

DEFENSE AND VETERANS BRAIN INJURY CENTER

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RESEARCH REVIEW ON CHRONIC TRAUMATIC ENCEPHALOPATHY

PURPOSE

The purpose of this Research Review is to summarize current peer-reviewed scientific literature and expert opinion regarding the pathology, genetic pre-disposition, causes, clinical manifestations, and neuroimaging of chronic traumatic encephalopathy (CTE). Updates from recent 2019 CTE conferences are included. Gaps and discrepancies in our understanding of CTE are discussed.

BACKGROUND

CTE is a progressive neurodegenerative disease pathologically distinct from other neurodegenerative diseases, including frontotemporal dementia and Alzheimer's disease (AD). There currently is no clinical, antemortem diagnostic profile for CTE, and the definitive diagnosis is based on a specific histopathologic pattern of phosphorylated tau (p-tau) protein deposition in the brain that can only be observed at autopsy. The cause of CTE has been attributed to repetitive head trauma, though not specifically repetitive traumatic brain injury. The clinical manifestations of a dementia-like syndrome, often accompanied by Parkinsonian and cerebellar motor signs, was first described nearly 100 years ago in former boxers ([Martland, 1928](#)). Initially called "punch drunk" syndrome ([Martland, 1928](#)), the presenting cognitive symptoms included slowed thinking, confusion, and short-term memory impairment. This syndrome was later called "dementia pugilistica" until the phrase "chronic traumatic encephalopathy" was coined in 1949 ([Critchley, 1957](#)). The onset of the clinical symptoms was noted to occur in middle age, a mean of 16 years after discontinuation of boxing, but disease progression was variable ([Critchley, 1957](#)). One early study on the prevalence of CTE among ex-professional boxers (n = 224) found that 17% had neurological symptoms consistent with the syndrome, and sub-syndromal cognitive impairment was apparent in 50% of these former athletes ([Roberts, 1969](#)). Postmortem cerebral histopathologic studies were not available for these boxers, so it was not possible to correlate the clinical signs and symptoms with brain pathology. It was not until CTE pathology was described in a former professional American football player in 2005 that there was a concerted effort to investigate the pathology and clinical manifestations of CTE ([B. I. Omalu et al., 2005](#); [Smith, Johnson, Trojanowski, & Stewart, 2019](#)). Given the variable CTE definitions as described below and ongoing efforts to define and reach consensus on postmortem CTE pathology, the term CTE in this review refers to the condition of interest, whether it is clinically presumed or histopathologically confirmed CTE using the 2015 Consensus criteria, and, when possible, the terminology used by the article referenced is maintained.

INFORMATION

Pathology

The earliest known description of the gross pathologic manifestations of CTE are those described from studies of deceased boxers and align under the “Classic” CTE definition to include reduced brain weight, cavum septum pellucidum, enlargement of the ventricles, and thinning of the corpus callosum ([Corsellis, Bruton, & Freeman-Browne, 1973](#)). The most striking neuropathological feature of CTE based on the more “Modern” CTE definition is the presence of neurofibrillary tangles (NFTs) composed of p-tau protein, which appear similar to NFTs found in AD but with specific differences in the neuroanatomical localization ([Hof et al., 1992](#); [S. Shively, Scher, Perl, & Diaz-Arrastia, 2012](#)). Two large case series from the primary CTE labs in the United States (Dr. Ann McKee at Boston University and Dr. Bennet Omalu at University of California Davis) have demonstrated similar NFT neuropathology among the brains of former National Football League (NFL) players and other professional athletes with a history of repetitive mild TBI. These individuals either a) developed dementia and other clinical manifestations of suspected CTE prior to death in middle age, or b) died (many via suicide) after displaying some of the cognitive features of suspected CTE prior to the development of dementia ([McKee et al., 2009](#); [B. Omalu, Bailes, et al., 2011](#)). While both labs recognize the presence of NFTs consisting of p-tau, the criteria used by each lab remain different. The Omalu lab identified 4 phenotypes, differentiated mainly by the frequency and location of NFTs and neuritic threads: 1) combination of sparse to frequent neuritic threads and NFTs in the cerebral cortex and brainstem without diffuse amyloid plaques in the cerebral cortex; 2) combination of sparse to frequent neuritic threads and NFTs in the cerebral cortex and brainstem with sparse to frequent diffuse amyloid plaques in the cerebral cortex; 3) combination of moderate to frequent neuritic threads and NFTs in the brainstem nuclei without diffuse amyloid plaques in the cerebral cortex; and 4) combination of none to sparse neuritic threads and NFTs in the cerebral cortex, brainstem, and subcortical nuclei without diffuse amyloid plaques in the cerebral cortex ([B. Omalu, Bailes, et al., 2011](#)). Alternatively, the McKee lab has used the following criteria to define CTE: 1) perivascular foci of p-tau immunoreactive astrocytic tangles and NFTs; 2) irregular cortical distribution of p-tau positive astrocytic and neurofibrillary tangles with a localization to the depths of cerebral sulci; 3) astrocytic tangles in the cerebral cortex, diencephalon, basal ganglia, and brainstem; and 4) NFTs in superficial layers of the cerebral cortex ([McKee et al., 2013](#)). Additionally, the McKee lab recognizes a progressive pathology from very mild (Stage I) to severe (Stage IV) ([McKee et al., 2013](#)). While these two primary investigators differ in histopathological definitions, both definitions offer greater specificity in presentation (i.e., phenotypes and stages) that is not present in the Classic CTE definition. However, neither Classic nor Modern approaches include criteria specific to clinical and behavioral manifestations associated with the observed pathology.

Given these prominent but discrepant histopathological definitions of CTE, a consensus conference sponsored by the National Institutes of Neurological Disorders and Stroke (NINDS), the Department of Defense, and the Department of Veterans Affairs was held in Boston in December 2015 to produce diagnostic criteria for CTE ([McKee et al., 2016](#)). This small group of 11 neuropathologists, neurologists, and TBI experts agreed that CTE should be defined as “...p-tau aggregates in neurons, astrocytes, and cell processes around small blood vessels in an irregular pattern at the depths of the cortical sulci” ([McKee et al., 2016](#)). Supportive criteria,

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defined as non-diagnostic in isolation, were identified related to p-tau pathology and provided details regarding the frequency, location, and form of p-tau aggregates. Two of the seven supportive criteria were unrelated to tau, where one specified macroscopic anatomical features and the other described inclusions and structures containing trans-activator regulatory DNA-binding protein 43 (TDP-43). While these supportive criteria were identified, consensus was only reached on the single criterion detailed above. Additionally, three non-diagnostic, non-supportive criteria were also identified and describe age-related p-tau pathology. Despite the description of four separate phenotypes from the Omalu lab ([B. Omalu, Bailes, et al., 2011](#)) and the description of progressive four stages of CTE pathology based on severity and clinical manifestation by the McKee lab ([McKee, Stein, Kiernan, & Alvarez, 2015](#); [McKee et al., 2013](#)), neither classification system was supported and incorporated at the consensus conference. Diagnostic criteria continue to be discussed and will be refined as evidence guides. In November 2019, a meeting entitled The Neuropathological Diagnosis of CTE: Next Steps was held at the National Institutes of Health (NIH) to set priorities on next research steps for the scientific community, and the official meeting results and conclusions are in preparation for publication.

Tau protein deposition is well known to be associated with other neurodegenerative diseases and dementias, particularly frontotemporal dementia and AD. At a 2012 NINDS workshop on CTE neuropathology, it was noted that “none of the individual pathologic features (such as tau pathology) are unique to CTE, but what confers uniqueness in CTE cases is the peculiar distribution within the brain” ([National Institutes of Neurological Disorders and Stroke, 2013](#)). Recent evidence published in the journal *Nature* demonstrates that the processing of tau in CTE results in a molecule that is structurally different from tau present in AD ([Falcon et al., 2019](#)), a finding which may have significant implications in attempts at antemortem diagnosis using positron emission tomography (PET) imaging techniques and ligands to tau. Under non-pathological conditions, the protein tau normally regulates microtubule stability in neurons. Repetitive mild TBI is thought to result in abnormal neuronal processing of protein tau and thereby contribute to neuropathology such as the wide-spread deposition of cortical tau NFTs consistently observed in the brains of autopsied individuals presenting with clinical symptoms prior to death ([McKee et al., 2009](#)). Neuroinflammation may also play a role in the development of CTE because activated microglia can contribute to p-tau deposition ([Makinde, Just, Cuda, Perlman, & Schwulst, 2017](#)); TBI is known to induce neuroinflammation ([Das, Mohapatra, & Mohapatra, 2012](#)), and inflammatory changes may persist for years post-injury in cases of moderate and severe TBI ([Smith, Johnson, & Stewart, 2013](#)). A recent neuropathological study by Cherry et al. (2016) examined inflammatory markers in the brains of deceased individuals with CTE (n = 48), individuals with head impact history but no CTE (n = 18), and individuals without repetitive head impact (n = 16). Results showed that chronic activation of microglia is associated with both repetitive head impact and p-tau pathology.

While tau processing may be associated with specific pathological conditions, primary age-related tauopathy (PART) is also of relevance in the discussion of CTE. In aged populations, NFTs similar to those seen with AD but without the co-occurring amyloid plaques have been observed nearly universally ([Crary et al., 2014](#)). Aging-related tau astrogliopathy (ARTAG) has also been discussed related to and in overlap with CTE pathology ([Forrest et al., 2019](#)). A recent study of 310 autopsy cases from an aged (76-91 years) European community-based population identified no cases meeting NINDS CTE criteria, yet ARTAG was identified in 117 cases, supporting the more common age-related proteinopathy over more rare CTE pathology ([Forrest](#)

et al., 2019). Future studies should continue to define the clinical and pathological boundaries between PART and/or ARTAG from other neurodegenerative and tauopathy conditions to prevent misdiagnosis of pathological conditions based on a ubiquitous aging phenomenon.

In an effort to diagnose CTE pathology antemortem or monitor cases of potential CTE, CSF and blood-based biomarkers have been examined in patients with a TBI history. Studies of CSF neurodegenerative biomarkers such as tau in patients with confirmed CTE have not yet been reported. However, elevated levels of tau in CSF and plasma may be associated with the accumulation of tau-reactive NFTs based on evidence from AD populations, which shows CSF p-tau concentrations appear to be a more specific marker of earlier neurodegenerative processes (Buerger et al., 2005; Hansson et al., 2006). Patients with severe TBI have transient elevations in CSF tau, which have been shown to correlate with clinical outcomes at one year post-injury (Ost et al., 2006). Olivera et al. (2015) reported on plasma tau levels measured in deployed military personnel with varied TBI status (Olivera et al., 2015). Tau levels were significantly higher in a) those reporting TBI as compared to those not reporting TBI, b) those with a medical record of TBI as compared to those with self-reported TBI, and c) those reporting three or more TBIs as compared to those reporting only one or two. Alternatively, in a cohort of retired NFL players, there were no significant differences in CSF levels of total tau, p-tau, the ratio of p-tau to total tau, amyloid beta (A β), or a measure of microglial activation when compared with age-matched controls (Alosco, Tripodis, et al., 2018). However, greater repetitive head impacts in former players did correlate with elevated total tau levels, and this relationship was observed to be mediated by increased microglial activation. A number of studies have quantified fluid biomarker levels in populations with repetitive head impacts, independent of mTBI (Alosco, Tripodis, et al., 2018; Neselius et al., 2012; Neselius, Zetterberg, Blennow, Marcusson, & Brisby, 2013; Oliver et al., 2018; Oliver et al., 2016; Zetterberg et al., 2006), but further research on biomarkers of repetitive head impacts, longitudinal changes of these biomarkers, and markers of early neurodegenerative changes is necessary to advance the field of fluid biomarkers of CTE.

Genetic Pre-disposition

Multiple genes have been investigated for their potential role in mediating pathology or symptomatology. Implicated in AD, the apolipoprotein E (*APOE*) gene, specifically the $\epsilon 4$ allele, has also been investigated in relation to both TBI and CTE (Deng et al., 2018). More directly associated with CTE, *APOE* $\epsilon 4$, specifically $\epsilon 4$ homozygote, has been reported to be overrepresented in a sample of neuropathologically confirmed CTE cases when compared to the population norms (Stern et al., 2013). Another gene under consideration for its known association with neuroinflammation and TDP-43 pathology is transmembrane protein 106b (*TMEM106B*). Exploratory genetic analysis by Bieniek et al. (2015) revealed a lower proportion of minor allele homozygotes with CTE compared to those without CTE pathology (Bieniek et al., 2015). Cherry et al. (2018) examined participants included in the Veterans Affairs-Boston University-Concussion Legacy Foundation Brain Bank who were Caucasian, had a history of American football, and had diagnosed CTE without significant co-morbid pathology. The presence of the *TMEM106B* minor allele, in a dose-dependent manner, was associated with lower p-tau, reduced neuroinflammation, higher synaptic density, and reduced odds of antemortem dementia (Cherry et al., 2018).

Causes of CTE

The cause or causes of CTE remain controversial. An association between CTE and brain trauma is assumed based largely on the fact that most known cases of CTE occurred in individuals with a history of head trauma, especially contact-sports athletes who had repetitive head trauma (Baugh, Robbins, Stern, & McKee, 2014; Erlanger, Kutner, Barth, & Barnes, 1999). Research teams led by Dr. Ann McKee have reported on a convenience sample where 177 (87%) of 202 deceased American football players were diagnosed with CTE based on neuropathological findings, many of whom had significant behavioral and cognitive problems prior to death (Mez et al., 2017). It has been estimated that football players at certain positions, such as the offensive line, may sustain as many as 1,444 head impacts in a single season (Crisco et al., 2010). Lehman et al. (2012) reported that professional football players exposed to high velocity injuries (e.g., non-linemen) had up to four times the rate of death from neurodegenerative diseases as the general population in the U.S., suggesting increased neurological risk with higher severities of head trauma (Lehman, Hein, Baron, & Gersic, 2012). Mez et al. has reported differential CTE findings associated with the level or length of play, where mild CTE pathology was more often observed among former high school and college players while severe CTE pathology was more often observed among the majority of semi-professional and professional football players (Mez et al., 2019; Mez et al., 2017).

It remains unclear, however, how common the pathologic features of CTE are in those who are not athletes because there are no age-matched, non-athlete control subjects included in the largest case series. Those reports are convenience samples of individuals, mostly athletes, identified by their families to have neurological abnormalities prior to death. As a result, the reports suffer from a significant selection bias (McKee et al., 2009; Mez et al., 2017). To date, a definitive cause-effect relationship between the degree of CTE pathology and history of brain trauma has not been demonstrated (Harmon et al., 2019; McCrory et al., 2013). Moreover, not all deceased individuals with a history of concussive or subconcussive head trauma have been found to have neuropathological features of CTE (Hazrati et al., 2013; B. Omalu, Bailes, et al., 2011; Stern et al., 2011). Alternatively, in a recent case series of men with no history of subconcussive or repetitive concussive history, CTE neuropathology was reported in 75% of cases (Iverson, Luoto, Karhunen, & Castellani, 2019). These reports emphasize the fact that the largest and most publicized case reports of CTE are “convenience samples” with severe selection bias, and comparisons of individuals with CTE to appropriate control subjects have not been reported. With these discrepant findings, it is prudent to identify what other factors may put individuals at risk for CTE. While almost all confirmed CTE cases have been in males, an association with gender has not been studied. Medical risk factors such as PTSD, depression, anxiety, individual genetics, and family history remain unclear. Environmental factors such as alcohol and drug use and abuse, socioeconomic status, and others have not been sufficiently explored. Continued research using larger samples sizes without selection bias is warranted to further elucidate factors related to CTE pathology and severity.

In addition to athletes, military Service members are another population that may sustain repeated head trauma and consequently remain a population of interest for ongoing CTE research. Specifically, blast exposure may be a risk factor for developing CTE (Goldstein et al., 2012; McKee & Robinson, 2014; B. Omalu, Hammers, et al., 2011). A recent study in a small sample of younger veterans ($n = 16$; mean age 35.2 years) revealed *in vivo* tau deposition on PET

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imaging associated with blast trauma, but not with blunt trauma or with the duration of TBI symptoms (Robinson et al., 2019). Case studies have confirmed postmortem CTE pathology in blast exposed veterans from the Iraq and Afghanistan conflicts, with blast exposed cases showing deposition of p-tau protein similar to that seen in non-blast CTE cases (Goldstein et al., 2012; B. Omalu, Hammers, et al., 2011). Conversely, a case series comparing cases of chronic blast exposure, acute blast exposure, chronic impact TBI, opiate exposure, and controls without known neurological disorder revealed that astroglial scarring was present in a novel neuroanatomical pattern to include tissues next to the ventricles, gray-white matter boundaries, and penetrating cortical blood vessels in only those cases with blast exposure (chronic and acute) but not chronic, blunt TBI or opiate use (S. B. Shively et al., 2016). However, just as with studies of CTE in athletes, these case studies of blast-exposed veterans suffer from selection bias since the majority of tissue samples were from individuals who died prematurely from suicide or drug overdose (Goldstein et al., 2012; B. Omalu, Hammers, et al., 2011; S. B. Shively et al., 2016). Outside of blast exposure, military service alone may not be a risk factor for CTE, and at least one study found no observable CTE-specific pathology in older (68.9 ± 16 years) veterans compared to age-matched controls (Tripathy et al., 2019). There are other reports of veterans who have postmortem CTE findings, but these individuals also were athletes prior to military service and may have been exposed to repeated blunt impacts earlier in life (perhaps in addition to Service-related exposures), thereby casting doubt on causal inferences (McKee et al., 2013; Reid & Velez, 2015).

Clinical Manifestations

There are no pathognomonic clinical manifestations of CTE, and the diagnosis can only be confirmed by postmortem examination (Harmon et al., 2019). However, reports of antemortem symptoms provided by the relatives of deceased individuals and reviews of medical records suggest that CTE may be associated with a variety of behavioral, emotional, cognitive, and neurologic symptoms (Lenihan & Jordan, 2015). Behavioral and emotional symptoms most commonly described include mood swings (Gardner et al., 2015), disinhibition, paranoia, irritability, violent outbursts (Lehman et al., 2012), and impulsiveness (Banks et al., 2014). Cognitive symptoms include episodes of confusion (Gardner et al., 2015), decreased attention and concentration (Lakhan & Kirchgessner, 2012), memory impairment, executive dysfunction, language impairment, and visuospatial difficulties (Mendez, 1995). Neurologic symptoms include tremor (Gardner et al., 2015), dysarthria, mild imbalance, and gait or limb ataxia, spasticity, and parkinsonism (Mendez, 1995). These symptoms derive in part from studies of probable CTE cases in boxers and football players with a history of repeated TBI.

However, these cognitive, emotional, and behavioral symptoms that have been attributed to CTE are non-specific and can be caused by numerous medical and psychiatric conditions (Hanlon, McGrew, & Mayer, 2017). As a result, the diagnosis of clinical CTE and symptom attribution to pathology present challenges for clinicians and researchers. One case series showed that 25 of 68 confirmed CTE patients also had motor neuron disease, AD, Lewy body disease, or frontotemporal lobar degeneration (McKee et al., 2013), thereby complicating whether any clinical symptoms are associated to the CTE pathology or other pathology.

Despite these challenges, four groups have developed distinct research diagnostic criteria for probable CTE in living persons (Jordan, 2013; Montenigro et al., 2014; Reams et al., 2016; Victoroff, 2013). The most recently published by Reams et al. (2016) required “self-report or

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observed report of cognitive dysfunction, confirmed with objective cognitive decline documented by results of formal neuropsychological testing” with supportive features highlighting emotional dysregulation, behavioral change, and motor disturbance (Reams et al., 2016). Montenigro et al. (2014) required at least one of three overall categories of disturbances: cognitive, behavioral, and mood; in addition, at least two of the following supporting features must be present: impulsivity, anxiety, apathy, paranoia, suicidality, headache, motor signs, progressive decline in function, or delayed onset (Montenigro et al., 2014). Unlike Reams et al. and Montenigro et al. which identified motor symptoms as supportive features, Jordan et al. and Victoroff et al. list motor symptoms as a diagnostic requirement. The research diagnostic criteria defined by Jordan et al. (2013) require motor signs such as dysarthria, spasticity, ataxia, parkinsonism, or gait disturbance (Jordan, 2013). Criteria published by Victoroff et al. (2013) describes 12 symptoms, of which at least two are required, and a total of 15 motor and behavioral signs, of which at least three are required (Victoroff, 2013). Studies of probable and confirmed CTE cases have identified different phenotypes (cognitive subtype vs behavior/mood subtype) potentially related to a complex long-term progression, but these studies do not agree on the earliest symptoms of CTE (Gardner et al., 2015; McKee et al., 2013; Stern et al., 2013). Other researchers have examined several specific symptoms attributed to probable CTE cases, including impulsiveness, cognitive impairment, and suicidality (Banks et al., 2014; Iverson, 2014; Randolph, Karantzoulis, & Guskiewicz, 2013; Seichepine et al., 2013; Wortzel, Shura, & Brenner, 2013). However, the link between postmortem pathology and antemortem symptomatology currently remains weak and insufficient for clinical use (Randolph, 2018).

In light of multiple criteria with varying degrees of sensitivity and specificity for the diagnosis of Traumatic Encephalopathy Syndrome/CTE (Laffey, Darby, Cline, Teng, & Mendez, 2018), a more standardized set of criteria based on extensive peer-reviewed evidence was required. In response, the First NINDS Consensus Workshop to Define the Diagnostic Criteria for Traumatic Encephalopathy Syndrome was held in April 2019, and the conclusions of that meeting are currently being prepared for publication.

Neuroimaging

Imaging techniques hold the most promise for the antemortem diagnosis of CTE and include PET and magnet resonance imaging (MRI) (Bazarian et al., 2014; Ng, Rademakers, & Miller, 2015; Sharp, Scott, & Leech, 2014). Brain tau deposits were examined in 5 retired NFL players (age 45-73 years) using FDDNP as a PET radioligand sensitive to tau (Small et al., 2013). FDDNP signals were higher in players compared with age-matched controls in all subcortical regions studied, including the amygdala. A second study by this group used FDDNP PET to examine tau deposition among suspected CTE cases ($n = 14$), controls ($n = 28$), and Alzheimer’s dementia patients ($n = 24$) (Barrio et al., 2015). They found patterns of white matter neuropathology in the suspected CTE cases in brain regions related to the processing of emotions, mood, and behavior, and these patterns were distinct from those in the Alzheimer’s dementia cases or controls. Similarly, Chen et al. (2018) examined tau deposition in military personnel ($n = 7$) and retired NFL players ($n = 15$) each with a history of mild TBI and cognitive/mood symptoms, AD patients ($n = 24$), and controls ($n = 28$) (Chen et al., 2018). Tau deposition was similar between military personnel and retired NFL players, and both groups had different tau deposition patterns than AD or control individuals. In a single player with a 22-year history of American football, a significant correlation between antemortem FDDNP PET binding

and post-mortem neuropathological evidence of tau pathology that met several diagnostic criteria for CTE was reported, suggesting that FDDNP is a valid PET ligand for the detection of tau ([B. Omalu et al., 2018](#)). Stern et al. (2019) utilized a different PET ligand, florataucipir, to measure tau levels in the brains of 26 former NFL players who had cognitive, mood, or behavioral symptoms, and compared them to 32 age-matched controls with no TBI history ([Stern et al., 2019](#)). Compared with the controls, tau deposition was inferred in the former players in 3 brain regions traditionally affected by CTE: bilateral superior frontal, bilateral medial temporal, and left parietal. However, while former players reported cognitive, mood, or behavioral dysfunction, tau deposition was not correlated with objective neurocognitive or neuropsychiatric measures ([Stern et al., 2019](#)). In light of the evidence from Falcon et al. (2019) on the structural difference between CTE tau and AD tau, it is possible that the PET tau ligands, developed by the AD scientific community and utilized in studies on CTE, are not specific to the unique structural conformation of CTE tau ([Falcon et al., 2019](#)). This is supported by Marquie et al. (2019) which noted "...[¹⁸F]-AV-1451 [florataucipir] may not have sufficient sensitivity to reliably detect and quantify tau pathology in CTE by *in vivo* neuroimaging particularly when confounding AD lesions are present in the context of aging" ([Marquie et al., 2019](#)). While PET imaging holds promise for the antemortem diagnosis of CTE, precise development of ligands unique to the structural conformation of CTE tau is required.

Microstructural damage can be detected with diffusion tensor imaging (DTI, a form of MRI). Stamm et al. (2015) used DTI to evaluate the white matter of 40 retired NFL players ([Stamm et al., 2015](#)). Those who had their first exposure to tackle football before the age of 12 years had DTI findings in the corpus callosum indicative of white matter damage, and this was observed more often than in the group first exposed to tackle football after the age of 12 years. Clinically, age at exposure to tackle football also was found to be significant in a study of 211 brain donors with CTE, 126 without comorbid neurodegenerative disease, in which exposure to tackle football before the age of 12 was associated with earlier onset of cognitive and mood symptoms ([Alosco, Mez, et al., 2018](#)). Holleran et al. (2017) examined tissue samples from 10 confirmed CTE cases using DTI and found that fractional anisotropy, an indicator of axonal disruption, was negatively correlated with tau pathology. Specifically, increased tau deposition was associated with decreased fractional anisotropy, suggesting a correlation of tau deposition with white matter injury ([Holleran et al., 2017](#)).

RECENT CTE CONFERENCES

Two conferences were hosted in November 2019 - The Neuropathological Diagnosis of CTE: Next Steps at the NIH, and the 4th Annual CTE Conference at Boston University. These conferences were intended as forums of CTE experts to discuss the most recent clinical and pathological evidence, and to identify current research gaps.

The Neuropathological Diagnosis of CTE: Next Steps conference at the NIH was intended for a scientific audience and largely attended by neuropathologists. The focus areas of the workshop were: state of the science on CTE neuropathology; sensitivity and specificity in relation to CTE diagnostic criteria; CTE progression, severity, stage, and grade; prevalence of CTE in the general population; and brain banking (e.g., acquisitions, logistics, systems, etc.). This conference presented far more debate than consensus, with disagreements on the histopathologic hallmarks of CTE (e.g., neuronal vs astrocytic p-tau), the clinical syndrome associated with CTE, as well as the cause of CTE (e.g., the environmental exposure from contact

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sports/military). The consensus of the experts was that there is no proven association between the histologic findings, primarily p-tau, with any specific mechanism of injury or any unique antemortem clinical disease or syndrome. Overall, there now appears to be less agreement among experts in the field regarding the specific histologic characteristics associated with CTE.

Contrary to the Neuropathological Diagnosis of CTE conference, the 4th Annual CTE Conference at Boston University was open to those outside of the scientific and medical communities and was attended by journalists, former NFL players, and family members of people suspected of having CTE. The conference's goal was to educate participants about multiple aspects of CTE, including its pathology, pathophysiology, risk factors, genetics, biomarkers, imaging, clinical syndromes, clinical criteria, differential diagnosis, impact on veterans and implications for the family, all from the viewpoint of the Boston University CTE Center and collaborators. Material from this conference was in alignment with the school of thought that identifies CTE as a neurodegenerative disease caused by repetitive sub-concussive hits or repetitive head impacts (including blast), with the accumulation of p-tau as a diagnostic feature but not the only pathology of relevance (e.g., microvascular and white matter rarefaction). This conference acknowledged the difficulty in distinguishing CTE from other tauopathies and neurodegenerative diseases, and included a lecture on the differential diagnostic process and various medications that can be beneficial to managing symptoms regardless of the true pathological diagnosis. It also emphasized the importance of using appropriate imaging methods for identifying neurodegenerative effects, damage to fiber tracts, and neuroinflammatory brain metabolites in CTE research. Discussions regarding future studies revealed a need for developing CTE specific biomarkers as well as establishing a way to confirm CTE antemortem.

RESEARCH/CLINICAL GAPS

Despite the numerous clinical and preclinical studies reviewed in this paper, there remain critical gaps and considerable disagreement within the scientific community regarding the causes of CTE, association of clinical manifestations with brain pathology, prognosis, and treatment options. To date, no controlled epidemiological studies exist to establish an increased risk for CTE in former athletes ([Randolph, 2014](#)). In cases of co-occurring diagnosed CTE and another neurodegenerative disease, current practice often entails characterizing the case as CTE rather than the alternative disease, a practice that may be inappropriate for many cases if the alternate condition is the primary neuropathology ([Iverson, Keene, Perry, & Castellani, 2018](#)). In fact, it is common to have cases identified as CTE co-presenting with another proteinopathy ([Ling et al., 2017](#); [McKee et al., 2015](#); [McKee et al., 2013](#)) and further research should work to more accurately categorize tissue samples with multiple patterns of protein deposition. Age-related protein deposition (i.e., PART and ARTAG) is pathologically normal and does not inherently indicate a pathological state ([Crary et al., 2014](#); [Forrest et al., 2019](#); [Randolph, 2014, 2018](#)). Additionally, there are multiple isoforms of tau in the brain and the accumulation of some types of p-tau (e.g., trans tau) may be innocuous ([Randolph, 2014](#)). Furthermore, the progressive nature of the observed pathology has not been confirmed, and the kinetics of tau specific to CTE require further research ([Iverson et al., 2018](#)). Moving forward, a large number of control subjects are required to tease apart the histological relevance of p-tau and NFTs in the brain of those with and without a history of head trauma, other neurological disorders, and the effect of age as well as other demographic and medical risk factors. While current post-mortem diagnostic

criteria is based on the presence of p-tau related pathology, the clinical relevancy of p-tau and NFT pathology to symptomology and behavioral presentation is currently under discussion. Studies reporting correlations between self-reported symptoms and the presence of specific histopathological findings in a diverse occupational cohort should not be taken to mean that the pathology is the cause of the symptomology (Iverson et al., 2018; Randolph, 2018). Additionally, even with the consensus criteria for clinical definition of Traumatic Encephalopathy Syndrome, there is insufficient evidence of a direct relationship between the observed postmortem neuropathology as the cause of the clinical presentation antemortem (Iverson et al., 2018; Randolph, 2018).

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