neuronal functioning, symptoms specific to the area(s) of that disruption will begin to exhibit. Based on our currently unpublished observations from our series of more than 50 cases, there may have been no earlier symptoms of concussion or PCS, and, therefore, the symptoms of CTE begin insidiously and are apparently unrelated to earlier impairment. In other cases, PCS symptoms may completely abate months or years before the onset of CTE symptoms. In still other cases, there may be overlap; that is, the PCS symptoms may begin to abate but CTE symptoms gradually worsen at the same time.

Typically, CTE symptoms present in midlife, usually years or decades after the end of exposure to repetitive brain trauma (ie, retirement from sports). Although we have seen the earliest stages of neuropathologic changes of CTE in the brains of individuals in their teens or early 20s, it is unclear if any cognitive, mood, or behavioral symptoms at that time

Table 3. Early clinical presentation of chronic traumatic encephalopathy

Short-term memory problems
Executive dysfunction (eg, planning, organization, multitasking)
Depression and/or apathy
Emotional instability
Impulse control problems (eg, disinhibition, having a "short fuse")
Suicidal behavior

Table 4. Later clinical presentation of chronic traumatic encephalopathy

Worsening memory impairment
Worsening executive dysfunction
Language difficulties
Aggressive and irritable behavior
Apathy
Motor disturbance, including parkinsonism
Dementia (ie, memory and cognitive impairment severe enough to impair social and/or occupational functioning)

were directly the result of the mild neuronal disruption caused by the disease. When symptoms begin, the onset is earlier than that of sporadic AD and usually earlier than that of frontotemporal lobar degeneration or frontotemporal dementia (FTD). Symptom progression is slow and gradual, often over several decades. Early symptoms (Table 3) are consistent with those expected from the neuropathologic changes observed at autopsy. These include impairments in cognition (eg, from medial temporal and dorsolateral frontal degeneration), mood (eg, amygdala degeneration), and behavior (eg, amygdala and orbitofrontal degeneration). Although the cognitive difficulties (including short-term memory problems and executive dysfunction) are similar to those seen in other neurodegenerative diseases, the mood and behavioral symptoms may be the most concerning, especially to family members and coworkers [35]. These include depressed mood and/or apathy, emotional instability, suicidal ideation and behavior, and problems with impulse control, especially having a “short fuse.” Substance abuse (sometimes fatal) and suicide are not uncommon.

As the disease progresses, symptoms become more severe and their scope broadens. The primary clinical features of worsening CTE are listed in Table 4, including worsening memory impairment (although it may not resemble the severe rapid forgetting typical of the hippocampal episodic memory impairment of AD), worsening executive dysfunction (eg, poor planning, organization, multitasking, judgment), language difficulties (including speech output), aggressive and irritable behavior (including physical aggression), apathy (sometimes profound and in contrast to the outward aggressive behavior), and motor disturbance (most frequently parkinsonism, as well as difficulties with gait and falling). As the condition progresses, instrumental activities of daily living worsen and the symptoms are severe enough to impair social and/or occupational functioning, with eventual dementia.

RISK FACTORS

Repetitive brain trauma appears to be a necessary variable for the development of CTE but may not be sufficient. All neuropathologically confirmed cases of CTE have had a history of brain trauma exposure but not all individuals with exposure to brain trauma develop CTE. A major goal of CTE research must be epidemiologic and prospective studies to

identify the specific risk factors for the development of this neurodegenerative disease.

An important potential risk factor for CTE may be genetic predisposition. There have been preliminary studies that linked the apolipoprotein E (APOE) gene, specifically the APOE $\epsilon 4$ allele, to worse cognitive functioning in boxers and professional football players, and to prolonged recovery after a single TBI [36-38]. In our case series of 12 professional football players and boxers with neuropathologically confirmed CTE, 5 were APOE $\epsilon 4$ carriers, and 2 of those were homozygous for the $\epsilon 4$ allele [32]. Although these findings taken together suggest that APOE may be a susceptibility gene for CTE, much more research is required. Moreover, because of the presence of TDP-43 in CTE brains and the similar clinical presentations between CTE and FTD, additional genes associated with familial FTD, and perhaps ALS, may prove to play a role in CTE risk.

There are many other nongenetic variables to consider when evaluating an individual's risk of developing CTE (Table 5). As stated above, all confirmed cases of CTE have had a history of repetitive brain trauma. However, the specific nature of the brain trauma exposure necessary for the development of the disease is not yet known. For example, it is unknown if CTE is any more likely to manifest after a few severe TBIs versus numerous repetitive subconcussive impacts. Further complications arise when comparing impact exposure and type both between and within sports. For example, although boxing and American football both have a high incidence of head impacts, results of a study have shown that boxers are exposed to a greater amount of rotational forces, whereas American football players receive more linear blows [39]. More recently, a study that used an accelerometer-based system in the helmets of 3 college American football teams throughout a season found that head-impact exposure differed significantly based on position [9]. Linemen (both offensive and defensive) and linebackers received more impacts per practice and game than other positions. Line-man, linebackers, and defensive backs received more impacts to the front of the head than the back, whereas quarterbacks had a higher percentage of impacts to the back of the head compared with the front [9]. Future implementation of similar technology will help clarify the type and volume of impacts in American football and other sports, which can be extrapolated to estimate total impacts received over the career duration and may translate to information on the risk of developing CTE based on the sport and position.

Age at the time of head injury also may affect an individual's risk of developing CTE later in life, although the relationship is not yet understood. It has been suggested that the increased plasticity of a younger brain may allow a younger individual to better compensate and recover after brain injury [40]. However, current literature indicates that a younger brain may be more susceptible to diffuse brain injury, which leads to more pronounced and prolonged

Table 5. Potential additional risk factors for chronic traumatic encephalopathy

Potential General Risk Factor	Specific Examples and/or Questions
Genetics	APOE ϵ 4; MAPT; GRN; TARDP
Family history	First- and/or second-degree relatives with history of dementia
Type of brain trauma exposure	Symptomatic concussions; asymptomatic subconcussive blows; blast wave; minimum gravitational force; degree of axonal injury and/or microhemorrhages
Age and duration of brain trauma exposure	Susceptibility period during youth; years of overall exposure
Frequency of brain trauma exposure	Minimum number of injuries (eg, can one moderate-severe TBI lead to CTE, without any additional repetitive concussions or subconcussive exposure history?); amount of "rest" (and overall time interval) between injuries
Chronic inflammation	Obesity, hypertension, diabetes, and heart disease may exacerbate neurodegeneration and NFT formation
Cognitive reserve	Greater cognitive reserve (or brain reserve capacity) may be less likely to display the clinical symptoms associated with the neurodegeneration or exhibit them later in the neuropathologic process
Gender	Are women at greater risk if they had the same exposure as men?
Race	Are there racial differences in risk?

CTE = chronic traumatic encephalopathy; NFT = neurofibrillary tangles; TBI = traumatic brain injury.

cognitive deficits [41,42]. Therefore, it is possible that exposure to repetitive brain trauma at an early age may increase the risk of CTE more than exposure later in life, although this has yet to be proven. Gender also may play a role, as girls and women appear to be at greater risk for concussion and PCS-related symptoms, although this may be due in part to girls and women being more forthcoming when reporting their symptoms [43,44]. Other health-related variables may affect the neurodegeneration and clinical symptom spectrum associated with CTE. For example, chronic inflammation associated with obesity, hypertension, diabetes, and heart disease may exacerbate neurodegeneration and NFT formation in AD [45-48]. Cognitive reserve (ie, differential resilience to the clinical presentation of underlying neuropathologic disease) also may play a role in the clinical manifestation of CTE neuropathology. That is, given identical neuropathologic severity, individuals with greater cognitive reserve may be less likely to display the clinical symptoms of the disease than individuals with less cognitive reserve [49].

ONGOING AND FUTURE RESEARCH

As stated above, CTE is a neuropathologically distinct disorder, different in many ways from AD, FTD, sporadic ALS, Parkinson disease, or other neurodegenerative diseases. Nevertheless, its clinical presentation can be similar to these diseases, especially in the later stages when subtleties in presentation are less likely to be delineated. In recent years, research to investigate other neurodegenerative diseases, for example, AD, has been moving toward the integration of clinical (eg, neurologic, neuropsychological), biologic (eg, cerebrospinal fluid [CSF] and/or functional neuroimaging measurements of proteins), anatomical (eg, structural neuroimaging), biochemical (eg, magnetic resonance spectroscopy), and genetic (eg, APOE genotype) information for the purposes of early detection, differential diagnosis, treatment,

and prevention [50]. In addition, recent advances in CSF biomarkers have resulted in a "signature" biomarker for AD of low CSF $A\beta$ and elevated CSF tau [51]. Our group has recently begun investigations aimed at developing biomarkers for CTE through funding from the National Institute of Neurological Disorders and Stroke, the National Institute on Aging, and the National Institute of Child Health and Human Development. Through this research on biomarker development for CTE, accurate diagnostic criteria will be able to be proposed and validated by using similar approaches to the recently published revised diagnostic criteria for Alzheimer disease [52-55]. This approach includes clinical symptoms and history combined with objective biomarker evidence of the disease. This method will allow for the detection and diagnosis of the CTE in the early symptomatic stages and, possibly, in the preclinical stages of the disease. Theoretically, the earlier in the disease process one can intervene, the more effective disease-modifying agents will likely be. If a disease-modifying agent (eg, a tau antagonist) can be developed, proven effective, and has an adequate risk profile, then preclinical intervention with the drug could result in such a long delay in symptom presentation that there would be de facto prevention of the clinical disorder or CTE.

DISCUSSION

There has been a tremendous growth in the awareness of CTE in both scientific and lay circles in recent years. What was believed to be a very rare disease only seen in boxers is now commonly discussed as a potential consequence of repetitive brain trauma seen in multiple different sports and at all levels of play. In contrast to the rapid increase in media coverage, new policies, and culture change, the rate of new published research on CTE has been relatively slow. Although we know much more about certain aspects of the disease now compared with just 5 years ago, especially the neuropathology

and clinical history associated with CTE, we remain in infancy in the study of CTE. Because it has been well over 100 years since AD was first described, and there remains no consensus as to the underlying causal mechanism of AD, no highly accurate method of in vivo AD diagnosis, and no available Alzheimer disease-modifying intervention, it should not be surprising that many critical questions remain regarding CTE. These questions include the following: What is the underlying mechanism of disease? What are the risk factors for disease (including susceptibility genes, brain trauma exposure variables, and others)? What is the population prevalence of CTE? What is the incidence of CTE? How common is the disease among individuals with specific athletic and/or military histories? How can CTE be detected and diagnosed accurately during life? How can CTE be prevented? What interventions can result in successful disease modification?

Only through further study (including animal modeling, basic and translational investigations, and clinical and epidemiologic research) can these questions be answered and can CTE move from a disease only diagnosed postmortem to one that can be identified in life and eventually be treated, prevented, and cured. In addition, by addressing these critical questions, new research findings will provide policy makers with urgently needed scientific knowledge to make appropriate guidelines regarding the prevention and required treatment of brain trauma in all levels of athletic involvement as well as the military theater.

CONCLUSION

CTE has been linked to participation in contact sports such as boxing, American football, and hockey, and has been seen in individuals with non-sports-related histories of repetitive head injuries. It is believed that repetitive brain trauma, with or without symptomatic concussion, sets off a cascade of events that results in neurodegenerative changes marked by a unique tauopathy and TDP-43 proteinopathy. Symptoms may begin years or decades after the cessation of brain trauma exposure although earlier than most other neurodegenerative diseases. Early symptoms include a decline of memory and executive functioning, depression, suicidal ideation and/or behavior, and poor impulse control. Disease progression is relatively slow and eventually leads to dementia. In some individuals, CTE may lead to a motor neuron disease, similar to ALS. Recent neuropathologic research suggests that CTE may be more widespread than previously believed. Given the millions of athletes participating in contact sports that involve repetitive brain trauma, as well as military troops exposed to repetitive brain trauma from blast and other injuries and others in society who experience repetitive head injuries, CTE represents an important public health issue.

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