Potential Long-Term Consequences of Concussive and Subconcussive Injury

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KEYWORDS

• Neuropathology • Trauma • Traumatic brain injury
• Chronic traumatic encephalopathy • Tau • Concussion • Subconcussion

KEY POINTS

- Individuals with a history of repetitive head impacts are at risk for developing chronic traumatic encephalopathy (CTE).
- CTE is a unique neurodegenerative disorder characterized by perivascular deposits of hyperphosphorylated tau at the depths of the cerebral sulci.
- The number of years of exposure to contact sports, not the number of concussions, is significantly associated with more severe tau abnormality in CTE, suggesting that repetitive head trauma, including subconcussive injury, is the primary driver of disease.
- Recent studies in neurodegenerative disease brain bank cohorts suggest that changes of CTE are relatively common.

Over the last decade, there has been considerable interest in the potential long-term effects of concussive and subconcussive injury that occur in association with the play of contact sports. Case reports and case series have described athletes who developed explosivity, loss of control, aggressive and violent behaviors, impaired attention,

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depression, executive dysfunction, and memory disturbances associated with chronic traumatic encephalopathy (CTE). There have been debates about how commonly CTE occurs, whether CTE is a distinct neurodegeneration, and if the repetitive head impacts that occur during the play of sports are causal to CTE development. The disease symptoms lack specificity, and the absence of longitudinal, prospective clinical studies with neuropathologic analysis limits understanding of the full clinical spectrum. However, current data indicate that the neuropathology of CTE is unique and can be readily distinguished from other neurodegenerative diseases; that exposure to repetitive head impacts, not the number of concussions, is the primary driver of CTE abnormality; and that CTE is more common than currently recognized.

The variety of clinical symptoms associated with boxing was first described by Harrison Martland[1] in 1928, who found abnormalities in "nearly one half of the fighters who stayed in the game long enough."[1] The general public referred to the condition as "punch drunk," "goofy," and "slug-nutty,"[2,3] and later the terms "dementia pugilistica"[4] and "chronic traumatic encephalopathy" or "CTE" were introduced.[5] Over the intervening decades since the recognition of CTE, clinical and neuropathologic evidence has emerged indicating that CTE occurs in association with American football, boxing, wrestling, ice hockey, baseball, and soccer. CTE has also been associated with other forms of mild repetitive head injury, such as physical abuse, epileptic seizures, head banging, and activities related to military service.[6–12]

CLINICAL SIGNS AND SYMPTOMS OF CHRONIC TRAUMATIC ENCEPHALOPATHY

The clinical symptoms of CTE typically develop insidiously, years to decades after exposure to repetitive brain trauma, and progress slowly over years to decades.[13–15] Occasionally, persistent symptoms develop while an individual is still active in a sport that may be difficult to distinguish from prolonged post-concussive syndrome.[16] In the authors' series of 119 neuropathologically confirmed CTE cases, the mean age at symptom onset was 44.3 years (standard error of the mean [SEM] = 1.5, range 16–83 years), 14.5 years after retirement from the sport (SEM = 1.6, n = 104). However, 22% of individuals later diagnosed with CTE were symptomatic at the time of retirement. The clinical course is often protracted (mean duration = 15.0 years, SEM = 1.2, n = 125).[14,17,18] It is unclear what factors mitigate the wide age range of clinical onset, and many are the focus of current research investigation. Genetics may play a role in an individual's relative susceptibility or resistance to the adverse effects of repetitive neurotrauma and factors such as cognitive reserve, including educational attainment and environmental enrichment, and age at first exposure may influence the clinical expression of the disease.

The clinical presentation of CTE characteristically begins in one or more of 4 distinct domains: mood, behavior, cognitive, and motor. Early behavioral symptoms include explosivity, verbal and physical violence, loss of control, impulsivity, paranoia, and rage behaviors.[15,19] Cognitively, the most prominent deficits are memory, executive functioning, and impaired attention. Approximately 45% of subjects with CTE develop dementia; of subjects older than the age of 60 years, 66% develop dementia. Complaints of chronic headaches occur in 30%[15]; motor symptoms, including dysarthria, dysphagia, coordination problems, and parkinsonism (tremor, decreased facial expression, rigidity, and gait instability), may also develop.[20]

Stern and colleagues[15] distinguished 2 courses of clinical presentation. The first type presents with mood and behavioral symptoms early in life (mean age = 35 years) and progresses in severity to include cognitive symptoms later in the disease course. The second course presents with cognitive symptoms later in

life (mean age = 60 years) and often progresses to also include mood and behavioral symptoms.

CLINICAL DIAGNOSIS OF CHRONIC TRAUMATIC ENCEPHALOPATHY

Like many neurodegenerative diseases, the current lack of available biomarkers for CTE precludes a definitive diagnosis during life, and the disease can only be diagnosed definitively at postmortem examination. Three groups have proposed preliminary diagnostic criteria for the clinical diagnosis of CTE.[19,21,22]

The proposed criteria differentiate between possible and probable CTE based on various clinical symptoms and follow a structure similar to the National Institute on Aging-Alzheimer's Association clinical diagnostic criteria for other neurodegenerative diseases.[23] The criteria of Montenigro and colleagues[19] distinguish between the clinical syndrome of CTE, referred to as Traumatic Encephalopathy Syndrome (TES), and the pathologic diagnosis of CTE, which is reserved for postmortem diagnosis. The TES syndrome is dichotomized into subtypes based on the presence or absence of various groups of symptoms, including Behavioral/Mood Variant, Cognitive Variant, Mixed Variant, and TES Dementia (for a full review, see Montenigro and colleagues[19]).

Whether the proposed clinical criteria are able to differentiate CTE from other abnormalities with a high degree of sensitivity and specificity in both research and clinical settings has not been determined.

Ongoing large-scale retrospective studies, such as the recently funded Understanding Neurologic Injury and Traumatic Encephalopathy (UNITE) UO1 project from the National Institute of Neurological Disease and Stroke (NINDS) and the National Institute of Biomedical Imaging and Bioengineering (NIBIB), examines the clinical presentation of brain donors designated as "at risk" for the development of CTE, develops a blinded consensus clinical diagnosis, and compares the clinical consensus diagnosis to equally blinded postmortem neuropathologic assessment.[24] Preliminary indications are that the clinical criteria for CTE are highly sensitive but lack specificity.[25] Additional analyses using data from the UNITE study will provide detailed information on the specificity of item-level symptoms to allow further refinements in the clinical criteria. To date, nearly all information collected regarding the clinical presentation of CTE has come from retrospective analysis of subjects analyzed after death.[14,15] Recent funding of large-scale longitudinal prospective studies will also help clarify the precise clinical distinctions between CTE and other neurodegenerative and neuropsychiatric disorders.

BIOMARKERS

The use of in vivo biomarkers could greatly improve the accurate clinical diagnosis of CTE as well as facilitate the monitoring of disease progression and the efficacy of disease-modifying therapies. Although no diagnostic biomarkers are currently available, several promising techniques are being developed. Tau-specific PET ligands have demonstrated encouraging results in Alzheimer disease (AD)[26,27] and detect the progression of AD tauopathy among individuals along the cognitive spectrum.[28] Studies using diffusion tensor imaging have also showed promise in their ability to detect changes to white matter integrity following head trauma.[29] In addition, functional connectivity (functional MRI [fMRI]) and other advanced imaging measures of axonal integrity, such as magnetic resonance spectroscopy, to detect biochemical metabolites as well as cerebrospinal fluid and plasma protein markers (including p-tau and total tau) are all under investigation.[23,30,31]

NEUROPATHOLOGY OF CHRONIC TRAUMATIC ENCEPHALOPATHY

Gross Abnormality

Grossly identifiable changes are usually minimal in the early stages of CTE; in advanced disease, there is often reduced brain weight, cerebral atrophy that is typically most severe in the frontal and anterior temporal lobes, enlargement of the lateral and third ventricles, cavum septum pellucidum with fenestrations, thinning of the corpus callosum, atrophy of the diencephalon and mammillary bodies, and depigmentation of the locus coeruleus and substantia nigra. Cerebellar scarring was commonly reported in the early reports of CTE in boxers; however, grossly identifiable cerebellar abnormalities are rarely present in CTE associated with football or other sports.[14]

Microscopic Abnormality

CTE is a tauopathy and is characterized by the deposition of hyperphosphorylated tau (p-tau) protein as neurofibrillary tangles NFTs, thorned astrocytes (TA), and neurites in a unique pattern in the brain. The tau pathology is characteristically perivascular in distribution and shows a predilection for the depths of the cerebral sulci. In 2013, McKee and colleagues[14] described a spectrum of p-tau abnormality in 68 male subjects with a history of exposure to repetitive brain trauma with neuropathologic evidence of CTE, ranging in age from 17 to 98 years (mean 59.5 years) and proposed provisional criteria for neuropathologic diagnosis. In young subjects with the mildest forms of CTE, focal perivascular epicenters of NFTs and TA were found clustered at the depths of the neocortical sulci; in subjects with severe disease, there was evidence of a widespread tauopathy with focal concentration of pathology perivascularly at the sulcal depths and in the superficial cortical layers. Other abnormalities encountered in advanced CTE include abnormal deposits of phosphorylated TAR DNA-binding protein of 43-kDa (TDP-43) protein that occasionally colocalizes with p-tau, and varying degrees of Aß abnormality, axonal dystrophy, and neuroinflammation.[14,32]

Recently, as the first part of a series of consensus panels funded by the NINDS/NIBIB to define the neuropathologic criteria for CTE, the McKee neuropathologic criteria were used by 7 neuropathologists to evaluate 25 cases of various tauopathies, including CTE, AD, progressive supranuclear palsy, argyrophilic grain disease, corticobasal degeneration, primary age-related tauopathy, and parkinsonism dementia complex of Guam. The neuropathologists evaluated the cases blinded to all information on age, gender, clinical symptoms, diagnosis, athletic exposure, and gross neuropathologic findings and determined that there was good agreement between reviewers and the diagnosis of CTE (Cohen's kappa: 0.78) and excellent identification of the cases of CTE. Based on these results, the panel refined the diagnostic pathologic criteria for CTE and defined a pathognomonic lesion. The lesion considered pathognomonic for CTE is an accumulation of abnormal tau in neurons and astroglia distributed around small blood vessels at the depths of cortical sulci and in an irregular pattern. The panel also defined supportive but nonspecific features of CTE.[33]

Staging of Chronic Traumatic Encephalopathy

McKee and colleagues[14] also described 4 distinct stages of CTE, defined by the extent of the tau abnormalities. Stage I CTE is characterized by isolated perivascular foci of p-tau as NFTs and TA at the sulcal depths of the cerebral cortex. In stage II CTE, multiple foci of p-tau are found in the cerebral cortices. In stage III CTE, NFT are found in the superficial cortices adjacent to the focal epicenters, and there is involvement of the medial temporal lobe structures (hippocampus, amygdala, entorhinal cortex). In stage IV CTE, there is severe widespread p-tau pathology in the cortices,

diencephalon, brainstem, and cerebellum (reviewed in McKee and colleagues[14]). Furthermore, among former American football players, the stage of CTE severity correlates significantly with the duration of exposure to football, age at death, and years since retirement from football.[14]

Recently, 2 large academic centers have reported comorbid CTE changes in their neurodegenerative disease brain banks.[34,35] In the brain bank series reported by Bieniek and colleagues,[34] 21 of 66 (31.8%) former athletes had cortical tau abnormalities consistent with CTE on postmortem neuropathologic examination. Moreover, CTE pathology was not detected in 198 individuals who had no exposure to contact sports, including 33 individuals with documented single-incident traumatic brain injury sustained from falls, motor vehicle accidents, domestic violence, or assaults. Ling and colleagues[35] found the occurrence of CTE in 11.9% of 268 screened cases of neurodegenerative diseases and controls.

Relationship of Tau Abnormality to Trauma

Although CTE is associated with repetitive head impacts, the pathophysiological mechanisms critical to developing a progressive tauopathy after repetitive trauma are only beginning to be identified. Traumatic axonal injury results in alterations in axonal membrane permeability, ionic shifts including massive influx of calcium, and release of caspases and calpains that trigger tau phosphorylation, misfolding, truncation, and aggregation, as well as breakdown of the cytoskeleton with dissolution of microtubules and neurofilaments.[36–38] Acceleration and deceleration forces on the brain, rotational as well as linear, cause the brain to elongate and deform. These shearing forces predominantly affect long fibers, specifically axons and blood vessels,[39,40] and are typically most severe at the depths of the cerebral sulci and at the interface between brain parenchyma and cerebral vasculature.[41] The irregular distribution of the p-tau abnormality in the perivascular region and sulcal depths of the neocortex corresponds to these areas of greatest tissue displacement. In addition, the early and predominant involvement of the superior and dorsolateral frontal lobes in former football players parallels the high frequency of impacts to the top of the head compared with those to the front, back, and side of the head in football players,[42,43] as well as fMRI data showing activation impairments in dorsolateral prefrontal cortex that is associated with significantly higher numbers of head collisions to the top-front of the head.[44]

Increasing evidence indicates that tau phosphorylation, truncation, aggregation, and polymerization into filaments represent a toxic gain of function, and continued accumulation of p-tau leads to neurodegeneration. This finding is supported by tau's involvement in some genetic forms of frontotemporal degeneration[45] and by work that shows that plasmids containing human tau complementary DNA constructs microinjected into lamprey neurons in situ produce tau filaments that accumulate and lead to neuronal degeneration.[46,47] However, it is also possible that the intracellular NFTs are the byproducts rather than the cause of cellular injury and that NFT formation indicates neurons that survived the initial injury and sequestered the abnormally phosphorylated, truncated, and folded tau.[48]

β-Amyloid

β-Amyloid (Aβ) plaques are found in 52% of individuals with CTE,[18] in contrast to the extensive Aβ plaques that characterize nearly all cases of AD. Although Aß plaques are typically abundant in AD and are essential to the diagnosis, Aβ plaques in CTE, when they occur, are less dense and predominantly diffuse.[7] In CTE, Aβ plaques are

significantly associated with accelerated tauopathy, Lewy body formation, dementia, parkinsonism, and inheritance of the ApoE4 allele.[18]

TDP-43

TDP-43 proteinopathy is also found in approximately 80% of subjects with CTE.[8] Moreover, some athletes with CTE also develop a motor neuron disease that is clinically indistinguishable from amyotrophic lateral sclerosis.[8] The presence of multiple abnormally aggregated phosphorylated proteins in CTE suggests that a common stimulus, such as repetitive trauma, provokes the accumulation of neurodegenerative proteins or that the presence of p-tau aggregates provokes the accumulation of other pathologic proteins such as Aß and TDP-43.[49] TDP-43 plays a critical role in mediating the response of the neuronal cytoskeleton to axonal injury by virtue of its capacity to bind to neurofilament messenger RNA (mRNA) and stabilize the mRNA transcript. TDP-43 is also intrinsically prone to aggregation and its expression is upregulated after experimental axotomy.[50] Traumatic axotomy may accelerate TDP-43 accumulation, aggregation, and dislocation to the cytoplasm, and enhance its neurotoxicity.

RISK AND PROTECTIVE FACTORS

There are many potential variables surrounding exposure to repetitive head impacts that might influence the risk for CTE later in life. The age at which athletes experience head impacts may influence CTE risk. Recent studies in retired National Football League athletes indicate that exposure to football before the age of 12 is associated with greater cognitive impairment and more white matter abnormalities on MRI.[51,52] It remains to be determined what other lifestyle factors might mitigate the risk for CTE. Chronic inflammation, such as accompanies obesity, hypertension, diabetes mellitus, atherosclerosis, and heart disease, may facilitate neurodegeneration and NFT formation.[53–56] In contrast, greater cognitive reserve might lessen or delay the development of clinical symptoms in CTE. Genetic variations are also likely to play an important role in moderating the relationships between exposure to head trauma, neuropathologic changes, and disordered cognition and behavior. A recent study indicated a slight increase in *MAPT* H1 haplotype in subjects with sports exposure and CTE abnormality compared with those without CTE abnormality.[34]

SUMMARY

CTE is a neurodegenerative disease that occurs after exposure to repetitive head trauma. CTE has been reported in association with American football, wrestling, soccer, ice hockey, rugby, physical abuse, poorly controlled epilepsy, head banging behaviors, and military service, suggesting that trauma of diverse origin is capable of instigating CTE. Cumulative exposure to trauma, not the number of concussions, is associated with the severity of p-tau abnormality, suggesting that subconcussive impacts are an important driver of disease. CTE most commonly manifests in midlife and produces clinical symptoms of disordered cognition, memory loss and executive dysfunction, depression, apathy, disinhibition, and irritability, as well as parkinsonism. The neuropathology of CTE is increasingly well defined; a NINDs/NIBIB panel of expert neuropathologists has defined preliminary criteria and a pathognomonic lesion for the neuropathologic diagnosis of CTE. Currently, neuropathologic examination of brain tissue is the only way to diagnose CTE, although intense research efforts are underway to identify biomarkers to detect and monitor the disease during life and to develop therapies to slow or reverse its course. Newly funded

longitudinal, prospective research efforts will shed additional light on critical variables related to head trauma exposure, genetics, and lifestyle factors that influence the development of CTE.

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