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**INFORMATION PAPER**

MCMR-DCV

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**SUBJECT: CHRONIC TRAUMATIC ENCEPHALOPATHY**

1. PURPOSE

The purpose of this IP 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, could inform the most appropriate prevention recommendations and allow clinicians to more effectively diagnose, manage, and treat CTE.

2. BACKGROUND

CTE is a progressive neurodegenerative disease associated with repeated head trauma. Of the approximately 153 autopsy-confirmed cases that have been reported, the overwhelming majority have been seen in the setting of extended periods of time playing contact sports, such as boxing, American football, and ice hockey. [1] 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 Martland in 1928 and initially called the "punch drunk" syndrome. [2] Cognitive symptoms include bradyphrenia (slowed thinking), confusion, and short-term memory impairment. The syndrome has historically been termed "dementia pugilistica." 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%. [3] The onset of the clinical symptoms was insidious and occurred in middle age, with a mean of 16 years after discontinuation of boxing. [4] 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.

### 3. INFORMATION

**Etiology & Epidemiology:** During the past 10-15 years, there has been a renewed interest in CTE, prompted by the postmortem identification of neuropathological features characteristic of CTE, such as cerebral atrophy, neurofibrillary tangles, and/or tau-immunoreactive neurites, in middle-aged American football players. [5, 6] In a 2009 article, McKee and colleagues summarized available data from 48 cases where brain pathology was previously reported to be consistent with CTE, and presented clinical and pathological findings from 3 newly identified cases. [7] Subsequently, Stern and colleagues reported on 14 American football players diagnosed with CTE based on characteristic neuropathological findings. [8] In 2011, Gavett and colleagues published their findings suggesting the presence of CTE pathology in 12 football players. [9] Goldstein and colleagues presented data in 2012 from an additional series including four military veterans with a history of blast exposure and/or concussive injury, and four cases of young athletes (ages 17 to 27) that suffered repeat head trauma. [10] They contrasted the postmortem findings in those eight cases with four controls without a history of blast exposure, concussive injury or neurologic disorders, and emphasized that none of the typical histopathologic features of CTE were present in those controls.

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." [11] 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. [12, 13] For example, 46 of the 51 cases summarized in the report by McKee and colleagues were athletes. [7] 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. [14]

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. [8, 15, 16] 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. [3] 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. [17] 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, 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 because 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 recent meta-analysis 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. [18] 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) 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. However, this is only speculation based on mechanism and associated white matter injury documented in at least one study. [19] Cases of CTE have been observed in military veterans exposed to blast. [10, 20, 21] 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. [10, 20] 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. [10, 20] Some of the former service members who have been found to have CTE at postmortem were also athletes [22, 23] 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.

The apolipoprotein E  $\epsilon$ 4 (ApoE $\epsilon$ 4) genotype is well-known as a risk factor for early onset AD, as well as poor behavioral and functional outcomes following TBI. [24] However, the relationship between

the ApoE $\epsilon$ 4 genotype and CTE is unclear. Among 10 cases of neuropathologically confirmed CTE for which there was ApoE genotype information available, McKee and colleagues reported that only five had at least one ApoE $\epsilon$ 4 allele. [7] In their study of seven athletes with CTE and known ApoE genotype, Omalu et al found that only two had an ApoE $\epsilon$ 4 allele, and the other five were homozygous for ApoE $\epsilon$ 3. [15]

**Clinical Manifestations:** Diagnosis of CTE can currently only be confirmed with postmortem histopathological analysis of brain samples, therefore, evidence regarding the clinical manifestations of confirmed CTE is limited to interviews of relatives of deceased individuals, or retrospective reviews of medical records. 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. [25] Behavioral and emotional symptoms attributed to CTE include: mood swings, [26] disinhibition, paranoia, irritability, violent outbursts [17] and impulsiveness [27]. Cognitive symptoms attributed to CTE include: confusional episodes, [26] decreased attention and concentration, [28, 29] memory impairment, executive dysfunction, language impairment, and visuospatial difficulties. [29] Motor function symptoms attributed to CTE include: tremor, [26] dysarthria, or mild imbalance, and eventually gait or limb ataxia, spasticity, and parkinsonism. [29] 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. [22] 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. [30, 31] 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. [32-34] All three sets of criteria require a history of brain trauma, but the specific symptom requirements differ. [12] 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. [32] The research diagnostic criteria defined by Jordan et al. in 2013 require motor signs potentially including: dysarthria, spasticity, ataxia,

parkinsonism, or gait disturbance. [34] 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. [33] 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. One highly cited paper by McKee et al. divided confirmed CTE cases into stages based on postmortem brain analysis. In that study, attention and memory symptoms were more common than depression or aggression symptoms among the six cases classified in the earliest stage. [22] Stern et al. retrospectively evaluated 36 confirmed CTE cases. [35] History and clinical presentation data revealed two distinct phenotypes: those for whom behavioral and mood disturbance develops at a younger age (n = 22; average 34 years at symptom onset), and those for whom cognitive impairment develops at an older age (n = 11; average 54 years at symptom onset). A recent study of 14 American football players who are probable CTE cases identified three phenotypes: chronic postconcussion syndrome, with symptom onset around 30 years of age; delayed-onset progressive behavior/mood syndrome, first observed around 52 years of age; and delayed-onset progressive cognitive or mood disorder, first observed around 60 years of age. [26] The patient population included one individual with parkinsonism, two individuals diagnosed with mild cognitive impairment, one individual with mild dementia, one individual with CTE confirmed by postmortem, and 12 individuals with a gross structural abnormality commonly observed in CTE. In contrast, one of the largest case studies to date (n = 68) identified a cognitive symptom, specifically short-term memory loss, as one of the first to arise. [22]

While the described phenotypes and symptom clusters may be diagnostically useful, other researchers have examined several specific symptoms attributed to probable CTE cases that warrant comment here. Those symptoms are impulsiveness, cognitive impairment, and suicidality. Banks et al. recently investigated a large group of active professional fighters, and found some associations of fight exposure with impulsiveness and reduction in volume of certain brain structures. [27] These findings suggest possible relationships that warrant further study to better understand the role of contact sports in developing clinical and behavioral manifestations later in life.

Cognitive impairment has been studied in groups at risk of developing CTE. In a survey of 513 retired NFL players, 35.1% of respondents (average age 64 years) had a score on a dementia screening questionnaire that suggested possible cognitive impairment. [36] A telephone screening of this cohort identified 41 NFL retirees with probable mild cognitive impairment (MCI). The authors noted that these retirees had a pattern of neuropsychological test scores somewhat similar to the

pattern of scores from a group of clinically diagnosed MCI patients (n = 81), however, a rigorous statistical comparison was not performed. A 2013 study by Seichepine et al. included 64 college and professional football players and age-matched controls with no history of contact sports. Results from the Behavior Rating Inventory of Executive Function showed that football players reported more-frequent problems with executive functioning than controls, and symptoms were worse for players over 40 years old. [37]

A number of high-profile cases of athlete suicide have raised questions about CTE and suicidality. Contrary to what media reports may suggest, recent studies of NFL retirees report that they have an all-cause mortality rate that is approximately half of the expected rate, and even lower suicide rates. [38] A systematic review of the medical literature of evidence for a relationship between CTE and suicide yielded two acceptable-quality case series that included autopsies from 17 unique cases, 5 of whom died by suicide. [39] Insufficient evidence exists to evaluate the relationship between CTE and suicide with any confidence. [40]

**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, 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. [41-43]

An imaging biomarker for AD has been described that uses an amyloid-binding radiotracer for positron emission tomography (PET) detection of  $\beta$ -amyloid. [44]  $\beta$ -amyloid deposition is not a defining feature of CTE, [45] despite occurring in a substantial number of cases, [7, 46, 47] 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. [48] FDDNP signals were higher in players compared with age-matched controls in all subcortical regions studied, as well as the amygdala. A more recent paper by the same team includes 14 suspected CTE cases, 28 controls, and 24 Alzheimer's dementia patients. [49] 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. [50] 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 recent 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. [51] 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. Recently, Stamm et al. used diffusion tensor imaging (DTI) to examine 40 retired National Football League (NFL) players. [52] 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.

**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. [53] 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. [54, 55] 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. [7, 15] 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. [10, 56] 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. [15] McKee et al. in 2013 described four stages of CTE pathology thought to occur in a progressive fashion. [22]

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. [57] 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, and specified: 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.” [57] 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.” [57]

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.” [58] 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. [7] 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. [59, 60] In contrast, CSF phosphorylated tau (p-tau) concentrations appear to be a more specific marker of earlier neurodegenerative processes in AD. [61, 62] Recently, 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. [63]



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. [64] Olivera et al. recently reported plasma levels of tau measured in deployed military personnel with varied TBI status. [65] 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. [64] 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. [57, 66] TDP-43 immunoreactivity was present in distributed brain regions in 10 of 12 CTE cases. [67] Three of the cases of CTE with increased TDP-43 immunoreactivity also developed motor neuron disease with extensive spinal cord involvement. Recent 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. [68]

Neuroinflammation may play a role in the development of CTE. TBI induces neuroinflammation, [69] which has been shown to persist for years in cases of moderate and severe TBI. [70] Neuroinflammation may have neuroprotective effects, [71] and it is not known whether neuroinflammation occurs as a response to observed neurodegenerative pathologies, or is a causative agent.

Beta amyloid (A $\beta$ ) deposition is evident at autopsy in a significant subset of reported cases of CTE. [7, 47] A recent study of 114 confirmed CTE cases found diffuse A $\beta$  plaques in 52% of cases, and neuritic A $\beta$  plaques in 36%. [46] It is not yet understood if A $\beta$  plays a role in CTE, or if its occurrence in CTE patients is related to aging [72] or a separate neurological pathology (i.e., AD).

Animal models of blast, blunt, and repeated TBI have been influential in CTE research. One study using a mouse blast model found that a single blast exposure induced phosphorylated tau pathology, myelinated axonopathy, microvasculopathy, and chronic neuroinflammation and neurodegeneration. [10] Blast exposure in these mice also was associated with learning and memory deficits, but these cognitive deficits were not found when the head was immobilized during the blast, and may therefore have been due to head acceleration. A follow-up study confirmed that

head acceleration was indeed responsible for producing acute TBI symptoms in mice, although nearly doubling the blast overpressure could produce acute symptoms even with head immobilization. [73] A recent study using rats exposed to repeat blast-like overpressures showed endoplasmic reticulum stress in brain cells, and this result was replicated in two confirmed human CTE cases. When the rats were administered docosahexaenoic acid, an endoplasmic reticulum stress inhibitor, cognitive outcomes at 3 weeks post-injury were improved. [74] A recently developed mouse model for CTE uses unanaesthetized, helmeted mice who receive 42 blunt concussive blows over a period of 7 days. [75] Researchers showed these mice demonstrate decreased motor function, decreased performance in a cognitive task, depression-like behavior, sleep disturbances, and initially increased anxiety, followed by later increased risk-taking behavior. A follow-up study by the same group examined the pathology of this model, and observed increased phosphorylated tau immunoreactivity, increased neuroinflammation, acute reactive astrocytosis, astrogliosis and microglial activation. [76]

#### 4. SUMMARY

The purpose of this Information Paper was to review the current state of 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. [77] While causality cannot be determined, CTE pathology has been described only in cases with a history of repeated head trauma. [45] 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.

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.
- Neuropathology protocols for minimal sampling requirements (i.e., the number and location of brain samples extracted for histology) for CTE in large autopsy-based studies are needed, including retrospective and prospective screening protocols that should be followed to facilitate identification of potential CTE cases in brain banks.
- Imaging (e.g. PET) and molecular biomarkers for CTE must be validated by autopsy confirmation.
- A validated animal model of CTE is 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.

- Traumatic risk factors for the development of CTE need to be much better defined, including mechanism, frequency, number, and severity of TBIs and subconcussive events.
- 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).
- Longitudinal 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.
- Ultimately, understanding the progression and causation of CTE may enable diagnosis and treatment of this disorder in living persons.

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