

# Is Chronic Traumatic Encephalopathy a Real Disease?

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## Abstract

Chronic traumatic encephalopathy (CTE) has received widespread media attention and is treated in the lay press as an established disease, characterized by suicidality and progressive dementia. The extant literature on CTE is reviewed here. There currently are no controlled epidemiological data to suggest that retired athletes are at increased risk for dementia or that they exhibit any type of unique neuropathology. There remain no established clinical or pathological criteria for diagnosing CTE. Despite claims that CTE occurs frequently in retired National Football League (NFL) players, recent studies of NFL retirees report that they have an all-cause mortality rate that is approximately half of the expected rate, and even lower suicide rates. In addition, recent clinical studies of samples of cognitively impaired NFL retirees have failed to identify any unique clinical syndrome. Until further controlled studies are completed, it appears to be premature to consider CTE a verifiable disease.

American football, or other sports involving repetitive head trauma. There have been only a couple of attempts to explore these risks via other methods. In 2005, Guskiewicz *et al.* (6) reported rates of mild cognitive impairment (MCI) and Alzheimer disease (AD) in retired National Football League (NFL) players that seemed to be higher than expected in comparison to population data. These results were based upon the responses to a survey sent to players who are members of the retired players association, and the results may have been subject to ascertainment bias. In addition, there were no controls.

## Introduction

A great deal of media attention has been paid in recent years to the possibility that a career in a contact sport like American football may result in late-life neurological or neuropsychiatric symptoms. Although to date there has not been a single controlled epidemiological study done to quantify this risk for any sport, this has done little to dampen speculation, and “chronic traumatic encephalopathy” (CTE) has entered the American lexicon within the last few years as an established disease entity, despite the fact that there are still no established clinical or pathological criteria for this disorder. The objective of this review is to examine critically the evidence that CTE exists as a unique neuropathological or clinical entity.

## Epidemiology of Risk

As noted above, there has not yet been one controlled epidemiological study looking at the risk of late-life cognitive impairment in any collision sport, including boxing,

A more recent study examined the cause of death in retired NFL players using a different database (pension fund database) and reported rates of death due to AD and amyotrophic lateral sclerosis (ALS) that were higher than would be expected for the general population (9). The results of this study must be interpreted with caution, however, because the overall rate of death due to any cause was much lower in retired NFL players than for men in the general population, and the number of cases of AD and ALS was also quite small. There were only about half as many deaths overall in the retired NFL sample than would be expected for an American male cohort with their age distribution, and there were only 6 deaths due to ALS and 2 deaths due to AD (with an additional 5 cases where AD was an associated diagnosis), out of 334 total deaths. Given the fact that the all-cause death rate in retired NFL players was cut in half, with lower rates of death due to cardiovascular disease and violence (for example) than in the general population, it is reasonable to assume that later-life neurodegenerative disorders may have emerged to a greater degree than would be observed in a population with higher rates of mortality at younger ages due to other causes.

Finally it is worth noting that in addition to having much lower overall rates of mortality than in the general population, retired NFL players also are much less likely to commit suicide. In another recent article, the rate of death due to suicide in retired NFL players was only approximately 40% of the general population (1). Given that suicidality is described as a key feature of CTE

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(see succeeding part of this article), this finding is difficult to reconcile with the high rates of CTE that has been speculated to occur in these retired athletes.

Overall, although retired NFL players have been the focus of more attention into the potential late-life neurological consequences of repetitive head trauma than athletes in any other sport, the risks for these retirees remains largely hypothetical. These retired athletes do have a much lower overall death rate and lower suicide rate than men in the general population, which would tend to rule against the probability of increased rates of any neurodegenerative or neuropsychiatric disorder with midlife onset. It does not, however, necessarily rule out increased rates of late-life cognitive impairment.

### The History and Evolution of Dementia Pugilistica and CTE

The term CTE dates back to the 1960s (12) and was used synonymously with dementia pugilistica, although it was never adopted in a widespread manner, and the term CTE fell out of use until being revived by Omalu *et al.* in 2005 (see succeeding part of this article). Dementia pugilistica is also a poorly-defined syndrome, used in case-based descriptions of various neurological symptoms in boxers, with most of the reports dating back to the first half of the 20th century. Many of these cases may have been due to AD or other neurodegenerative diseases, and the literature does not provide evidence of any unique disorder with clear clinical-pathological correlation. There also appears to have been some debate about whether dementia pugilistica/CTE was progressive or reflected a static encephalopathy. In a 1966 article, Miller (12) pointed out the lack of any evidence suggesting that a neurodegenerative disorder could be triggered by head trauma, and with respect to CTE, stated “there is no firm evidence that dementia progresses once successive injuries have ceased.”

In 1973, Corsellis *et al.* (3) published an article on “punch drunk syndrome,” reporting a neuropathological study of the brains of 15 former boxers. These authors acknowledged the controversy about the syndrome and the disparate clinical and neuropathological findings in the literature. They also acknowledged the inherent ascertainment bias in the fact that those boxers studied were to come more likely to autopsy because of the fact that they were institutionalized prior to their death. There were no neuropathological findings that were common to all 15 cases, but the most commonly observed findings were neurofibrillary tangles (NFT) in the cortex, loss of pigmented cells in the substantia nigra, cavum septum pellucidum, and cerebellar scarring. Senile plaques were observed in only 4 of 15 cases, suggesting some difference from classical Alzheimer-type pathology.

In what remains perhaps the best-controlled study of neuropathological findings in boxers to date, Roberts *et al.* (16) reexamined 14 of the 15 brains from the Corsellis study, added 6 new cases of boxers, and compared these to 20 cases of AD and 20 age-matched controls. They utilized immunocytochemical methods for identifying amyloid plaques (in contrast to the silver staining done by Corsellis *et al.*). Their conclusion was that “The molecular markers present in the plaques and tangles of dementia pugilistica are the same as

**Table 1.**

**The evolving neuropathological criteria for dementia pugilistica/CTE**

Dementia Pugilistica (as Classically Described by Corsellis <i>et al.</i> , 1973; Roberts <i>et al.</i> , 1990)	CTE as of 2009 (Omalu <i>et al.</i> , 2005, 2006; McKee <i>et al.</i> , 2009)	CTE as of 2012 (McKee <i>et al.</i> , 2012)
NFT in cortex	+ + + + +	Tau pathology only requirement.
Loss of pigmented cells in the substantia nigra	+ + + + -	Five “progressive” stages identified
Cavum septum pellucidum	- + - + +	
Cerebellar scarring	- - - - -	
Amyloid deposition, but less so in most cases than for typical AD	+ - - + -	

+, finding evident in one of the five cases; -, finding not evident or not reported.

those in AD. Similarities in the clinical symptoms, distribution of pathology and neurochemical deficits also exist” (p. 373). Their essential conclusion was that dementia pugilistica and AD shared a common pathogenesis.

The term CTE was resurrected by Omalu *et al.* (13,14) in two articles reporting neuropathological findings from two retired NFL players. The first case was a 50-year-old man who died from a myocardial infarction. There were no documented premortem psychiatric or neurological diagnoses, or documented evidence of cognitive decline. The authors reported that telephone interviews with his family revealed evidence of a “dysthymic disorder.” Pathological findings were diffuse amyloid plaques in the cortex and sparse cortical neuropil threads and NFT, without any subcortical evidence of these pathologies. The second case was a 45-year-old man who committed suicide by consuming antifreeze. He had a history of multiple psychiatric hospitalizations and prior suicide attempts, with a psychiatric diagnosis of major depression. Pathological findings were an absence of amyloid plaques, with diffuse cortical and subcortical NFT and neuropil threads.

These articles were followed by a publication by McKee *et al.* (10) in 2009, reporting on 3 additional cases: a retired NFL player who died from an accidental cause at the age of 45 years, a retired boxer with a history of progressive dementia who died at the age of 80 years, and a retired boxer with a history of progressive dementia who died at the age of 73 years. The pathological findings of these three cases were also markedly disparate, with the only commonality being the presence of cortical NFT and neuropils, although the distribution and density of these varied from case to case. The retired boxers who both had a history of progressive dementia also had evidence of gross atrophy and neuronal loss, with amyloid plaques evident in one case. Despite the disparate neuropathological findings, the authors included a

review of 47 prior published cases of dementia pugilistica (including the 2 cases reported by Omalu) and reclassified all of these as “neuropathologically-verified CTE” (p. 709).

In more recent discussions of CTE, the focus has shifted to aggregation of tau as the diagnostic hallmark. McKee *et al.* (11) recently reported that they had identified evidence of CTE in 80% of subjects (age, 17 to 98 years) with some history of repetitive head trauma. CTE was identified in 33/34 retired NFL players who constituted part of this sample. The authors proposed a staging system for CTE severity, and the only requirement for satisfying a neuropathological diagnosis of CTE was the presence of tau-positive astrocytic tangles and NFT. Table 1 illustrates the changing pathological definition of dementia pugilistica/CTE.

### Pathological Significance of Cerebral Tau Deposition?

Because NFT is present in a variety of neurodegenerative disorders and is also evident in most normal older individuals, this classification criterion deserves further scrutiny. There are six isoforms of tau in human brain tissue, distinguished on the basis of their binding domains. Tau is a microtubule-associated protein thought to play a role in neuronal microtubule stability. When tau is hyperphosphorylated, it leads to aggregation in the form of tangles. Tau hyperphosphorylation can occur as a result of a wide variety of factors, including brain trauma (5), hypoglycemia (8), hypoxia (4), and stroke (17), and is even very common in normal aging. As an example, NFT (Braak stage 1 or higher) were identified in nearly all (97%) of cognitively normal older individuals in a large prospective study, and 37% of these cognitively intact individuals met the criteria for a diagnosis of AD at an intermediate or high likelihood (2). Even in diseases that are defined as “tauopathies,” such as progressive supranuclear palsy, it is unclear whether the tau aggregation that is a diagnostic hallmark of the disease is a precipitating cause of the disease or a consequence of the disease process. Table 2 contains a list of conditions in which elevated levels of tau aggregation have been observed.

Although McKee *et al.* attempted to define a staging system for CTE and make some distinctions between AD and CTE pathologies, there remains substantial pathological overlap and a lack of clear clinical-pathological correlation. Even if repetitive head trauma led to transient abnormal phosphorylation of tau and subsequent aggregation, it is unclear that this would have any direct behavioral effects, nor can the finding of tau in the cerebrum be taken as evidence of the presence of a neurodegenerative disease. Without appropriate controls, therefore, it is impossible to determine whether these neuropathological findings in athletes exposed to repetitive head trauma are atypical or whether there are any behavioral consequences thereof.

### Is There a Clinical Syndrome That Defines CTE?

While there are no defined clinical diagnostic criteria currently for CTE, there have been some attempts to describe a clinical syndrome on the basis of retrospective review of premortem information from selected cases. McKee *et al.* (11), for example, reported that “CTE is clinically associated with symptoms of irritability, impulsivity, aggression, depression, short-term memory loss and heightened suicidality that usually begins 8 to 10 years after

**Table 2.**

**Conditions associated with high levels of cerebral tau aggregation**

AD
Argyrophilic grain dementia
Frontotemporal dementia
Corticobasal degeneration
Creutzfeldt-Jakob disease
Down syndrome
Ganglion cell tumors (ganglioglioma and gangliocytoma)
Gerstmann-Straussler-Scheinker disease
Hallervorden-Spatz disease
Inclusion body myositis
Lewy body dementia
Moderate-severe traumatic brain injury
Multiple system atrophy
<i>Normal aging</i>
Myotonic dystrophy
Neuronal lipofuscinosis
Parkinson disease
Parkinson-dementia complex of Guam
Pick disease
Postencephalitic Parkinsonism
Presenile dementia with tangles and calcifications
Prion protein cerebral amyloid angiopathy
Progressive supranuclear palsy
Subacute sclerosing panencephalitis
Tangle-only dementia
Tuberous sclerosis

experiencing repetitive mild traumatic brain injury” (p. 2). The claim of heightened suicidality particularly is interesting given the fact that retired NFL players have a significantly lower risk of suicide (less than half of the expected rate) than the general population of men their age in the United States (1). In addition, the list of symptoms that McKee *et al.* reported in the given article as being associated with CTE is so broad as to be essentially meaningless in any attempt to define a clinical syndrome, as they encompass a range of symptoms from those that are common in the normal healthy population to those observed in a variety of neurological diseases. They include the following:

- attentional impairments
- paranoia
- executive impairments
- suicidality
- memory loss
- language impairment
- visuospatial impairment
- apathy

- gait disturbance
- dysarthria
- parkinsonism
- post-traumatic stress disorder
- headache
- depression
- impulsivity
- explosivity
- aggression

There are two recent studies that have looked at patterns of cognitive impairment in retired NFL players. One of these studies involved the recruitment of NFL retirees with evidence of MCI for a treatment study. Forty-one retirees were recruited and administered a brief battery of neurocognitive tests. They were compared to 41 healthy controls and to a sample of 81 patients with amnesic MCI who had no history of repetitive head trauma. The NFL retirees performed more poorly than their controls, but their pattern of neurocognitive impairments was essentially identical to that of the patient sample (15). This was interpreted as ruling against the probability that cognitive impairment in the NFL retirees was due to any type of atypical or unique neuropathological process.

The second study reached fairly similar conclusions (7). This study actively recruited retirees with cognitive and neurobehavioral symptoms, with a total sample size of 34. They concluded that rates of MCI and depression were slightly higher than would be expected for the population but that “none of the retired players fit the reported profile for CTE at the time of examination” (p. 331).

## Conclusions

CTE has received substantial media attention and appears to have entered the American lexicon as a verifiable disease, despite a lack of clear epidemiological data on increased risk of dementia in boxers or football players, a lack of controlled pathological studies to substantiate neuropathological finding as occurring at an increased rate in these retired athletes, a lack of consistent pathological criteria, and a lack of specific clinical criteria for diagnosis.

The concept of dementia pugilistica in boxers was a subject of controversy from the beginning of study in this area. Some investigators argued that any cognitive impairments incurred as a result of boxing remained static upon retirement, and indeed, the term “chronic traumatic encephalopathy” appears to have been coined by researchers with that point of view (12). The issue of ascertainment bias in pathological studies was recognized in these early studies, as these were generally focused only on individuals who were institutionalized at the end of their life for disabling mental illness, typically dementia. There was such pathological overlap in these studies with AD that it led Roberts *et al.* (16) to conclude that perhaps AD and dementia pugilistica shared a common pathogenesis.

The term CTE was revived by Omalu *et al.* in 2005 and applied by this group and McKee *et al.* (11) to a few cases that were markedly disparate in terms of clinical features and neuropathological findings that were published between 2005 and 2009. In 2012, McKee *et al.* published an article that essentially redefined CTE as the presence of

abnormally phosphorylated tau in the brain, with five proposed “stages.” There are two basic problems with their hypothesis, however. The first of these is that the presence of abnormally phosphorylated tau in the brain is not specific to CTE and occurs in a variety of conditions, including normal aging (Table 2). The second is that the presence of tau is not intrinsically indicative of a neurodegenerative process, nor does it guarantee any associated cognitive or behavioral changes.

McKee *et al.* reported finding CTE in 97% of the brains of retired NFL players that they examined, and they define the condition as a neurodegenerative disorder with suicidality as a key feature. This is highly inconsistent, however, with epidemiological data. Retired NFL players have an all-cause mortality rate that is only half that of men their age in the United States, with suicidality rates of only 40% of expected. Although there have been no controlled epidemiological studies of dementia incidence in any population of retired athletes, the recently published data on cause of death in NFL retirees do not support the probability of a markedly elevated risk.

Finally in the two recent studies that were the first to examine clinical/neuropsychological features in samples of retired NFL players with cognitive impairment, no unique clinical syndrome was identified. In fact, MCI in these players was indistinguishable from MCI in a clinical sample of nonathletes, suggesting the probability of a common neuropathology (*i.e.*, prodromal AD) (7,15). In summary, there is no compelling evidence that retired boxers or football players experience an increased incidence of dementia, there are no controlled studies that suggest that these individuals exhibit any type of unique neuropathological findings, and retired NFL players who do have cognitive impairment are clinically similar to nonathletes, arguing against a unique neuropathophysiological substrate for their impairments. Until carefully controlled epidemiological and prospective clinical-pathological studies are done in this area, it is premature to suggest that these retired athletes are at risk for any type of neurodegenerative disease. Furthermore it is not only premature to suggest that contact sport retirees are at risk for CTE, it is potentially dangerous, as this type of information may lead individuals experiencing depression to misinterpret their symptoms as indicative of the first stages of a fatal neurodegenerative disorder.

The first step in further elucidating risk would be a carefully controlled epidemiological study. For example, a large, randomly selected sample of retired NFL players could be compared to a sample of demographically matched men without a history of involvement in collision sports. If there is no evidence of increased rates of cognitive impairment or neuropsychiatric symptomatology in the NFL retirees, there would be no compelling reason to study these individuals further. If there was an increased risk in the NFL sample, a prospective study could be implemented to follow these individuals over time, with further controlled clinical, imaging, and ultimately neuropathological investigations to characterize any identified disorder(s).

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