Chronic Traumatic Encephalopathy: A Literature Review

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Abstract

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease that exhibits abnormally high amounts of tau, a protein found in brain cells. The cause of CTE is still relatively unknown. One's prolonged experience of head trauma leads the medical community to believe that CTE is the main culprit. The phenomenon, occurring primarily with American football players, was first referred to as "punch drunk syndrome" in 1928. Currently, CTE cannot be diagnosed premortem. Examining the brain tissue post-mortem is the only way to officially diagnose CTE. Unfortunately, there are no known cures. However, pharmacologic and nonpharmacologic interventions can be used to lessen the symptoms. The purpose of this study was to critically analyze current methods of diagnosing CTE and identify limitations within the diagnostic methods by reviewing peer reviewed articles from various credible databases (PubMed, JSTOR, ClinicalKey) and journals. As more studies are conducted and technology advances to allow brain tissue diagnosis premortem, a cure for chronic traumatic encephalopathy may arise.

Introduction

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease that typically comes from head impact related injuries (1). It can cause memory loss, changes in behavior, and cognitive impairment (2). In those under 50 with continual head trauma, it has been seen that traumatic brain injuries can also cause severe disabilities such as seizures, psychiatric disorders, and personality changes (3). In general, CTE is affiliated with serious morbidity and mortality rates (4). It is often found in people who partake in contact sports (1). However, in some cases, CTE has been found in people with no known history of neurotrauma (5). Typically, brain injuries have two phases, the initial injury and then the cascade or progressive aftermath to follow, which is common in repetitive injuries like CTE which often progress after multiple blows to the head (6). Currently there are no diagnostic criteria, which makes it hard to differentiate CTE from other neurodegenerative diseases (7). The only identification marker for risk factor is repetitive head trauma (8). Along with this, the only time a diagnosis is possible is postmortem, which makes CTE hard to detect and find (9). During the last decade, there are a lot of unanswered questions about the disease, which are slowly being discovered.

Until recently, CTE was not as widely researched, and much of the research performed had sans primary data collection, potentially leading to biases and inaccuracies (10). The progressing recognition recently has caused an increase in the awareness and there has been an uptick in conferences and activity centered around the gaps in CTE (11, 12). Recently, many different sports leagues have been looking into means of prevention and enforcing rules and regulations to avoid head trauma that may lead to CTE (13). The first reported case of CTE in a football player was in 2005, which ushered in a newfound interest in the topic (8). For athletes, this can cause long-term effects that lead to mental health issues such as anger, depression, and suicidal ideation that may result in death by suicide (14). There have been numerous studies that look at the psychological consequences, and the correlation between those with a diagnosis of CTE (postmortem), and suicide (2, 15). In some cases, CTE and post-traumatic stress disorder have been shown to overlap (16). The correlation between CTE and Alzheimer's is also a frequently researched topic (17). At this point in time, pathological findings have shown that the brain has an increase in a protein called tau in the superior colliculus (18, 19). There is an extreme need for a new diagnosis process, as the suspicion in many causes added distress and anxiety (17). In lieu of this, there has been an increased use of magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) on live subjects to diagnose prior to death. This has the potential to pave the way to track patterns that can be diagnosed in vivo (20). While there is research in the literature on CTE pathology and diagnosis, disadvantages in the developments in the literature can still be found.

Methods

A critical examination of CTE pathology and diagnosis was conducted and several credible databases and scholarly articles on CTE were utilized. We conducted this study by gathering peer-reviewed literature from our databases. References were obtained through ClinicalKey, JSTOR PubMed, Elsevier, Springer, and NCBI. The journals completed a peer-review process and were deemed reliable and acceptable. Keywords searched for included: chronic traumatic encephalopathy, neuropathology, brain trauma, neurodegenerative, traumatic brain injury, Alzheimer's, and tau phosphorylation.

Discussion

Clinical symptoms of CTE

Repetitive brain trauma can eventually lead to the deterioration of the brain. It is often seen in individuals that partake in aggressive contact and collision sports such as football, boxing, soccer, ice hockey or even rugby (21). Boxers were the first to be officially diagnosed with CTE, and the first bull rider to be diagnosed with CTE was in 2018 (22, 23). Fourteen retired soccer players who were considered headers participated in a longitudinal study from 1980 to 2010 monitoring their cognitive diseases that developed around 60 years old (24). In addition to the development of concussion through these sports, CTE can also manifest through minor repeated blows to the head via physical abuse from another individual or self-harm (25). Through brain tissue analysis, the gross neuropathological findings included cerebral, thalamus, and hypothalamus atrophy

(reduced gray and white matter), enlarged ventricles, cavum septum pellucidum and depigmentation of the substantia nigra and locus coeruleus, with microscopic evidence of neurofibrillarytangles (NFT) in the cortex and brainstem, sometimes associated with senile plaques or neuronal loss (26, 27). This may lead to a variety of behavioral, physical, and psychological symptoms.

CTE is clinically associated with symptoms of irritability, aggression, depression, short-term memory loss, and heightened suicidality that usually begins 8 to 10 years after experiencing repetitive mild traumatic brain injury (25, 28). There are four stages of physical symptoms in CTE. Frequent headaches, loss of attention, mild aggressive symptoms, and lack of concentration are seen in stage one (29). As the symptoms progress to stage two, individuals suffer from depression, loss of short-term memory, and sudden outbursts of anger, in addition to the symptoms from stage one. Some other less-common symptoms seen at this stage are executive dysfunction, language difficulties, and impulsivity (30). Stage three continues with a compilation of the previously mentioned symptoms with the addition of suicidal thoughts. Patients typically display more cognitive deficits, ranging from memory loss to executive and visuospatial functioning deficits and apathy (29). A study demonstrated that cognitive impairment symptoms were significantly higher in participants self-reporting CTE (31). The most severe stage is stage four, in which the development of memory loss with dementia, aggressive tendencies, paranoia, and issues with gait occur (30). A study explains that the most common causes of death for those with CTE are respiratory failure, cardiac disease, overdose, and symptoms associated with end-stage dementia and malignancy (30). A study showed that adverse events in childhood and ongoing life stressors can result in depression based on symptoms from neuropathology characteristic of CTE (32). All these clinical symptoms are linked to certain pathological abnormalities in the brain. Although these clinical symptoms can be identified pre-mortem, many of these are not diagnosed as CTE, but rather as a presenting symptom of other diseases. Due to this, diagnoses are often misinterpreted as comorbidities. Hence, the importance of evaluating CTE pathology is critical to identify unique differences in its physical presentations.

CTE pathology

Along with the symptoms, there are also pathological defects to the brain. Gross anatomical abnormalities found during brain autopsies are consistent with the current understanding of CTE. These abnormalities, which may result from underlying neurodegenerative processes, include an overall reduction in brain weight (33). In Figure 1, the four stages of CTE symptoms are depicted. In stage I, there are perivascular phospho-tau neurofibrillary tangles in focal epicenters at the depths of the sulci which are measured in the dorso-lateral prefrontal cortex (34, 35). In stage II, there is a progression of neurofibrillary tangles in the superficial cortical layers adjacent to the focal epicenters and in the nucleus basalis of Meynert and locus coeruleus (34). In stage III, there is a mild cerebral atrophy, septal abnormalities, third ventricular dilatation, depigmentation of locus coeruleus and substantia nigra, dense phospho-tau pathology in the cortex, medial temporal lobe, diencephalon, brainstem, and spinal cord (34, 21). Lastly in stage IV, there is further advanced cerebral, medial temporal lobe, hypothalamic, thalamic, and mammillary body atrophy, septal abnormalities, ventricular dilatation, and pallor of substantia nigra and locus coeruleus; phospho-tau in widespread regions including white matter, with prominent neuronal loss, gliosis of cortex, and hippocampal sclerosis. These stages build on one another, carrying on the symptoms and pathologies from the previous stage (34).

Traumatic brain injury (TBI) can result in intracranial hemorrhage, which may lead to brain herniation across dural or skull-defined compartments. Because increased intracranial pressure can often lead to deterioration and death, herniation of the brain will be considered before other types of injuries are addressed (36). Based on the Glasgow Coma Scale (GCS), which measures the level of consciousness in a person, TBI severity ranges from a scale of zero (most severe) to 13 (minor) (37, 38). In the absence of hypoxic-ischemic injury, children with traumatic brain injury and Glasgow Coma Scale scores of 3 to 5 can recover independent function (39). In some circumstances, some individuals with CTE neuropathology show no symptoms or clinical indicators that correlate with TBI (40).

Pediatric TBI occurs mostly in adolescents and young adults, followed by a secondary peak in infancy. Motor vehicle accidents, assault, and concussions in lieu of contact during sports are the most frequent causes for head injuries in children. Children are most susceptible to falls at age 5 and under, and infants are vulnerable to abusive head trauma (AHT) which causes severe TBI. TBI is two times more frequently found in boys than in girls, with a period of distinction between the childhood and adolescent years (41). One of the main contact sports played by children that may later result in the development of CTE is rugby. It has been demonstrated that children who participate in rugby have an increased risk of concussion, which may consequently result in serious impairments later in adulthood (42). The benefits of physical activity do not outweigh the costs when it comes to childhood

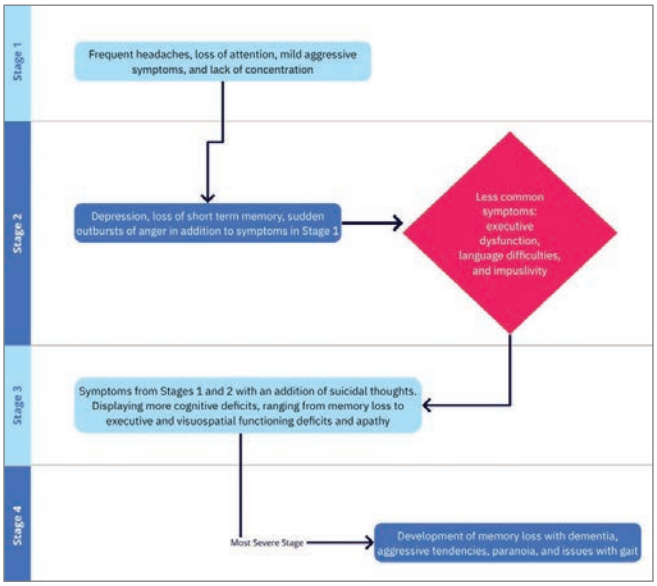

Figure 1. This figure shows the progression and development of symptoms of CTE.

brain trauma and injuries. The long-term effects are not worth the risks when it comes to the health of young children and adolescents (43).

Based on the ongoing CTE research, current results demonstrate that there are no significant differences in the neuro pathological and clinical outcomes in all contact sports. However, does one have an increased chance of developing CTE depending on the position played in collision sports? Although unknown for all positions in collision sports, there needs to be more systematic research about all the possible contact sports in the world in order to further evaluate and understand this hypothesis. It is also unknown if the duration of time in recovery after a collision has an effect in the development of CTE. A larger longitudinal study should be conducted amongst athletes that have encountered repetitive head injuries throughout their lifetime for future research. These findings will be informative to understand the specific collision injury variables that may influence CTE.

Clinical presentation: cognitive, motor, behavioral, psychiatric, neuroendocrine

Current data suggests that there are three possible domains that CTE symptoms fall under for clinical presentation: motor functioning, cognition, and behavior/mood (44). In stages I through IV, symptoms such as mood swings, suicidality, paranoia, dementia, memory loss, and cognitive impairment are observed (45). By stage IV, about 10% of patients develop a motor neuron disease that closely resembles amyotrophic lateral sclerosis (ALS) (46). Currently, there is no distinct clinical diagnostic criteria for CTE, as symptoms are varied and not yet agreed upon (47, 48). The current symptoms of CTE that have been supported by literature consist of anxiety, anger, depression, headaches, suicidality, anger management problems, dysarthric speech, mild cognitive impairment, ataxia, Parkinsonism, and dementia (49). Furthermore, some people that do not exhibit any clinical features of CTE have still been diagnosed with the disease based solely on neuropathology (49, 50). There are reportedly four stages of CTE (45). Typically, the onset and advancement of the disease is slow and usually occurs 8 to 10 years after the first concussions (51). There is still much uncertainty regarding the causality of CTE (52, 53).

Multiple studies on CTE research utilize recall of clinical symptoms from the deceased patient's close family and friends. Moreover, the disease can only be positively diagnosed postmortem (46). For example, the high-profile case of retired NFL player, Junior Seau, whose family donated his brain to the National Institutes of Health (NIH) after his suicide, was affirmatively diagnosed with CTE postmortem (54, 55). Observed in multiple cases of individuals suffering from CTE is a cavum septum pellucidum (56). Additionally, reported findings associated with this condition include volume loss in the cerebellum and hippocampus (56). Furthermore, amygdala atrophy is compatible with suicidal ideation (56). One study of a 39-year-old man and retired NFL player observed white matter damage and loss of brain volume (as shown in Figure 2) in deep gray matter structures utilizing diffusion tensor imaging (57). Severe CTE has been linked to impulsivity, anxiety, depressive symptoms, and explosivity, which are associated with prefrontal cortex, amygdala, and locus coeruleus regions of the brain (58). CTE often clinically presents indistinctly but is often distinguished by two apparent phenotypes: affective changes and cognitive impairment (59). Genetics have not been linked to any clear risk factors (59). TBI impairs cognitive control, which is the capability to manage actions and achieve goals (60). TBI can impact individuals in early childhood and can be evaluated using the Physical and Neurological Examination of Subtle Signs (PANESS), which examine subtle motor signs, utilizing MRI to measure total cerebral/motor/premotor volume (61). In addition to the clinical symptoms of CTE, the phosphorylation of tau and Aβ pathologies is also identified in Alzheimer's disease (62, 63). Our understanding of CTE is still developing and many important questions remain unanswered. The causality of CTE is still not fully understood; is it a result of repetitive blows to the head or concussions or a combination? Diagnosing CTE postmortem does not allow for true intervention or prevention of the disease. Future studies should explore the effects of genetics, comorbidities, and lifestyle factors. Thus, there is room for further studies to be conducted.

CTE and association with dementia/Alzheimer's disease

CTE is often correlated with Alzheimer's disease due to similarities in their pathologies and cellular mechanisms, and PET imaging (64, 65, 66). Although it is unclear whether CTE is progressive or solely linked to repetitive head trauma, scientists can agree that a key player in both CTE and Alzheimer's disease is tau (67). Tau is a protein in neurons that is encoded by a single gene on chromosome 17. As a result of alternative splicing, Tau can have six different isoforms that aid in stabilizing microtubules (64, 68). Tau proteins can precipitate into aggregates which can result in diverse neurofibrillary tangles (69). Upon aggregation in the central nervous system, Tau prions can cause tauopathies such as Alzheimer's disease and CTE (71, 72). This happens in mice with repeated head trauma and causes severe frontal brain injury to humans (73, 74). This aggregation is caused by the level of phosphorylation of tau. Hyperphosphorylation of tau catalyzes microtubule detachment, the inhibition of axonal transport between the soma and synapse which subsequently results in neurodegeneration (71, 72).

Various analyses have demonstrated this neurodegeneration may be linked to abnormal phosphorylation in the sulci and peri-vascular

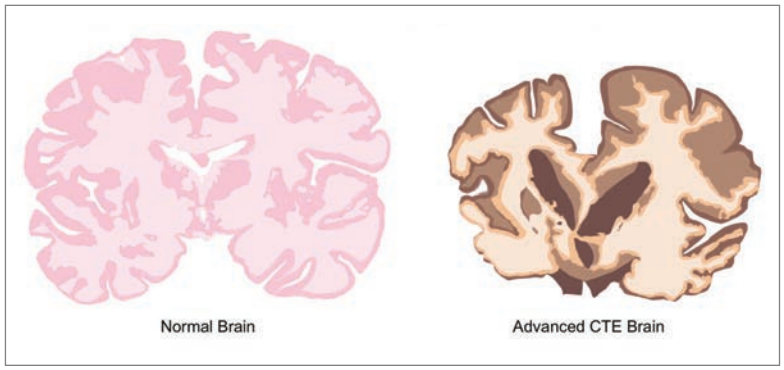

Figure 2. This figure shows the difference between a normal brain and an advanced CTE brain. A decrease in brain volume is demonstrated.

regions, microgliosis, and astrocytosis (75, 76). Other studies specifically looked at the neuropathological changes in the cortical degeneration of CTE and Alzheimer's disease patients, and results indicated that tau pathologies in CTE and Alzheimer's were more prevalent in the upper cortex in both disorders (70, 79). However, the neurodegeneration mechanism remains undiscovered (80). Additionally, the tau proteins were found to be more widely distributed in Alzheimer's disease, which suggested that in the later stages of CTE, patients may develop Alzheimer's disease (76). Although there is agreement on where the tau protein aggregates, there is still some debate about whether this may be surrounding the blood vessel or containing a blood vessel (66).

Another investigation focused on identifying whether patients with CTE and dementia have distinct clinical features when compared to patients with Alzheimer's disease (81). In this study, the researchers performed neurological examinations, neuropsychological testing, and emotional/behavioral testing. After testing, it was found that CTE's clinical presentation was not significantly different from Alzheimer's disease. Additionally, neurocognitive impairments and neurobehavioral symptom differences were not significant (81). These findings implied that the neuropathologic processes between Alzheimer's disease and CTE may be associated (81). An additional study confirmed a correlation between these diseases' neuropathologic processes through postmortem analyses, which demonstrated white matter with oligodendrogenesis in both CTE and Alzheimer's disease patients (82). However, this study indicated that even with the similarities between the two diseases, it is still unclear how the severity of these neuropathologic processes play a role in triggering unfavorable behavioral outcomes (82).

Some studies have suggested that neuroinflammation may drive the onset of tau phosphorylation, which consequently may lead to neuronal loss and synaptic dysfunction (83, 84). Because there is a long latency period between a history of TBI and the later onset of dementia symptoms, there may be a possibility of intervention in the early stages of CTE and Alzheimer's disease (83, 84). One approach is the use of non-steroidal anti-inflammatory drugs (NSAIDs) and anti-inflammatory minocycline. The latter has been shown to reduce tau phosphorylation in serine residues in mice, reduce astrocytosis, and pro-inflammatory cytokines (83). Additionally, researchers believe NSAIDs may be able to modulate γ-secretase, which may decrease Aβ production, which may help in Alzheimer's disease and traumatic brain injuries (83). Some investigators have analyzed targeted gene profiling in which downregulation of microtubule associated proteins may help with CTE pathology (80). All treatments are promising, but further research is needed into these new developments (83).

As indicated by these studies, the pathological processes of CTE are still very unclear. Although some treatments have been suggested through mice studies, there is currently no definitive way of preventing CTE. Additionally, there is controversy with regards to the similarities between Alzheimer's and CTE's clinical and pathological features which demands further research into this topic. Further research may be limited due to the inability to diagnose pre-mortem; therefore, it may be of importance to focus research on distinct clinical symptoms and pre-mortem diagnosis. Possible imaging technologies may be able to help with analysis of neural changes while patients may still be alive.

Examining CTE genetics in contact sports through imaging technology

CTE has various potential genetic distinctions. A variant in the TMEM106B gene is associated as a potential risk for developing CTE (84). Quantitative proteomics is a process used to identify certain proteins, such as high levels of tau, in CTE brain tissues (85). The expression of another gene, claudin-5, observed in areas of high levels of phosphorylated tau suggests that CTE may also cause blood-brain barrier dysfunction (86). A study that utilized brain tissue of military veterans from the Department of Veterans Affairs Biorepository Brain Bank (VABBB) found that the regions of the brain most affected by hyperphosphorylation of tau were the middle frontal gyrus, superior temporal gyrus, inferior parietal lobule, and hippocampus (87).

Another study compared the positron emission tomography (PET) with 2-(1-{6-[(2-[F-18] fluoroethyl) (methyl)amino]-2-naphthyl} ethylidene)malononitrile (FDDNP) that detects brain patterns of tau neuropathology distribution via β-pleated sheet conformation (88, 89). Results showed that military veterans have similar brain-binding compared to retired football players. Identifying CTE patterns in living brains with methods such as FDDNP-PET is giving researchers hope for a cure in the future (90).

Ultimately, there are not many CTE studies that have female participants. This could continue to limit our understanding of CTE, thus prolonging the discovery of a cure. It must be addressed that one possibility for less female participation in such studies could be due to less female enrollment in contact sports compared to males. However, comparisons of CTE diagnosis between female and male participants of activities with repetitive head injuries should also be explored due to gonadal hormone levels affecting female and male brain structures and function differently, especially in response to trauma (91).

Conclusion

The purpose of this paper was to explore the history, current science, and limitations behind CTE, its association with Alzheimer's, dementia, and other diseases, and future CTE diagnosis developments. There are currently no standard guidelines for diagnosing CTE. Identifying CTE symptoms in patients premortem rely heavily on self-reporting which runs the risk of misdiagnosing patients with CTE (92). Factors such as standard aging, retirement lifestyle, substance abuse, sleep patterns, demographics, and surgical procedures should be considered before prematurely diagnosing patients with CTE (93). Male patients with a history of depression can exhibit clinical symptoms of CTE (94). Additionally, male patients with anger control problems could also be misdiagnosed with CTE if they have a history of repetitive head trauma (95). As previously mentioned, there is currently no cure for CTE, however, pharmacologic and nonpharmacologic interventions are available to treat symptoms of CTE. Medications like selective serotonin reuptake inhibitors or SSRIs, can help improve cognitive function (96). Cholinesterase inhibitors and antipsychotics can also be used to treat CTE symptoms. Nonpharmacologic treatments include living a healthy lifestyle by getting proper sleep, having a healthy diet, and getting

physical activity (96). Research has shown that the younger the person is exposed to contact sports, the earlier neurobehavioral symptoms are reported (97). In other words, the longer the participation in such activities, the greater the severity of CTE (98). Studies have evaluated the changes in white brain matter in ages 8- to 13-year-old tackle football players, and results suggest that children who play tackle football begin to see a decrease in neurodevelopment (99). This reduced density of white brain matter has been associated with dementia (100). Further research is needed to confirm that younger football players are at higher risk for developing CTE later in life. As more studies are conducted and technology advances to allow brain tissue diagnosis premortem, a cure for chronic traumatic encephalopathy may arise.

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