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Potential Long-Term Consequences of Concussive and Subconcussive Injury

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Abstract

Keywords

Neuropathology; Trauma; TBI; CTE; Tau; Concussion; Subconcussion

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, 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 neuropathological analysis, limit

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our 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 pathology; and that CTE is more common than currently recognized.

The variety of clinical symptoms associated with boxing was first described by Harrison Martland 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 neuropathological 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 with military service.[6-12]

Clinical Signs and Symptoms of CTE

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 our series of 119 neuropathologically confirmed CTE cases, the mean age at symptom onset was 44.3 years (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 range age 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 pathology.

The clinical presentation of CTE characteristically begins in one or more of four 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 over 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 distinguished two courses of clinical presentation.[15] 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 CTE

Like many neurodegenerative diseases, the current lack of available biomarkers for CTE precludes a definitive diagnosis and the disease can only be diagnosed definitively at post-mortem examination. 3 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 symptomology and follow a structure similar to the National Institute on Aging - Alzheimer's Association clinical diagnostic criteria for other neurodegenerative diseases.[23] The Montenigro et al. criteria distinguishes between the clinical syndrome of CTE, referred to as Traumatic Encephalopathy Syndrome (TES), and the pathological diagnosis of CTE, which is reserved for post-mortem 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 et al.[19]).

Whether the proposed clinical criteria are able to differentiate CTE from other pathologies 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 and the National Institute of Biomedical Imaging and Bioengineering, 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 neuropathological 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. While no diagnostic biomarkers are currently available, several promising techniques are being developed. Tau specific PET ligands have demonstrated encouraging results in Alzheimer's disease (AD)[26, 27] and detect the progression of AD tauopathy among individuals along the cognitive spectrum.[28] Studies utilizing diffusion tensor imaging (DTI) have also showed promise in their ability to detect changes to white matter integrity following head trauma.[29] Additionally, functional connectivity (fMRI) and

other advanced imaging measures of axonal integrity such as magnetic resonance spectroscopy (MRS) to detect biochemical metabolites as well as CSF and plasma protein markers (including p-tau and total tau) are all under investigation.[23, 30, 31]

Neuropathology of CTE

Gross Pathology

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 pathology

CTE is a tauopathy and is characterized by the deposition of hyperphosphorylated tau (p-tau) protein as NFTs, thorned astrocytes (TA) and neurites in a unique pattern in the brain. The tau pathology is characteristically perivascular distribution and shows a predilection for the depths of the cerebral sulci. In 2013, McKee and colleagues described a spectrum of p-tau pathology in 68 male subjects with a history of exposure to repetitive brain trauma with neuropathological evidence of CTE, ranging in age from 17 to 98 years (mean 59.5 years) and proposed provisional criteria for neuropathological 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 is evidence of a widespread tauopathy with focal concentration of pathology perivascularly at the sulcal depths and in the superficial cortical layers.[14] Other abnormalities encountered in advanced CTE include abnormal deposits of phosphorylated TAR DNA-binding protein of 43 kDa (TDP-43) protein that occasionally co-localizes with p-tau, and varying degrees of Aβ pathology, 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 neuropathological criteria for CTE, the McKee neuropathological criteria were used by 7 neuropathologists to evaluate 25 cases of various tauopathies, including CTE, Alzheimer's disease, 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 neuropathological 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 pathological 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 non-specific features of CTE. [33]

Staging of CTE

McKee et al. also described four distinct stages of CTE, defined by the extent of tau pathology.[14] Stage I CTE is characterized by isolated perivascular foci of p-tau as NFTs and TA present 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 et al.[14]). Furthermore, among former American football players, the stages of CTE severity correlate significantly with the duration of exposure to football, age at death and years since retirement from football.[14]

Recently, two large academic centers have reported co-morbid CTE in their neurodegenerative disease brain banks.[34, 35] In the brain bank series reported by Bieniek et al., 21 of 66 (31.8%) former athletes had cortical tau pathology consistent with CTE on post-mortem neuropathological 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 (TBI) sustained from falls, motor vehicle accidents, domestic violence, or assaults.[34] Ling et al. found the occurrence of CTE in 11.9% of 268 screened cases of neurodegenerative diseases and controls.[35]

Relationship of tau pathology 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 pathology 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 to 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 represents a toxic gain of function, and continued

accumulation of p-tau leads to neurodegeneration. This 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]

Beta-amyloid

Beta-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 Aβ 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 reported 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 (ALS).[8] The presence of 2 abnormally aggregated phosphorylated proteins in CTE suggests that a common stimulus, such as repetitive trauma, provokes the accumulation of both proteins.[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 NFL 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 pathology compared to those without CTE pathology.[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 pathology 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 neuropathological 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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Synopsis

Repeated concussive and sub-concussive trauma is associated with the later development of chronic traumatic encephalopathy (CTE), a neurodegenerative disease associated with clinical symptoms in multiple domains and a unique pattern of pathological changes. CTE has been linked to boxing and American football; CTE has also been identified in soccer, ice hockey, baseball and rugby, and military service. In cases associated with contact sports, the mean length of exposure to repetitive head trauma is 15.4 years. The clinical symptoms of the disease begin after a mean latency period of 14.5 years with a mean age at death of 59.3 years. Most subjects have a history of concussions, however, 16% of CTE subjects have no history of concussion suggesting that subconcussive hits and cumulative exposure to trauma are sufficient to lead to CTE. CTE is neuropathologically unique and characterized by perivascular deposits of hyperphosphorylated tau at the depths of the cerebral sulci. The pattern of p-tau pathology occurs in regions of the brain that are most susceptible to shearing forces and displacement during trauma. Overall, the number of years of exposure, not the number of concussions, is significantly associated with hyperphosphorylated tau (p-tau) pathology in CTE. TDP-43 pathology is found in 80% and beta amyloid plaques are found in 52 % of CTE cases. Beta amyloid plaques are associated with more severe cognitive impairment, Parkinsonism and accelerated tau and alpha-synuclein pathology. To date, most large studies of CTE have come from enriched cohorts associated with brain bank donations for traumatic brain injury, although several recent studies re-examining neurodegenerative disease brain banks suggest that CTE is more common than is currently appreciated.

Key Points

Individuals with a history of repetitive head impacts are at risk for developing chronic traumatic encephalopathy. Chronic traumatic encephalopathy 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 pathology 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.