Chronic traumatic encephalopathy: understanding the facts and debate

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INTRODUCTION
A diagnosis of chronic traumatic encephalopathy (CTE) currently requires postmortem identification of a solitary phosphorylated tau aggregate in an irregular pattern in neurons, astrocytes, or cell processes around small blood vessels at the depths of cortical sulci [1]. To date, it appears that only approximately 300 cases with CTE have been reported in the scientific literature. Dementia has been attributed to the presence of CTE lesions based on a wide-array of cognitive, behavioral, and emotional symptoms described by next of kin in several CTE convenience samples [2,3]. Brain injury and repetitive head trauma, so-called ‘subclinical’ impacts received during contact sport, have been claimed to lead to the development of CTE and consequently dementia [3]. There are even reports that earlier participation in contact sport is associated with an earlier development of symptoms believed to relate to CTE. A recent study of former professional football players with CTE (N = 211) suggested symptoms reportedly began 13 years earlier for those who started playing before the age of 12 years (N = 87) compared with those 12 years and older (N = 127) [4]. However, several other studies have failed to support an association between age when beginning sport and the later development of cognitive/behavioral symptoms [5,6,7]. Nonetheless, the claims about CTE have made their way into public awareness and become widely accepted, persuading many to focus on ways to avoid developing CTE and/or seek restitution because of an assumed relationship between CTE and head trauma. For example, the public’s perception of CTE has contributed to some parents restricting their children from playing certain sports, local agencies limiting sports programs to those age 12 years and older, and class action lawsuits being

Purpose of review
Chronic traumatic encephalopathy (CTE) is hypothesized to be a progressive neurodegenerative disease leading to dementia after repetitive head impacts. This review summarizes the recent evidence on CTE to highlight the facts currently known and the areas that remain poorly understood.

Recent findings
Increasing evidence suggests that many of the prior assertions about CTE in relation to repetitive head trauma are premature. First, CTE lesions have been observed in individuals with no history of head trauma/impacts. In addition, attempts to characterize possible clinical markers of CTE have had several shortcomings, notably an absence of detailed clinical assessments during life, vague/nonspecific symptom reports, and crude methodology. Moreover, recent studies demonstrate that current CTE pathological criteria have limitations and are in need of refinement/validation.

Summary
CTE is still in the early stages of research as a neuropathological condition and no specific clinical criteria exist. Claims about CTE being a progressive disease entity and caused exclusively by head trauma/impacts are not well supported at present. Such assertions may have impeded our understanding of the frequency and significance of this disorder. Refining diagnostic criteria to reduce ambiguity in classifying cases will be essential before risk factors and/or possible clinical markers may be identified.

Keywords
concussion, dementia, traumatic brain injury, traumatic encephalopathy

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**KEY POINTS**

- Neuropathological abnormalities may not be associated with cognitive decline, and the scientific community is moving towards isolating neuropathological definitions from possible clinical markers.
- Recent studies illustrate that ambiguity and lack of a lower threshold in CTE pathological diagnostic criteria can lessen reliability/validity in CTE diagnoses.
- The neuropathological changes associated with CTE are not unique to individuals with a history of head trauma/impacts.
- CTE often co-occurs in the context of other neuropathological conditions.
- Refinement and validation of CTE pathologic diagnostic criteria are needed before risk factors and/or clinical markers can be appropriately studied.

filed against various organizations/institutions when cognitive difficulties manifest years after contact sports participation [8–10]. Although CTE is reportedly associated with dementia and brain trauma, there is significant disagreement within the scientific community because of contradictory findings, uncertainty about the sensitivity/specificity of CTE pathological lesions, lack of scientific rigor in many CTE studies, and overinterpretation of correlational findings. The purpose of this review is to highlight the current facts and topics of debate relating to CTE, discuss recent scientific advances that serve to better understand its implications, and underscore the need for future research.

**PROBLEM WITH DEFINING CHRONIC TRAUMATIC ENCEPHALOPATHY AS A NEURODEGENERATIVE DISEASE**

Two opposing perspectives exist about CTE and how to define it. Some believe CTE is a progressive neurodegenerative disease with specific neuropathologic findings and neurobehavioral correlates. The flip side is that CTE is merely a neuropathological condition with no relation to a clinical syndrome or degenerative process. Assertions that CTE is a neurodegenerative entity are based on retrospective descriptions of a gradual decline in cognitive/behavioral functioning from next of kin in those identified with CTE postmortem [2]. Interestingly, earlier diagnoses of dementia have become increasingly common overall, with a push in the scientific/community to identify and track those who are likely to manifest neurodegenerative disease.

However, information from detailed clinical assessments during life documenting a progressive decline has yet to be published in those later recognized with CTE. This is a puzzling phenomenon in today’s era, and allows for ambiguity in reporting the hypothesized clinical effects of CTE, as inconsistencies between perceived impairments and measured neuropsychological functioning often exist. For instance, a recent study compared neuropsychological functioning of former professional football/hockey athletes to age-matched athletes from a noncontact sport [11\*]. Although the football/hockey athletes rated themselves as having impairments in cognitive functioning, this was not actually substantiated with neuropsychological data. Furthermore, the largest systematic study to date in individuals with possible CTE was completed by Roberts nearly 50 years ago, wherein he found many former boxers had motor symptoms and cognitive deficits that did not progress [12]. Thus, assertions about CTE’s implications during aging appear to be premature and based on minimal evidence.

Doubt for CTE being a progressive neurodegenerative disease is further raised from the fact that many individuals with CTE often have other co-occurring neuropathological processes. Alzheimer’s disease [13], Lewy body disease [14\*], cerebrovascular changes [15\*], Creutzfeld–Jacob disease [16], and other well known conditions have frequently been found in individuals with CTE, which would be expected to cloud a potential association CTE may have with aging, if any. Oddly, the effects of these processes have largely been downplayed or ignored in many prior studies, with cognitive/behavioral declines attributed to CTE rather than the other and better understood comorbid pathological processes. Ideally, a reversed approach should be taken, wherein co-occurring processes are presumed to carry the weight in producing cognitive deterioration in aging over that of CTE. A recent review by Brett et al. [17\*\*] detailed the lack of scientific rigor in previous attempts to link CTE pathological changes with a clinical presentation. The authors highlight that previous studies relied on simple observations that lacked appropriate statistical paradigms, cautioning that these do not offer any information about the sensitivity/specificity of CTE pathological lesions in producing symptoms. There is a clear need for a sophisticated attempt to correlate CTE pathological changes with clinical assessments in individuals with CTE alone, as well as in individuals with CTE and co-occurring neuropathological processes. Such an approach would avoid confirmatory bias and allow for a more clear understanding of CTE’s implications during aging.
REASONS FOR DEFINING CHRONIC TRAUMATIC ENCEPHALOPATHY AS A NEUROPATHOLOGICAL CONDITION ONLY

Defining CTE solely as a neuropathological condition with no link to being a degenerative disease should become the standard until robust evidence is available. Numerous case studies show that differences exist between neuropathology and clinical presentations prior to death. For example, neuropathological abnormalities at autopsy have been reported in as many as 40% of cognitively normal older individuals [18], including a small percentage (8%) of those with severe Alzheimer’s neuropathology [19]. The presence of phosphorylated tau aggregates, as seen with CTE, have previously been posited to cause an extremely wide-array of nonspecific symptoms, but in some CTE cases, cognitive functioning has even been reported to be normal [13,20]. Herein, a causal relationship between phosphorylated tau and cognitive/behavioral symptoms has not been established. Interestingly, aging-related tau astrogliopathy (ARTAG) is a neuropathological condition identified within the past few years that commonly occurs in aging brains, neurodegenerative disorders, and even those with CTE [20]. However, although there have been questions about cognitive decline with ARTAG, it is currently only defined as a pathological entity because of minimal evidence. It would seem reasonable to treat CTE similarly, especially as there have been prominent movements to separate pathological definitions from possible clinical consequences for other more common neuropathological conditions, such as Alzheimer’s disease [21].

LACK OF A CLEAR NEUROPATHOLOGICAL THRESHOLD FOR CHRONIC TRAUMATIC ENCEPHALOPATHY

Classifying CTE using the pathological diagnostic criteria developed in 2016 out of an initial consensus meeting (the only such meeting to date) has proved challenging and highlighted several important limitations. For instance, several scientists have found ambiguity in classifying CTE [22**,23**,24], owing to a lack of a clear threshold when small amounts of phosphorylated tau are seen that do not meet other criteria. As CTE is currently considered an ‘all-or-nothing’ diagnosis (present versus absent), there is potential for CTE to be overdiagnosed in individuals with very few CTE-like lesions. Along these lines, CTE has been reported to be common in individuals with prior participation in football, ranging from 64 to 99% of individuals who played beyond the high school level (college, semi-professional, and professional) [2]. Although these percentages sound high (which likely have led many to assume contact sports will result in CTE), the frequency of CTE has been much lower in more recent studies that more clearly document the number of cases having some CTE features without meeting full neuropathologic criteria [23**,24]. For example, a recent investigation by Bieniek et al. [23**] assessed CTE pathological lesions in 750 individuals, 300 of whom were blindly identified to be former athletes of contact sports after reviewing public records (online obituaries and high school yearbooks). Less than 6% of all individuals were found to have CTE pathological features, whereas less than 3% actually met full CTE neuropathological criteria. Furthermore, among the 15 former athletes who played football beyond the high school level, 7 had some CTE features, but only 3 were actually diagnosed with CTE neuropathologically. CTE then, appears to not only be far less common than previously suggested, but there is increasing data calling into question when a neuropathological diagnosis of CTE should be considered definite or meaningful. Moreover, there has only been one reliability study of the diagnosis of CTE, and notably, neuropathologists disagreed in 22% of CTE cases considered being moderate/severe [25**]. Taken together, refinement/validation of CTE pathological criteria is needed, wherein a lower bound threshold is developed, ambiguity is measured objectively, and robust reliability studies are completed.

EFFECTS OF CHRONIC TRAUMATIC ENCEPHALOPATHY VERSUS ALTERNATIVE EXPLANATIONS

Clinical symptoms of ‘modern’ CTE (i.e. 2005 onward) have been reported to include depression, anger/irritability, explosivity, suicidality, substance use, apathy, headaches, motor abnormalities, and cognitive decline based on postmortem case reviews [2,13,26,27]. Four diagnostic frameworks have been published (most recently in 2016), all of which involve degrees of clinical certainty (e.g. possible, probable, definite) based on clinical symptomatology [28–31]. However, each of these include a wide range of cognitive, psychiatric, and motor symptoms that vary in specificity and the domains of cognitive impairment, disease course, degree of head injury exposure, and symptom duration required for diagnosis. Additionally, these criteria were developed exclusively using retrospective descriptions from next of kin in those with CTE pathological lesions, which is problematic for a number of reasons. First, many of CTE’s purported symptoms are broad and highly nonspecific. It would seem that physical, emotional, and/or cognitive ailments could be attributed to CTE when other factors, including
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non-neurological explanations, may be the actual source. Along these lines, depression is common in middle-aged men and many stressful life events and health problems may be associated with depression/suicidality, suggesting a complex multifactorial psychological process [32]. Second, a causal direction of symptoms is unknown. For example, it is unknown if depression/apathy is the result of CTE pathological lesions, or related to potential functional decline, adjustment to life stressors (e.g. retirement from professional sports), or even other symptoms attributed to CTE (e.g. substance abuse). Though as it stands currently, much of the research appears to assume that any symptom found in those with CTE pathological lesions is inevitably associated with the neuropathology. In fact, a literature review on numerous case series used to develop clinical criteria consisted of at least 18 behavioral features, 16 mood/psychiatric features, 12 cognitive features, and 10 motor features, encompassing 56 possible features of CTE [30]. Others have suggested reasonable alternative explanations for these wide-ranging features. A recent study found that ~5% of middle-aged men in the general population often feel angry and ~11% endorsed they would hit someone if provoked, suggesting that anger and aggression can also occur in middle-aged men [33*], and may be even more common in retired professional athletes who have engaged in a lifelong history of aggressive sports. Finally, the current hypothetical clinical framework of CTE differs from historical observations of CTE in two major ways. First, motor symptoms are often not considered a core criterion in ‘modern’ CTE, found in only about one-third of cases with CTE and never the initial feature [26]. In contrast, motor abnormalities were very frequent and often the initial presentation in older reports of former boxers [34]. Second, ‘modern’ CTE has been posited as a progressive tauopathy, which contrasts Roberts’ detailed 1967 in-vivo examination of boxers that suggested a stable, nonprogressive course [12]. Importantly, no diagnostic framework has been clinically accepted and there has not been a single validation study to determine if any of these clinical features are reliably associated with CTE pathological lesions or differentiate CTE from other neurodegenerative diseases.

CAUSE OF CHRONIC TRAUMATIC ENCEPHALOPATHY

CTE is claimed to occur as a result of brain injury and repetitive head impacts. Interestingly, a recent study re-examined brain tissue from 14/15 retired boxers previously described as having punch-drunk syndrome, one of the earliest descriptions of CTE [35*]. Only 7 of 14 cases were found to have CTE, which also co-occurred with ARTAG. On the basis of the findings, it is reasonable to assume that brain injury/repetitive head impacts alone may not be sufficient to cause CTE. This position is becoming well supported, as a growing number of case studies are finding CTE in individuals with no history of head trauma/impacts. For instance, a detailed review of medical records and surveys with next of kin were completed in a small sample with CTE to determine the frequency of head trauma [22**]. Of the six cases with CTE, only one had a history of head impacts. Another study assessed for CTE among 18 former military members between the ages of 32 and 94, with 3 having a history of head trauma and/or blast exposure [36**]. In this investigation, no cases were identified as having CTE pathological lesions. An increasing number of studies are also identifying CTE pathological lesions in subjects with a wide-array of neurological/psychiatric conditions and no history of brain injury/repetitive head impacts, including those with a history of alcohol use disorder [24], opioid/other substance use [37], schizophrenia with surgical leucotomy [38], temporal lobe epilepsy [39], amyotrophic lateral sclerosis [40], and multiple system atrophy as well as other neurodegenerative disorders [41]. These findings illustrate that CTE does not appear to be unique to brain injury and/or head impacts, and further suggests that prior reports of a clear link between CTE and head trauma were premature. Thus, there is now mounting evidence showing a disconnect between the public’s perception about developing CTE following participation in contact sports and the actual data.

CONCLUSION

Recent studies demonstrate that CTE is currently not well understood and remains in the very early stages with regard to being a clinical condition. Many claims about CTE, such as it being a progressive neurodegenerative disease, an ‘all-or-nothing’ process, producing cognitive/behavioral changes, and directly or solely tied to head trauma/impacts, have generally not been well supported in the scientific literature. In fact, such assumptions/assertions may have impeded our understanding of the significance of CTE pathological changes. Moving forward, studies should revert to defining CTE as a neuropathological condition and aim efforts towards refining/validating diagnostic criteria. Establishing criteria that are on a continuum, similar to other well known neuropathological conditions, and involving a lower bound threshold for recognizing CTE is clearly needed to advance its understanding. For example, moving to a scale comparable with what is now used in Alzheimer’s disease
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This is a case-series study of retired professional hockey and football athletes matched to noncontact sport athletes that systematically examined subjective cognitive complaints compared with objective neuropsychological measures. The study highlights that reported cognitive difficulties is often not substantiated with neuropsychological data.


This retrospective analysis reports that Lewy body disease pathology is seen in individuals with chronic traumatic encephalopathy and a history of contact sports participation and can be associated with motor abnormalities and reported functional changes.


This retrospective analysis reports that cerebrovascular-related lesions are common in individuals with chronic traumatic encephalopathy and a history of contact sports participation and can be linked to reported functional changes.


This retrospective study reports that sporatic Creutzfeld–Jakob disease co-occurs with chronic traumatic encephalopathy at a higher frequency than would be expected per population numbers.


This systematic review is the first to critically explore the differences between Alzheimer’s disease, Lewy body disease, and chronic traumatic encephalopathy neuropathological and diagnostic criteria. The article highlights how chronic traumatic encephalopathy is lacking in robust studies as well as investigations about its reliability/validity.


This is one of the first studies to document an absence of brain injury and head impact exposure history in subjects with chronic traumatic encephalopathy disorder.


This is the largest study to date to examine the frequency of chronic traumatic encephalopathy in a diverse population that includes former athletes and non-athletes, males and females, and a wide age-range. The results show that the prevalence of the disorder is markedly lower than previously reported in the literature and reports ambiguity in diagnosing the condition.


This comprehensive narrative review highlights the history of chronic traumatic encephalopathy and is one of the first to point out limitations in the pathological diagnostic criteria.


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This study reports on the frequency of anger and depression among a community cohort with no participation in contact sports. The observation that irritability and anger are fairly common in middle-aged men has importance in suggesting that these symptoms can be common outside of neurological/neuropathological conditions and may not necessarily relate to chronic traumatic encephalopathy as is reported in prior studies.


