

**RESEARCH REVIEW  
ON  
CHRONIC TRAUMATIC ENCEPHALOPATHY**

**PURPOSE**

The purpose of this Research Review is to summarize the available peer-reviewed scientific literature regarding the epidemiology, risk factors, clinical manifestations, and pathology of chronic traumatic encephalopathy (CTE). A section on relevant emerging neuroimaging methods is also included. Specific gaps in our understanding of the disease are identified that, if addressed, these could inform the most appropriate prevention recommendations and allow clinicians to more effectively diagnose, manage, and treat CTE.

**BACKGROUND**

CTE is a progressive neurodegenerative disease associated with repeated head trauma. Of the approximately 153 autopsy-confirmed cases reported in a 2015 systematic review, the overwhelming majority were found in persons with a history of extended periods of time playing contact sports, such as boxing, American football, and ice hockey. (Maroon et al., 2015) It appears to be a pathologically distinct entity from other neurodegenerative disease classifications, including frontotemporal dementia and Alzheimer's Disease (AD). At this time, diagnosis of CTE may only be determined by postmortem neuropathological examination.

Appreciation of CTE as a distinct neurodegenerative disease has developed from case studies of athletes with a history of repetitive head trauma. A dementia syndrome occurring in former boxers, frequently accompanied by Parkinsonian and cerebellar motor signs, was first described by Harrison Martland in 1928 and initially called the "punch drunk" syndrome. (Martland, 1928) Cognitive symptoms included bradyphrenia (slowed thinking), confusion, and short-term memory impairment. The syndrome has historically been termed "dementia pugilistica." The phrase "chronic traumatic encephalopathy" was coined in 1949 by M. Critchley. (Critchley, 1957) One early study of a sample of 224 retired boxers found that 17% had neurological symptoms consistent with the syndrome, and sub-syndromal cognitive impairment was apparent in 50%. (Roberts, 1969) The onset of the clinical symptoms occurred in middle age, with a mean of 16 years after discontinuation of boxing. (Critchley, 1957) Disease progression was variable, and survival after the onset of neurologic or cognitive impairment ranged from 7-35 years. Postmortem cerebral histopathologic studies were not available for the boxers in that study, so it was not possible to correlate these clinical signs and symptoms with the pathologic changes associated with CTE.

**INFORMATION**

**Etiology & Epidemiology:**

During the past 10-15 years, there has been a renewed interest in CTE. This was prompted by the postmortem identification of characteristic neuropathological features of CTE (e.g., cerebral atrophy, neurofibrillary tangles, and/or tau-immunoreactive neurites) in middle-

aged American football players. (Omalu et al., 2006; Omalu et al., 2005) In a 2009 article, McKee and colleagues summarized the available data from 48 cases where brain pathology was reported to be consistent with CTE, and also presented clinical and pathological findings from 3 newly identified cases. (McKee et al., 2009) Subsequently, research teams led by McKee have reported on a convenience sample of 202 deceased American football players. They diagnosed CTE in 177 (87%) of them based on neuropathological findings and retrospective reports of behavioral and cognitive symptoms. (Mez et al., 2017) In 2011, Gavett and colleagues published findings suggesting the presence of CTE pathology in 12 football players. (Gavett et al., 2011) Goldstein and colleagues presented data from another series, including four military veterans with a history of blast exposure and/or concussive injury and four young athletes (ages 17 to 27) who suffered repeat head trauma. (Goldstein et al., 2012) They contrasted the postmortem findings in those eight cases with four controls without a history of blast exposure, concussive injury, or neurologic disorders. None of the typical histopathologic features of CTE were present in the controls. Additionally, CTE has been reported in retired soccer players. (Ling et al., 2017)

There is no evidence that a single concussion causes CTE. Furthermore, a 2013 consensus conference on concussion in sport concluded "... a cause and effect relationship has not as yet been demonstrated between CTE and concussions or exposure to contact sports." (McCroory et al., 2013a) The association between CTE and brain trauma is based on the fact that the known cases of CTE occurred in individuals with a history of head trauma, most of whom were contact-sports athletes, and especially those who had repetitive head trauma. (Baugh, Robbins, Stern, & McKee, 2014; Erlanger, Kutner, Barth, & Barnes, 1999) For example, 46 of the 51 cases summarized in the report by McKee and colleagues were athletes. (McKee et al., 2009) Of these, 39 were boxers, five were football players, one played soccer, and one was a professional wrestler. 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) A number of the athlete case series studies cited here are convenience samples of individuals identified by their families to have neurological abnormalities. (McKee et al., 2009; Mez et al., 2017) However, neuropathological features related to Alzheimer's have previously been identified in deceased individuals with normal cognitive function (Gelber, Launer, & White, 2012), and it is not known to what extent features considered pathognomonic for CTE occur in the general population.

A dose-response relationship between the degree of CTE pathology and history of brain trauma has not been demonstrated. Moreover, not all of the deceased individuals with a history of concussive or subconcussive head trauma that have been studied by researchers have been found to have neuropathological features of CTE. (Hazrati et al., 2013; Omalu et al., 2011a; Stern et al., 2011) An early study found that among boxers there appears to be a positive relationship between development of neurologic symptoms associated with CTE and the number of rounds fought, but not the number of knockouts. (Roberts, 1969) While this study did not confirm CTE through neuropathology examination, it suggests that the risk of developing a clinical syndrome resembling CTE may be more related to the frequency of concussive or subconcussive blows to the head than to the severity of each blow. Additionally, Lehman, et al. reported that professional football players exposed to high velocity injuries (e.g., non-linemen) had as much as four times the rate of death from neurodegenerative diseases as the general population in the U.S., suggesting increased neurological risk with increased exposure to head trauma. (Lehman, Hein, Baron, & Gersic, 2012) While almost all confirmed CTE cases have

been in males, an association with gender has not been studied. Environmental factors such as alcohol and drug use and abuse, socioeconomic status, and others, have not been explored. A determination of the true incidence and prevalence of CTE in the general population is not possible at this time as there are no objective diagnostic criteria that can be used to reliably detect CTE prior to death, such as specific clinical criteria or imaging or molecular biomarkers. Efforts towards improving the diagnostic, research, and prognostic utility of neuroimaging approaches are discussed below.

A meta-analysis by Perry et al. presented the hypothesis that “CTE may be a pathological process that unites seemingly disparate clinical syndromes” and that a variety of neurological and psychiatric illnesses associated with TBI history are in fact potential manifestations of CTE. (Perry et al., 2015) Although this provocative hypothesis will doubtless prove controversial, the meta-analysis of 57 studies on TBI history and diagnoses after 1 year post-injury is useful. The pooled odds ratio (OR) for any neurological diagnosis was 1.55 (95% confidence interval 1.31–1.83), and the pooled odds ratio for any psychiatric diagnosis was 1.67 (95% confidence interval 1.44–1.93).

It has been suggested that blast exposure may be a risk factor for developing CTE. Evidence supporting this hypothesis is limited to mechanistic inference, results from animal models, (DoD Blast Injury Research Program Coordinating Office, 2015a) and a handful of cases. CTE has been observed in military veterans exposed to blast. (Goldstein et al., 2012; McKee & Robinson, 2014; Omalu et al., 2011b) Among these five reported blast-related cases, at least three were complicated by blunt concussive injury, and three were complicated by post-traumatic stress disorder. (Goldstein et al., 2012; Omalu et al., 2011b) In each of the cases with blast exposure, deposition of phosphorylated tau protein was similar to that seen in other CTE cases without a history of blast exposure. (Goldstein et al., 2012; Omalu et al., 2011b) Some of the former service members who have been found to have CTE at postmortem were also athletes (McKee et al., 2013; Reid & Velez, 2015) who may have been exposed to repeated blunt impacts (perhaps in addition to blast exposure), a fact which casts doubt on causal inferences. However, just as with studies of CTE in athletes, selection bias was inherent in the study of these veterans because they died prematurely. Their relatives agreed to the donation of their decedent’s brains for neuropathological studies with the hope of better understanding the cause of death.

### **Pathology:**

The earliest known description of the gross pathologic manifestations of CTE are those described from studies of deceased boxers, and include reduced brain weight, cavum septum pellucidum (separation and tearing of a double membrane located at the midline of the brain), enlargement of the ventricles, and thinning of the corpus callosum. (Corsellis, Bruton, & Freeman-Browne, 1973) The most striking neuropathological feature of CTE is the presence of neurofibrillary tangles (NFTs), which appear similar to NFTs found in AD, but with specific differences in the neuroanatomical localization. (Hof et al., 1992; Shively, Scher, Perl, & Diaz-Arrastia, 2012) Two large case series have demonstrated similar NFT neuropathology among the brains of former NFL players and other professional athletes with a history of repetitive mild TBI. These individuals either developed dementia and other clinical manifestations of CTE and died in middle age, or died (many via suicide) after displaying some of the cognitive features of CTE, but prior to the development of dementia. (McKee et al., 2009; Omalu et al., 2011a) CTE pathology has been observed in postmortem studies of young football players aged 17-26 years,

and boxers in their 20s, but it is not known whether these athletes were symptomatic. (Geddes, Vowles, Nicoll, & Revesz, 1999; Goldstein et al., 2012) In the case studies, separate phenotypes or stages have emerged. Omalu et al. in 2011 described four CTE phenotypes differentiated mainly by the frequency and location of neurofibrillary tangles and neuritic threads. (Omalu et al., 2011a) McKee et al. in 2013 described four stages of CTE pathology thought to occur in a progressive fashion. (McKee et al., 2013)

The first consensus diagnostic criteria for CTE were published in December 2015, and based on a conference sponsored by the National Institutes of Neurological Disorders and Stroke (NINDS), the Department of Defense, the Department of Veterans Affairs, and other organizations. (McKee et al., 2015) McKee et al. arrived at one required criterion for postmortem CTE diagnosis, and seven supportive criteria. The required neuropathology was lesions consisting of “p-tau aggregates in neurons, astrocytes, and cell processes around small [blood] vessels in an irregular pattern at the depths of the cortical sulci.” Five of the seven supportive criteria related to p-tau pathology. These five criteria provided details regarding the frequency, location, and form of p-tau aggregates: p-tau is found in more superficial layers of the cortex in CTE than in Alzheimer’s disease; p-tau may be found in the hippocampus, subcortical nuclei, or subpial and periventricular regions; p-tau may form grain-like, dot-like, or thread-like structures. Two of the seven supportive criteria were unrelated to tau. One specified macroscopic features including “disproportionate dilatation of the third ventricle, septal abnormalities [such as cavum septum pellucidum], mammillary body atrophy, and contusions or other signs of previous traumatic injury.” (McKee et al., 2015) The other supportive criteria described inclusions and structures containing trans-activator regulatory DNA-binding protein 43 (TDP-43) that may be present in the hippocampus, anteromedial temporal cortex and amygdala. Three non-diagnostic, non-supportive criteria included describe age-related p-tau pathology. The article noted that the defining lesion of CTE “has only been found in individuals who were exposed to brain trauma, typically multiple episodes.” (McKee et al., 2015)

Tau protein deposition is well known to be associated with other neurodegenerative diseases and dementias, particularly frontotemporal dementia and AD. Indeed, 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 their peculiar distribution within the brain.” (National Institutes of Neurological Disorders and Stroke, 2013) Under non-pathological conditions, the protein tau regulates microtubule stability. In the case of repetitive mild TBI-associated neurodegenerative dementias, considerable evidence points to abnormal neuronal processing of tau protein as an important contributor to neuropathology, such as the wide-spread deposition of cortical NFTs that are consistently observed in the brains of autopsied individuals with clinical symptoms prior to death. (McKee et al., 2009) Results from studies of patients with AD, stroke, frontotemporal dementia, Creutzfeldt-Jakob disease, major head trauma, and aging non-demented subjects suggest that tau accumulation is a general marker of neuronal damage. (Sjogren et al., 2001; Sunderland et al., 2003) In contrast, CSF phosphorylated tau (p-tau) concentrations appear to be a more specific marker of earlier neurodegenerative processes in AD. (Buerger et al., 2005; Hansson et al., 2006)

Kondo et al. presented evidence that *cis* p-tau is an even more specific marker for brain injury-related pathology. Using antibodies that can distinguish *cis* from *trans* p-tau, researchers

found *cis* p-tau, but not *trans* p-tau, in the brains of 16 confirmed CTE cases. (Kondo et al., 2015)

Elevated levels of tau in plasma and CSF after TBI may contribute to the accumulation of tau-reactive NFTs. Patients with severe TBI exhibit transient elevations in cerebral spinal fluid (CSF) tau protein levels, which correlate with clinical outcomes at one year. (Ost et al., 2006) Olivera et al. reported plasma levels of tau measured in deployed military personnel with varied TBI status. (Olivera et al., 2015) Tau levels were significantly higher in those reporting TBI as compared to those not reporting TBI, those with a medical record of TBI as compared to those with self-reported TBI, and those reporting three or more TBIs as compared to those reporting one or two. For the self-reported TBI group, about half of them were less than a year post-deployment, and for the medical record of TBI group, most were within 6-12 months of their most recent deployment at assessment. (Ost et al., 2006) Cerebral spinal fluid studies of neurodegenerative biomarkers such as tau in patients with confirmed CTE have not yet been reported.

TDP-43 reactive lesions support a diagnosis of CTE, according to the consensus diagnostic criteria by McKee et al., and TDP-43 has previously been associated with CTE and other neurodegenerative conditions. (Bosque, Boyer, & Mishra, 2013; McKee et al., 2015) TDP-43 immunoreactivity was present in distributed brain regions in 10 of 12 CTE cases. (McKee et al., 2010) Three of the cases of CTE with increased TDP-43 immunoreactivity also developed motor neuron disease with extensive spinal cord involvement. Findings of the McKee group suggest that more than 85% of CTE cases have abnormal accumulation of TDP-43 that are at least partially co-localized with phosphorylated tau protein. (Stein, Alvarez, & McKee, 2014)

Neuroinflammation may play a role in the development of CTE. TBI induces neuroinflammation, (Das, Mohapatra, & Mohapatra, 2012) which has been shown to persist for years in cases of moderate and severe TBI. (Smith, Johnson, & Stewart) A recent neuropathological study by Cherry et al. examined inflammation markers in the brains of deceased subjects with CTE (n = 48), with head impact history but no CTE (n = 18), and without repetitive head impact (n = 16). Results showed that chronic activation of microglia is associated with both repetitive head impact and phosphorylated tau pathology. (Cherry et al., 2016) Neuroinflammation may have neuroprotective effects, (Patterson & Holahan, 2012) but may also contribute to observed neurodegenerative pathologies.

Beta amyloid (A $\beta$ ) deposition is evident at autopsy in a significant subset of reported cases of CTE. (Allsop, Haga, Bruton, Ishii, & Roberts, 1990; McKee et al., 2009) A study of 114 confirmed CTE cases found diffuse A $\beta$  plaques in 52% of cases, and neuritic A $\beta$  plaques in 36%. (Stein et al., 2015) It is not yet understood if A $\beta$  plays a role in CTE, or if its occurrence in CTE patients is related to aging (Dickson et al., 1992) or a separate neurological pathology (i.e., AD).

### **Clinical Manifestations:**

As diagnosis of CTE can only be confirmed with postmortem histopathological analysis of brain samples at this time, evidence regarding the clinical manifestations of confirmed CTE is limited to symptom reports from interviews of relatives of deceased individuals, or retrospective reviews of medical records. Symptom reports from interviews of relatives of deceased individuals cannot be independently verified, and validity data is unavailable. As of yet, there

have not been any prospective studies linking CTE to specific clinical signs, symptoms or behaviors in living persons. CTE is believed to be associated with a variety of behavioral, emotional, cognitive, and motor function symptoms. (Lenihan & Jordan, 2015) Behavioral and emotional symptoms attributed to CTE include: mood swings, (Gardner et al., 2015) disinhibition, paranoia, irritability, violent outbursts (Lehman et al., 2012) and impulsiveness (Banks et al., 2014). Cognitive symptoms attributed to CTE include: episodes of confusion, (Gardner et al., 2015) decreased attention and concentration, (Lakhan & Kirchgessner, 2012; Mendez, 1995) memory impairment, executive dysfunction, language impairment, and visuospatial difficulties. (Mendez, 1995) Motor function symptoms attributed to CTE include: tremor, (Gardner et al., 2015) dysarthria, or mild imbalance, and eventual gait or limb ataxia, spasticity, and parkinsonism. (Mendez, 1995) These symptoms derive in part from studies of probable CTE cases including boxers and American football players with a history of repeated TBI.

Most agree that the cognitive, emotional, and behavioral symptoms that have been attributed to CTE are non-specific, and can be caused by numerous medical and psychiatric conditions. CTE cases are often complicated by additional neurological conditions; one case series showed that 25 of 68 confirmed CTE patients were also diagnosed with motor neuron disease, Alzheimer's disease, Lewy body disease, or frontotemporal lobar degeneration. (McKee et al., 2013) Even the symptom patterns typical of the acute or sub-acute phase of concussion/mild TBI, such as headache, dizziness, or sleep disorders, are non-specific and occur at a high base rate in persons without TBI history. (Rapp & Curley, 2012; Wang, Chan, & Deng, 2006) For these reasons, diagnosis and symptom attribution present challenges for clinicians and researchers.

Despite these challenges, three groups have developed distinct research diagnostic criteria for probable CTE in living persons. (Jordan, 2013; Montenigro et al., 2014; Victoroff, 2013) All three sets of criteria require a history of brain trauma, but the specific symptom requirements differ. (Baugh et al., 2014) The most recently published criteria, by Montenigro et al. requires at least one of three overall categories of disturbances for a research diagnosis of probable CTE: cognitive, behavioral, and mood. In addition, this criteria requires at least two of the following supporting features: impulsivity, anxiety, apathy, paranoia, suicidality, headache, motor signs, progressive decline in function, or delayed onset. (Montenigro et al., 2014) The research diagnostic criteria defined by Jordan et al. in 2013 require motor signs potentially including: dysarthria, spasticity, ataxia, parkinsonism, or gait disturbance. (Jordan, 2013) The research diagnostic criteria published by Victoroff et al. in 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) These criteria will be of use to researchers investigating neuroimaging and neuropsychological diagnostics.

Studies of probable and confirmed CTE cases have identified different phenotypes 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. Those symptoms are impulsiveness, cognitive impairment, and suicidality. (Banks et al., 2014) (Randolph, Karantzoulis, & Guskiewicz, 2013) (Seichepine et al., 2013) (Randolph, 2014;

Wortzel, Shura, & Brenner, 2013) Insufficient evidence exists to evaluate the relationship between CTE and these symptoms with any confidence. (Iverson, 2014)

**Neuroimaging:**

A number of imaging studies have demonstrated the diagnostic and research promise of imaging approaches to detect and characterize neurodegeneration in living persons, including probable or suspected CTE cases. Findings discussed here must be interpreted with caution, since observed symptoms and neuropathologies can arise from related but distinct illnesses or medical conditions, and CTE diagnosis cannot be confirmed in living persons. Researchers interested in CTE have mainly focused on positron emission tomography (PET) with radioligands, but some advanced magnetic resonance imaging approaches have also been applied. (Bazarian et al., 2014; Ng et al., 2014; Sharp, Scott, & Leech, 2014)

An imaging biomarker for AD has been described that uses an amyloid-binding radiotracer for positron emission tomography (PET) detection of  $\beta$ -amyloid. (Price et al., 2005)  $\beta$ -amyloid deposition is not a defining feature of CTE, (National Institutes of Neurological Disorders and Stroke, 2015) despite occurring in a substantial number of cases, (Allsop et al., 1990; McKee et al., 2009; Stein et al., 2015) so this PET technique would not be expected to be sufficient for the pre-morbid identification of CTE.

Investigators have used PET with emerging and established tau-binding tracers to investigate individuals at risk for or showing clinical signs of CTE. Brain tau deposits were examined in 5 living retired National Football League (NFL) players (age 45-73) using 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP) as a radioligand sensitive to tau. (Small et al., 2013) FDDNP signals were higher in players compared with age-matched controls in all subcortical regions studied, as well as the amygdala. A second paper by the same team includes 14 suspected CTE cases, 28 controls, and 24 Alzheimer's dementia patients. (Barrio et al., 2015) PET scanning with FDDNP revealed patterns of white matter neuropathology in the suspected CTE cases consistent with observed symptoms related to emotions, mood, and behavior. The patterns were distinct from those in the Alzheimer's dementia cases or controls. In 2014, Mitsis et al. reported a case study of a former NFL player showing clinical signs of CTE imaged with [<sup>18</sup>F]-T807 PET. Imaging results showed tau accumulation in the globus pallidus and the substantia nigra in the patient, and the authors claimed these findings improved the accuracy of the diagnosis. (Mitsis et al., 2014) However, confirmed diagnosis is impossible without postmortem autopsy confirmation, therefore, living persons such as those discussed in these studies should be regarded as probable or suspected CTE cases.

While there is much interest in PET with tau-binding ligands, other imaging approaches may have research utility in populations at risk for CTE. A study by Coughlin et al. used a PET ligand that targets translocator protein, which is a marker of brain injury and repair, and served as a proxy for neuroinflammation in this study. (Coughlin et al., 2015) Imaging of former NFL players (n = 9) and healthy controls (n = 9) all over the age of 55 showed significantly more neuroinflammation (i.e., ligand binding) in the former NFL players than the controls, specifically in the right amygdala and the supramarginal gyrus.

Diffusion tensor imaging (DTI) has also been applied to possible CTE cases and CTE tissue samples. Stamm et al. used DTI to examine 40 retired National Football League (NFL) players. (Stamm et al., 2015) Results showed that those with an age of first exposure to tackle football under 12 had DTI readings in the corpus callosum region more indicative of damage than the group first exposed to tackle football after age 12. Holleran et al. recently examined tissue samples from 10 confirmed CTE cases using DTI and found that fractional anisotropy, an indicator of axonal disruption, was negatively correlated areas of tau pathology. (Holleran et al., 2017)

## **DISCUSSION**

This Research Review provides an overview of current state of science/evidence for CTE. A thorough search of MEDLINE, CINAHL, EMBASE, Mosby's Index, PsycEXTRA, PsycINFO and Scopus has not found any published epidemiological, cross-sectional or prospective studies relating to CTE. (McCrary, Meeuwisse, Kutcher, Jordan, & Gardner, 2013b) While causality cannot be determined, CTE pathology has been described only in cases with a history of repeated head trauma. (National Institutes of Neurological Disorders and Stroke, 2015) The extent to which age-related changes, psychiatric or mental health illness, alcohol/drug use or coexisting dementing illnesses contribute to the process of the development of CTE is largely unknown.

A 2015 Department of Defense State of the Science Meeting hosted by the Blast Injury Research Coordinating Office identified a number of research and knowledge gaps. (DoD Blast Injury Research Program Coordinating Office, 2015b) Many of these gaps are relevant beyond the study of blast-related injury. Notable gaps include:

- Limited tissue available for research. The field would benefit from protocols for minimal sampling requirements (i.e., the number and location of brain samples extracted for histology) for CTE. Well-annotated medical and TBI exposure history would facilitate identification of potential CTE cases in brain banks.
- Traumatic risk factors for the development of CTE need to be much better defined, including mechanism, frequency, number, and severity of TBIs, blast exposures, and subconcussive events.
- Validated and clinically relevant animal models of CTE are needed to better demonstrate the mechanism of injury relative to the neurodegenerative cascade and neuropathological features. The human neuropathological features of tau aggregation must be adequately modeled to contribute to mechanistic studies and screening of potential therapeutics.
- Longitudinal and prospective studies that track TBI, subconcussive events, and non-traumatic risk factors for CTE, and include postmortem brain histopathology would advance understanding of the etiology of CTE and other neurodegenerative diseases.
- Non-traumatic risk factors that increase susceptibility to CTE must be identified, such as history of depression, stress, alcohol and other drug use, age, gender, and genotype (e.g. ApoE alleles).
- Imaging (e.g. PET) and fluid biomarkers for CTE are needed for diagnosis and treatment, but must be validated by autopsy confirmation.

Other significant gaps in our understanding of CTE remain:

- A case definition for probable CTE that includes cognitive, behavioral, neuropsychological, and neuroimaging data. To the extent possible, contrasts should be drawn with neurological and mental health conditions that share components of CTE symptoms. The progression of manifestations should be delineated.
- Ultimately, understanding the progression and causation of CTE may enable diagnosis and treatment of this disorder in living persons.

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