Traumatic Brain Injury (JR Couch, Section Editor)

Current Understanding of Chronic Traumatic Encephalopathy

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Opinion statement

Chronic traumatic encephalopathy (CTE) is a unique neurodegenerative disease found in individuals with a history of repetitive head impacts. The neuropathology of CTE is increasingly well defined. Prospective, longitudinal studies with post-mortem neuro-pathologic validation as well as in vivo diagnostic techniques are needed in order to advance the understanding of CTE clinically. Given the large number of individuals who incur concussions and other forms of brain trauma, this is an important area for scientific and public health inquiry.

Introduction

Chronic traumatic encephalopathy (CTE) is a neuro-degenerative disease thought to be associated with a history of repetitive head impacts [1–8, 9••, 10, 11, 12•], such as those sustained through contact sports or military combat. CTE, a distinct neurodegeneration, was first introduced in the literature as "punch drunk" or dementia pugilistica in the early 1900s because of its association with boxing [13]. In fact, much of the

early literature about the disease focused on the boxing population [1, 13, 14]. However, the disease is found in a more diverse group of individuals with a history of repetitive head impacts including a variety of contact sport athletes, military veterans, domestic abuse victims, and individuals with self-inflicted head banging behavior [7]. Although significant media attention has been brought to this disease, there is relatively little known regarding the pathobiological mechanisms underlying CTE, and a large number of questions remain. The preponderance of the literature has consisted of postmortem neuropathologic assessments with retrospective clinical interviews. As such, the neuropathology of CTE is currently better understood than the clinical presentation or course, and there is a need for prospective longitudinal clinical studies with in vivo diagnostic techniques or neuropathologic validation. This article reviews the current state of our knowledge concerning CTE, including neuropathologic characteristics, clinical features, proposed clinical and pathologic diagnostic criteria, possible risk factors, and future research needs.

Neuropathologic characteristics

Much of the scientific literature on CTE, to-date, is derived from clincopathologic case series of the disease [1–4, 6–8, 9••, 15]. The neuropathology of CTE is increasingly well defined. In 2013, McKee and colleagues published the largest case report to date of individuals with neuropathologically confirmed CTE, presenting proposed criteria for four stages of CTE pathology based on the severity of the findings [9••]. Formal validation of the reliability of these criteria and the staging system are currently being performed by a team of nine neuropathologists, funded by a National Institutes of Health (NIH) U01 grant (1U01NS086659-01, National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Biomedical Imaging and Bioengineering (NIBIB); PI, Ann McKee). Detailed criteria of McKee et al.'s pathologic staging criteria can be found in Table 1.

CTE is characterized by the deposition of hyperphosphorylated tau (p-tau) protein as neurofibrillary tangles (NFT) beginning perivascularly and at the depths of the cortical sulci. Later stage p-tau pathology becomes more widespread, particularly dense in the medial temporal lobes, also present in the white matter, and leads to prominent neuronal loss and gliosis. The irregular and perivascular nature of the p-tau neurofibrillary tangles, the proclivity for the sulcal depths, and the marked subpial and periventricular involvement are unique features of the disease that distinguish it from other tauopathies. TAR DNA-binding protein 43 (TDP-43) is present in about 80 % of cases. Early stages show sparse TDP-43 positive neurites in cortex, medial temporal lobe, and brainstem. Late-stage pathology presents with TDP-43 intraneuronal and intraglial inclusions in the frontal subcortical white matter and fornix, brainstem, and medial temporal lobe. In most cases of CTE, there are no beta amyloid 1–42 ($A\beta_{1-42}$) positive neuritic plaques. Evidence of axonal injury is common and ranges from multifocal axonal varicosities in earlier stage pathology to severe axonal loss in later stage pathology. Stage I and II CTE can present macroscopically with mild enlargement of the lateral ventricles or third ventricle and/or mild septal abnormalities. Grossly, advanced CTE is characterized by enlargement of the lateral and third ventricles, cavum septum pellucidum, septal perforations, and pallor of the substantia nigra and locus coeruleus. In addition, severe

Table 1. Description of McKee et al.'s (2013) proposed neuropathologic staging of CTE

	Stage I	Stage II	Stage III	Stage IV
P-Tau	Focal perivascular NFTs at depths of cortical sulci	NFTs adjacent to focal epicenters and in nucleus basalis of Meynert and locus coeruleus	Dense in medial temporal lobes and widespread in cortex, diencephalon, brainstem, and spinal cord	P-Tau pathology widespread including in white matter; prominent neuronal loss and gliosis of cortex; hippocampal sclerosis
Macroscopic	Mild lateral ventricle enlargement in some cases	Mild enlargement of the frontal horn of the lateral ventricles or third ventricle in a majority of cases; small cavum septum pellucidum in some cases	Mild cerebral atrophy; enlarged ventricles; depigmentation of locus coeruleus and substantia nigra; septal abnormalities in some cases	Increased cerebral, medial temporal lobe, hypothalamus, thalamus, and mammillary body atrophy; septal abnormalities; enlarged ventricles; pallor of locus coeruleus and substantia nigra
TDP-43	Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem	Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem	Sparse TDP-43 neurites in cortex, medial temporal lobe, brainstem	Severe intraneuronal and intraglial inclusions in cortex, white matter, diencephalon, basal ganglia, brainstem
Axonal Injury	Multifocal axonal varicosities in cortex and subcortical white matter	Multifocal axonal varicosities in cortex and subcortical white matter	Severe axonal loss in cortex and white matter	Severe axonal loss in cortex and white matter
$A\beta_{1-42}$	Present in less than half of subjects with CTE and less than one-third of pure CTE cases. Those with $A\beta_{1-42}$ deposits were significantly older than those without.			

cases may also show profound atrophy of the medial temporal lobes or profound global atrophy. In reports examining former football players [9••] and former boxers [1], the severity of pathology appears to correlate to duration of athletic career. McKee et al. also found an association between severity of pathology to years since retirement from athletics and age at death [9••].

Clinical presentation

Clinical symptoms of CTE generally present years or decades after exposure to trauma [1, 9••, 16••]. Although there are some symptom overlaps between the acute concussive injury and the later-life neurodegenerative process of CTE (eg, attention and concentration loss, headache), it is thought that CTE is distinct from the acute concussion or postconcussion sequelae [17]. That is,

although a history of repetitive brain trauma is thought to be necessary to cause CTE (ie, all neuropathologically confirmed cases of CTE to date have had a history of repetitive brain trauma), CTE symptoms are not just the cumulative effects of this process. Furthermore, there is no clear relationship between prolonged acute concussion symptoms (eg, postconcussion syndrome) and the pathology of CTE.

Evidence to-date suggests that CTE presents clinically with symptoms in one or more of four possible domains: mood, behavior, cognition, and motor [9••, 16••]. Commonly noted mood features include depression, irritability, and hopelessness. Behavioral features may include impulsivity, explosivity, and aggression. Cognitive features can include memory impairment, executive dysfunction, and in severe cases dementia. Motor features, including parkinsonism, ataxia, and dysarthria, appear in a subset of cases, predominantly boxers. In addition, chronic headache is also experienced in some cases [7, 9••, 15, 18, 16••, 19, 20•, 21•]. Two distinct clinical presentations of CTE have been described in a recent study by Stern et al., substantiating evidence from earlier literature regarding this possibility [1, 16••, 22–24] According to Stern and colleagues, the first type of clinical presentation initially presents with mood and behavioral symptoms earlier in life (mean age approximately 35) and progresses to include cognitive symptoms later in the disease course. The second clinical presentation begins with cognitive impairment later in life (mean age approximately 60), which may progress to include mood and behavioral symptoms [16••].

Earlier cases of CTE tended to report a higher prevalence of motor features than more recent reports. Differences in symptom profile have led some researchers to differentiate "classic" and "modern" CTE clinically [25•]. It is worth noting that "classic" cases were predominantly boxers, whereas more recent descriptions have been dominated by football players. Differences in the nature of exposure could account for differences in presentation— biomechanical comparisons of head impact dynamics in boxing and football have shown that boxers experience proportionally more rotational acceleration than in football [26, 27]. Further, computational modeling of boxing impacts suggests that stress in boxing impacts is greatest on midbrain structures, and midbrain damage may account for the parkinsonian features found in CTE [27, 28]. Supporting this theory, in the case series of neuropathologically confirmed CTE by McKee and colleagues [9••], professional boxers and professional football players with neuropathologically confirmed CTE, professional boxers exhibited significantly more motor symptoms (eg, ataxia dysarthria) relative to football players. This clinical difference between boxers and football players was mirrored in the pathology: boxers displayed more cerebellar scarring than football players. Thus, although there is a notable difference in the presence of motor symptoms between the earlier and more recent CTE literature, this may be attributable, at least in part, to the variance in head impact exposure types experienced by boxers and football players.

The question of suicide in CTE remains contentious [29•]. Several CTE case series have included victims of suicide.[6, 7, 9••, 16••] However, our lack of understanding of the population incidence of CTE limits our ability to attribute a complex and multifactorial behavior such as suicide to underlying CTE proteinopathy. The issue is further complicated considering that well

established risk factors for suicide and suicidal ideation such as substance use and depression [30, 31] are often comorbid in cases of CTE [9••, 16••]. The current literature does not provide means to separate the contribution (or lack thereof) of these different potential factors to the act of completing suicide. Further, premature association between repetitive brain trauma and suicidality could result in a 'self-fulfilling prophecy' prompting wider suicides in exposed individuals irrespective of contribution (or noncontribution) from CTE symptoms. Available scientific evidence cannot wholly support the notion that CTE *causes* suicidal thoughts or behaviors, and such assumptions or assertions should be avoided without further evidence.

All efforts to define the clinical presentation of CTE are also limited due to the lack of in vivo diagnosis and use of retrospective reviews of case reports[15, 20•, 21•] or family interviews [9••, 16••]. This information is valuable to determine initial correlations between presence of neuropathology and clinical manifestation; however, because of their retrospective third-party nature, there are significant limitations to these data. Although some of the earlier literature includes clinical evaluations [13, 32], the findings and their generalizability is limited by the technology of the era [25•]. Increased prospective and longitudinal clinical research in this area is critically needed.

Clinical diagnosis and in vivo biomarkers

Several important studies are underway to develop reliable biomarkers for CTE during life, although like most neurodegenerative diseases, the definitive diagnosis of CTE is based on neuropathologic examination. To date, three groups of authors have proposed preliminary clinical and/or research diagnostic criteria [20•, 21•, 33•]. The three independently proposed criteria are largely comparable and follow a structure similar to the National Institutes on Aging—Alzheimer's Association clinical diagnostic criteria [34] by differentiating between probable and possible cases based on endorsement of various signs and symptoms. All criteria require a patient to have a history of brain trauma, and to exhibit symptoms consistent with the clinical presentation of CTE described in the literature that could not likely be explained by another condition. All three criteria identified behavioral and cognitive disturbances as important for a diagnosis of CTE. Research groups differ concerning the importance of motor features; Jordan has suggested that motor features resulting from injury to the pyramidal tracts, extrapyramidal system, and cerebellum are necessary for CTE, whereas both Montenigro et al. and Victoroff have suggested a less central role of motor features in diagnosing clinical CTE [20•, 21•, 33•]. Montinegro et al. suggested codifying the clinical syndrome associated with repetitive brain trauma as Traumatic Encephalopathy Syndrome (TES), and reserving CTE for postmortem neuropathologic diagnoses [33•]. In order to confirm the utility of these criteria in either research or clinical settings, future studies will need to demonstrate an ability to reliably differentiate between cases and noncases with a high degree of specificity. A comparison of these proposed criteria can be found in Table 2.

Table 2. Description of existing proposed research or clinical diagnostic criteria for CTE

	Jordan (2013)	Montenigro et al. (2014)	Victoroff (2013)
Disease/disorder	CTE	Traumatic encephalopathy syndrome (TES), a clinical syndrome associated with history of repetitive brain trauma	CTE
Subclassifications	Definite, Probable, Possible, Improbable	behavioral/mood variant (BMv), cognitive variant (COGv), mixed variant (MIXv), dementia (D); differentiated depending on the presence of motor features or clinical course, or probable, possible, or unlikely CTE based on biomarkers.	Clinically probable, Clinically possible; acute onset, delayed onset; apparently persistent, apparently progressive, apparently improving.
History of brain trauma	No specific guidance as to the specific type or amount of brain trauma required.	History of multiple head impacts (mTBI, TBI, or subconcussive trauma) from high exposure contact sports, other significant exposure to repetitive hits, or any activity resulting in TBI.	Probable or definite exposure to one or more of the following: TBI, concussion, subconcussion.
Duration of symptoms onset of symptoms	No guidance provided. Typically manifest later in life after a period of latency.	Symptoms must be present for a minimum of 12 months. Symptom onset must be delayed by at least 2 years from exposure to brain trauma.	Symptoms must last for at least two years after impact. *Acute onset* cases have no period of recovery in the 6–12 months following concussion. *Delayed onset* cases have evidence of decline following apparent recovery post-impact.
Differential diagnosis	*Definite* (neuropathologically confirmed) and *Probable* cases of CTE involve ruling out of other possible neurological causes. *Possible* CTE can potentially be explained by other known neurological causes. *Improbable* CTE can be explained by a pathophysiological process unrelated to brain trauma.	Must rule out other neurological disorders, including residual symptoms from acute TBI or postconcussion syndrome that could account for symptoms. Comorbidities such as substance use, other neurodegenerative diseases can be present.	Must rule out other medical or psychiatric diagnosis that could explain symptoms.
Clinical features	*Behavioral and psychiatric features:* aggression or agitation, apathy, impulsivity, depression, delusions, suicidality.	*Core clinical features:* Difficulties in cognition substantiated with scores of ≥1.5 SD below norms on standardized mental status	*Symptoms:* headache, speech changes, tremor, deterioration in stance or gait, falls, cognitive decline, mood changes, anxiety

Table 2. (Continued)

	Jordan (2013)	Montenigro et al. (2014)	Victoroff (2013)
	Cognitive features: impaired attention and concentration, memory problems, executive dysfunction, dementia, visuospatial difficulties, language impairment. *Motor features:* dysarthria, spasticity, ataxia, parkinsonism, gait disturbance, motor neuron disease (possibly).	or neuropsychological tests; behavior issues (eg, short fuse, violence); mood disturbance (eg, depression). *Supportive features:* impulsivity, anxiety, apathy, paranoia, suicidality, chronic headache, motor signs (eg, parkonsinism), documented functional decline, delayed onset. Potential Biomarkers for Diagnosis of Probable CTE: cavum septum pellucidum, normal beta amyloid CSF levels, elevated CSF p-tau/tau ratio, negative amyloid imaging, positive tau imaging, cortical atrophy based on neuroimaging, cortical thinning based on neuroimaging.	paranoia, personality change (eg, irritability, apathy), alcohol abuse dependence or sensitivity, anger or aggression. *Neurological signs:* nystagmus, dysarthria, reduced facial expression, hypertonia or rigidity, hyperreflexia, hemiparesis, tremor, limb ataxia, disorders of gait or stance. *Neurobehavioral signs:* memory loss, other cognitive impairment (eg disorientation, confusion), mood disturbance (eg depression), thought disorder, pathological personality traits (eg, irritability, apathy), anger or aggression.
Symptom requirements for diagnosis	*Definite:* neurological process consistent with clinical presentation of CTE along with pathological confirmation. *Probable:* two or more of the following conditions: cognitive and/or behavioral impairment, cerebellar dysfunction, pyramidal tract disease or extrapyramidal disease; distinguishable from other disease processes and consistent with the clinical presentation of CTE. *Possible:* neurological process consistent with clinical presentation of CTE but potentially explained by other neurological disorders. *Improbable:* inconsistent with clinical description of CTE and be explained by a process unrelated to brain trauma.	At least one core clinical feature must be present and considered a change from baseline functioning, at least two supportive features must be present. *TES-BMv:* behavioral and/or mood core features without cognitive core features. *TES-COGv:* cognitive core features without behavioral and/or mood core features. *TES-MIXv:* both cognitive core features and behavioral and/or mood core features. *TES-D:* progressive course of cognitive core features, evidence of functional impairment. *Probable CTE:* meets TES criteria, progressive, >1 positive CTE biomarker. *Possible CTE:* meets TES criteria, either has not undergone biomarker testing or has had a negative biomarker (other than tau imaging) or has another disorder that may account for presentation. Unlikely CTE: does not meet TES criteria and/or has had negative tau imaging.	*Clinically* probable diagnosis requires at least two symptoms and three signs. Clinically possible diagnosis requires at least one symptom and two signs. Cases should be identified as acute onset or delayed onset. (See onset of symptoms above.) Cases should be identified as either apparently persistent (clinical features last more than two years), apparently progressive (clinical features last for more than two years and are unequivocally progressing), or apparently improving.

CTE chronic traumatic encephalopathy.

To date, there are no objective, validated in vivo biomarkers of CTE. However, important work in the area of CTE biomarkers is currently underway. Several research groups[18, 21•, 35•, 36] have suggested that negative amyloid PET imaging in the presence of positive tau PET imaging could provide a reliable way to differentiate between cases of CTE and Alzheimer's disease (AD). Small and colleagues published preliminary findings in a study of five former professional football players using the PET ligand ^{18}F-FDDNP, which binds to both tau and amyloid [35•, 37]. Although they suggested that positive findings (higher signals) using this technology could be indicative of underlying CTE pathology, the nonspecific binding of ^{18}F-FDDNP means that the signal cannot be solely attributed to the presence of tau. Thus, neuropathologic confirmation is needed to determine the underlying pathology. Alternatively, a tau-specific PET ligand, such as those in preliminary studies by Chien et al. [38••], may be used to measure tau in vivo as a potential biomarker for CTE. Preliminary work using diffusion tensor imaging has shown evidence of persistent changes in white matter integrity after periods of head impact exposure [39•, 40•], which may prove useful in distinguishing CTE. Magnetic resonance spectroscopy (MRS), a method of measuring brain metabolites, has shown promise in preliminary studies by Lin and colleagues [41•]. Cerebrospinal fluid (CSF) markers have been useful in the AD diagnostic process [34] and CSF p-tau levels have been shown to correlate with levels of p-tau NFT deposition in the brain [42]. Thus, CSF protein measures may useful biomarkers for CTE, and in the differentiation of CTE from other neurodegenerative diseases.

Risk factors

As stated above, to-date, all individuals with neuropathologically confirmed CTE have a history of repetitive head impacts. Although this type of exposure seems to be *necessary* for the occurrence of CTE, it does not appear to be *sufficient*. That is, not all individuals with a history of repetitive head impact exposure get CTE. As previously noted, detailed relation between head impact exposure (eg, frequency, magnitude, age of first exposure) and later-life neurologic outcomes is not well understood. To date, other risk factors for CTE, beyond head impact exposure, are unknown.

Genetics

Genetic risk factors may play a role in development of CTE. The apolipoprotein (ApoE) ε4 allele is the most powerful predictor of sporadic AD [43]. There have been several reports linking the ApoE ε4 allele and head injury with a variety of negative outcomes, including prolonged recovery and poor cognitive performance [44–47]; however, these studies lacked neuropathologic disease confirmation of disease. Findings in neuropathologically confirmed studies are mixed. In the series studied by Stern et al. [16••] and McKee et al. [7], there was an overrepresentation of ε4 carriers in a cohort of neuropathologically confirmed CTE relative to population norms. However, in a study with a larger sample size (N=103), the effect failed to reach significance [9••]. While early clinical findings established a link between clinical outcomes and APOE ε4

expression, the literature has not definitively established a link between APOE genotype and CTE pathology. Future research should examine the association between APOE genotype and CTE, as well as other possible genetic risk factors for CTE such as the MAPT gene or the TARDBP gene.

Lifestyle

One important challenge to accurately describing the clinical presentation and course of CTE are the lifestyle comorbidities associated with contact sport athletes and military veterans, in whom the disease has been most studied. Comorbidities such as alcohol abuse or dependence, recreational drug use, and performance enhancing drug use can all lead to personality changes and neuropsychiatric difficulties [48–51]. A non-negligible portion of individuals with neuropathologically confirmed CTE have had reported substance abuse [16••]. However, there are neuropathologically confirmed cases of CTE without a history of any of these afflictions, indicating that they are not causative factors. Therefore, understanding whether and to what extent lifestyle issues, such as those noted, influence the clinical manifestations of CTE is necessary.

Conclusions

Both in CTE and other neurodegenerative diseases, neuropathologic abnormalities are not always directly correlated with specific clinical signs and symptoms. There are likely other factors that influence disease occurrence, progression, and clinical presentation. To date, our understanding of the clinical presentation of CTE is heavily reliant on retrospective interviews with family members of individuals with neuropathologically confirmed CTE. Currently, our neuropathologic understanding of CTE is based on a biased sample of individuals who are who are predominantly among those most exposed to repetitive head impacts (eg, professional football players, professional boxers). What we understand less well is how repetitive head impacts from other less severe and less predictable exposures, such as the occasional concussion or fall, may or may not relate to the development of CTE. However, despite these limitations, there is sufficient scientific evidence to reasonably conclude that CTE is a distinct pathology that is caused, at least in part, by repetitive head impacts.

Our understanding of CTE has progressed considerably in the last several years. However, important gaps still exist in our understanding such as the incidence and prevalence of CTE, nonhead trauma risk factors for the disease, and in vivo diagnostic techniques. There are a variety of factors beyond a history of repetitive head impacts (eg, personality, lifestyle) that differentiate collegiate or professional contact sport athletes from the general public. Understanding to what extent these other factors influence clinical signs and symptoms is critical. Furthermore, there are other non-CTE results of repetitive head impacts. For example, in a 2012 study by Lehman et al. retired NFL athletes were found to have a neurodegenerative mortality rate three-times that of the U.S. population generally, and when AD and amyotrophic lateral sclerosis were examined specifically NFL mortality rates were four times that of the general population [52••]. Differentiating the clinical manifestations of CTE and non-CTE results of head impacts is needed. In order to facilitate clinical understanding of CTE, the most

pressing issue we are faced with is developing an in vivo diagnostic tool. With an in vivo diagnosis, we could begin to directly assess clinical symptomatology and progression, research incidence and prevalence in a living population, and begin therapeutic studies. Without an in vivo diagnosis, the questions we can accurately address are limited by the methodologies we are able to employ.

As CTE research has a particular ability to be misunderstood by the lay public and sensationalized in the media, caution needs to be exercised when discussing results of scientific studies and generalizing the results to the population as a whole. Many individuals have some history of head impacts incurred through sports participation or other activities [53]. However, the pathophysiological mechanism linking this initial trauma, whether concussive or subconcussive, to later-life CTE pathology has yet to be elucidated. Furthermore, without a more complete understanding of the incidence, prevalence, and possible risk factors that lead to the development of CTE, it is impossible for the general population to accurately assess their risk of CTE. Unfortunately the popular media, which has reported on CTE because of its association with professional athletics, often does not present findings with the same accuracy, caution, or contextualization as the original peer-reviewed scientific publications. In order to avoid causing undue panic in individuals who have a history of concussions or other traumatic brain injuries, the scientific community and the media need to clearly address the considerable gaps that exist in our understanding of CTE [54].

Compliance with Ethics Guidelines

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