An Overview - Chronic traumatic encephalopathy (CTE)

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Abstract:
Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative disease thought to be caused, at least in part, by repetitive brain trauma, including concussive and subconcussive injuries. It is thought to result in executive dysfunction, memory impairment, depression and suicidality, apathy, poor impulse control, and eventually dementia. Beyond repetitive brain trauma, the risk factors for CTE remain unknown. CTE is neuropathologically characterized by aggregation and accumulation of hyperphosphorylated tau and TDP-43. Recent postmortem findings indicate that CTE may affect a broader population than was initially conceptualized, particularly contact sport athletes and those with a history of military combat. Given the large population that could potentially be affected, CTE may represent an important issue in public health. Although there has been greater public awareness brought to the condition in recent years, there are still many research questions that remain. Thus far, CTE can only be diagnosed post-mortem. Current research efforts are focused on the creation of clinical diagnostic criteria, finding objective biomarkers for CTE, and understanding the additional risk factors and underlying mechanism that causes the disease. This review examines research to date and suggests future directions worthy of exploration.

Keywords: Chronic traumatic encephalopathy. Traumatic brain injury. Dementia. Concussion. Tauopathy. Dementia pugilistica
Repeated concussions and injuries less serious than concussions ("sub-concussions") incurred during the play of contact sports over a long period can result in CTE. However, there is no solid proof that sub-concussions alone can cause the disease. Statistics do not support this theory either considering that the CDC found that it is speed position players that have a 33% higher risk of this disease. If sub-concussions alone were able to cause it, then it would be lineman, not speed position players who have the highest risk and prevalence. They can however do damage if they are piled on top of an unhealed concussion, but by themselves they are far too weak to produce damage. If they could, then the statistics would support the theory. In the case of blast injury, a single exposure to a blast and the subsequent violent movement of the head in the blast wind can cause the condition.¹¹

Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative disease thought to be caused, at least in part, by repetitive brain trauma that can occur during contact sport and military participation.² This trauma can include mild traumatic brain injury (mTBI), or concussions, as well as sub concussive injuries, that is, mild brain trauma that does not result in the readily observable signs and symptoms of a concussion.³⁻⁵ CTE is distinct from the acute sequelae of concussion or traumatic brain injury (TBI), and is not merely prolonged postconcussive syndrome (PCS).⁶ While post-concussive syndrome symptoms endure following an acute concussion without complete relief of symptoms of the initial injury, the symptoms of CTE typically do not present until years
after the trauma-producing activity, and the symptoms of initial injury, if any, have ended. CTE is pathologically distinct from other neurodegenerative diseases, including Alzheimer’s disease and Frontotemporal Lobar Degeneration[7, 2]. For almost a century, it has been known that repeated blows to the head are associated with cognitive and behavioral impairments later in life. One of the first publications on the topic was a 1928 paper by Martland who called the condition he observed in boxers, “punch drunk.” Martland hypothesized that the symptoms he observed resulted from the repeated blows to the head that these fighters took during their careers (1928). In 1937, Millspaugh outlined the disease marked by motor deficits and cognitive dysfunction under the name “dementia pugilistica,” as he too observed the disorder primarily in boxers. Corsellis and colleagues presented a 15 case series in 1973 that neuropathologically distinguished dementia pugilistica from other neurodegenerative disorders. Although the term Chronic Traumatic Encephalopathy (CTE) was first used in the literature in the 1960’s, the disease’s ability to affect a broader population beyond boxers was not fully recognized until more recently[2,8,9]. Since that time, CTE has been found in others with a history of repetitive concussions from sports (e.g., American football players, professional wrestlers, professional hockey players) and from other activities (e.g., a victim of physical abuse, an epileptic, a self-injurer, a circus clown who was repeatedly shot out of a cannon)[6,10,11,2,8,9,12,13,5]. Also, in recent years, our group at the Boston University Center for the Study of Traumatic Encephalopathy (CSTE) has found neuropathologically confirmed CTE in football players with no history of diagnosed or reported concussions (but who played positions, such as lineman, with the greatest exposure to repetitive hits to the head[14], suggesting that repetitive subconcussive trauma, not just symptomatic concussions, may also lead to the development of this neurodegenerative disease [32]. This paper will review research on CTE to date including its risk factors, clinical presentation, and neuropathology. In addition it will explore future directions for CTE research with a specific focus on methods that may be useful for in vivo diagnosis, including neuroimaging techniques.

Causes:
Researchers have found a link between repetitive head injuries and CTE. The head injury may involve:

- A blow or jolt to the head
- Severe jarring or shaking
- Abruptly coming to a stop

Over time, these injuries can lead to abnormal groups of tau proteins. These proteins can create tangled masses in the brain. The tangles can block normal brain function. Similar tangles are seen in people with Alzheimer’s disease.

Risk Factors

Having a history of head injuries puts you at risk for CTE later in life. People who may be at the highest risk include those who:

- Participate in contact sports, especially professional boxers, football players, hockey players, wrestlers, and soccer players
• Have been in combat military service
• Have been physically abused
• Have severe seizures

• Have a developmental disability and engage in self-abusive behavior (head banging)

**Early symptoms of chronic traumatic encephalopathy**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Cognitive</td>
<td>Memory Impairment</td>
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<td>Executive Dysfunction (e.g., problems with planning, organization, multi-tasking, judgment)</td>
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<td>Mood</td>
<td>Depression</td>
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<td>Apathy</td>
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<td>Irritability</td>
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<td>Suicidality</td>
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<td>Behavior</td>
<td>Impulse Control Problems (e.g., “short fuse,” “out of control”)</td>
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<td>Disinhibition</td>
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<td>Substance Abuse and Other Addictions</td>
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<td>Aggression and Increased Violence</td>
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**Neuropsychological and neuropsychiatric changes**

The cognitive and behavioral symptoms associated with CTE are reflective of the regions that have been pathologically determined to be most affected by CTE. As will be explained in further detail in the neuropathology section of this paper, the regions of the brain most severely damaged by CTE include the cerebral cortex and the medial structures of the limbic system (amygdala, mammillary bodies, hippocampus, etc.)[^3,^5]. The severity of the clinical manifestation progresses through the course of the disease as the neurodegeneration increases[^5]. The neuropsychological and neuropsychiatric changes associated with CTE can be classified into the categories of cognition, mood, and behavior. CTE presents with changes in each branch of this symptom triad and the severity of the symptoms appears to progress with the course of the disease. These symptoms generally begin years or decades after repeated brain trauma, when the neurodegeneration is severe enough to manifest clinical symptoms[^5]. The earliest neuropathological stages of CTE may present without clinical symptoms[^5]. Early cognitive symptoms primarily include learning and memory impairment as well as executive
dysfunction. Mood changes typically include depression, apathy, and irritability, as well as suicidality. The behavioral changes primarily include poor impulse control, with individuals described as having a “short fuse” or being “out of control.” Aggression and increased violence are often experienced. Disinhibition and problems with substance and other forms of abuse also occur. Later in the disease course, these cognitive, mood, and behavioral impairments worsen, with dementia evident in all older cases (i.e., 65 years or greater) with advanced stage CTE. As with most neurodegenerative causes of dementia, the later in the course a patient with CTE is seen, the more difficult it is to differentiate the specific underlying disease based on clinical presentation. That is, once an adequate amount of neural tissue is destroyed, differential diagnosis of most cases of moderate-severe dementia is difficult just based on current presentation. However, the early presentation and course of CTE can distinguish it from most other causes of dementia. The closest symptom profile to CTE is that caused by FTLD, behavioral variant. The symptoms of FTLD typically begin between the ages of 45–65, there is a somewhat rapid symptom progression, and there is a positive family history in approximately 40% of cases. In contrast, the early symptoms of CTE typically present between the ages of 30 and 50, there is a slow, prolonged course of progression, and there does not appear to be a familial risk. Although not a completely definitive method of distinguishing between CTE and FTLD behavioral variant, all cases of CTE will have had a history of exposure to repetitive brain trauma, whereas FTLD will not typically have such a history. It is important to note that although CTE is thought to result from repeated mTBI, it is separate from the acute PCS, and it is not the accumulation of immediate symptoms from multiple concussive or subconcussive events. PCS is not thought to directly cause CTE pathology. Given the noticeable overlap in symptomology between PCS and CTE and the fact that, in some cases, there may be overlap in the onset and expression of the two disorders, differentiating between the two can sometimes be difficult[5]. In a review of the world’s published case studies of neuropathologically confirmed CTE (the vast majority being boxers), McKee et al. noted that 63% (32 of 51) had memory loss (2009). Like AD, those with CTE appear to have anterograde amnesia, or difficulty remembering newly learned information[15]. This is consistent with the deterioration of the hippocampus and other medial temporal structures seen in cases of CTE. Further, individuals with CTE commonly have executive dysfunction[16]. Executive functions refer to a group of cognitive abilities responsible for goal-directed behaviors[17]; individuals with CTE often have impaired judgment, poor insight, and disinhibition[3]. This symptomatology seems to reflect the neuropathologic changes and atrophy of the frontal lobes described by McKee et al. in almost all CTE cases (2009). Mood and behavior changes are hallmark features of CTE[2,16]. As with changes from other neurodegenerative diseases, the mood and behavioral changes associated with CTE are often the most concerning to family members and caregivers[17].
manifestations are consistent with the neuropathologic changes in the medial temporal lobe (especially the amygdala) and orbitofrontal regions. The combination of altered emotional responses (including rage) from amygdala involvement and disinhibition and reduced impulse control from frontal involvement appears to lead to many of the more significant clinical manifestations of the disease, including suicidality.[6]

**Neurological and motor changes**
CTE often results in neurologic dysfunction, especially alterations in movement and motor coordination. These signs include difficulty with balance and gait (Parkinsonism) and speech changes (including slowed, slurred, and dysarthric speech).[2]. In a smaller portion of cases, there appears to be abnormalities in gaze.[2]. A small subset of individuals with CTE have a variant referred to as chronic traumatic encephalomyelopathy (CTEM) that also affects the spinal cord and is associated with motor neuron disease, clinically mimicking Amyotrophic Lateral Sclerosis (ALS), or Lou Gehrig’s disease.[18]. These individuals have a different and more severe neurologic profile including clinical evidence of motor neuron disease as marked by progressive muscle weakness and atrophy, fasciculations, balance and gait problems, dysphagia, and hyperactive deep tendon reflexes.[18].

**Neuropathological characteristics**
Neuropathological findings of CTE were first described by.[7]. McKee and colleagues at the CSTE reviewed the world’s literature of neuropathologically confirmed CTE and found 49 cases at the time (2009). These 49 cases, along with three new cases from the CSTE were described in 2009 by McKee et al. Since that time, the VA CSTE Brain Bank has grown from the original three to over 100 brains with over 60 cases of neuropathologically diagnosed CTE thus far (i.e., not all of the remaining 40 brains have had completed examinations to date), making it, by far, the largest CTE tissue repository in the world. The gross and microscopic neuropathology of CTE described below is based on the combination of the previous literature review and the findings from the VA CSTE Brain Bank.

**Gross pathological characteristics**
Advanced stages of CTE are accompanied by generalized atrophy of the brain with reduced brain weight, as well as atrophy of the frontal and temporal cortices and medial temporal lobe.[2]. There is often pronounced atrophy of the thalamus, hypothalamus, and mammillary bodies. Thinning of the corpus callosum and generalized atrophy of the cerebral subcortical white matter is common. Pallor of the substantia nigra and locus coeruleus is also a typical feature of advanced CTE. Dilation of the lateral and third ventricles, anterior cavum septum pellucidum, and posterior septal fenestrations are frequent findings.[2]. A cavum septum pellucidum occurs when the leaflets of the septum pellucidum are separated and the space is filled with cerebrospinal fluid.[19]. Repetitive concussive and subconcussive brain trauma likely produces a fluid wave within the ventricles that damages the septum pellucidum.[3,2].
Cavum septum pellucidum was found in 12 of 13 boxers studied by\[^7\].

**Microscopic neuropathological characteristics**

Microscopically, CTE is characterized by accumulation of phosphorylated tau protein as neurofibrillary tangles (NFTs), neurites, and glial tangles (GTs) throughout the frontal, insular, and temporal cortices; diencephalon; brainstem; cerebellar dentate nucleus and spinal cord. Figure 1 demonstrates phosphorylated tau deposition in CTE brains as compared to normal control.

![Image](image_url)

**Fig.1** Neuropathological analysis section. Coronal sections of a brain immunostained for hyperphosphorylated tau protein and counterstained with cresyl violet. The normal brain on the left shows no deposits of hyperphosphorylated tau protein. The brain on the right with CTE shows irregular tau deposits (dark brown discoloration) in the cerebral cortex. There are also dense tau NFTs in the amygdale (asterisk), entorhinal cortex and medial temporal lobe.

Accumulations of TAR DNA-Binding Protein 43 (TDP-43) as neuronal and glial inclusions, neurites and intranuclear inclusions are also found in CTE and are usually most prominent in cases with severe tau pathology. Prominent neuronal loss is seen in the hippocampus, entorhinal cortex, and amygdala as well as less severe degrees of neuronal loss in the subcallosal and insular cortex, olfactory bulbs, mammillary bodies, locus coeruleus, substantia nigra, medial thalamus and cerebral cortex\[^2\]. The tau-immunoreactive neurofibrillary pathology is characteristically irregular and affects primarily the superficial cortical layers with focal epicenters at the depths of the sulci and surrounding small blood vessels. Tau-immunoreactive NFTs may be particularly dense in the hippocampus, amygdala, entorhinal cortex and olfactory bulbs in advanced stages of the disease\[^3,2\]. Although the specific tau isoforms found in CTE are indistinguishable from AD\[^20\], the irregular nature of tau deposition and the perivascular clustering of tau-immunoreactive abnormalities at the depth of the sulci are unique to CTE and distinguish it from other tauopathies, including AD\[^21\]. In addition, the density of the NFTs and GTs is often far greater in CTE than in other tauopathies\[^3\]. TDP-43 immunoreactivity is most commonly seen in the frontal and medial temporal cortices, brainstem, diencephalon, insula, subcortical white matter, substantia nigra pars compacta, amygdala, hippocampus, caudate, putamen, thalamus, and hypothalamus\[^17,5\]. TDP-43 immunoreactive inclusions have been found throughout the anterior horn of the spinal cord and motor cortex in a subset of individuals with CTE\[^17,5\]. Aβ deposition is an inconsistent finding in CTE. While neuritic Aβ plaques are an essential feature of AD, Aβ is found in only 40–45 % of CTE cases\[^2\]. When Aβ is present in CTE,
it generally consists of primarily diffuse plaques with relatively few neuritic plaques\cite{2}. The presence of tau proteinopathy has been shown to enhance Aβ neurotoxicity\cite{21,22}.

**Diagnosis**
- CT scan
- MRI scan
- PET scan
- Blood tests
- Neuropsychological tests

**CT Scan of the Head**

Fig.1 At the present time, the only way to clearly diagnose CTE is for a doctor to examine the brain after a person has died. This is how researchers are learning more about CTE.

**Treatment**

Treatment for CTE is an area that is being studied. Depending on your symptoms, taking certain medicines (eg, antidepressants, antipsychotics, mood stabilizers)

- Making lifestyle changes, such as exercising regularly, eating a healthy diet, and avoiding alcohol and drugs
- Working with a therapist and joining a support group to help with the emotional challenges

You may be referred to a doctor who specializes in head injuries.

**Prevention**

When playing sports, you can reduce your risk of CTE by:
- Following your doctor’s instructions after suffering a concussion—This includes waiting to return to sports until your doctor says it is safe to do so.
- Avoiding dangerous game play
- Wearing proper protective equipment (such as helmets)

Other steps that you can take to reduce head injuries off the field include:
- Wear a helmet when doing any at-risk activity, like riding a motorcycle or bicycle, skiing, snowboarding.
- Wear a seatbelt in the car.
- Do not drink and drive or get into a vehicle with someone who is under the influence.
- Make your home safe (eg, remove items that you could easily trip over, install night lights).
- Get help right away if you are in an abusive relationship.

**Conclusion**

CTE is a progressive neurodegenerative disease linked to repetitive brain trauma from contact sports and other activities. The disease is distinct from post-concussive syndrome or the additive symptomatic effect
of multiple concussions. Rather, symptoms begin years or decades after brain trauma exposure and include a triad of cognitive, mood, and behavioral impairments. Neuropathologically distinct from other neurodegenerative diseases, CTE is characterized by hyperphosphorylated tau and TDP-43 deposition. As with other neurodegenerative diseases, such as AD, CTE can only be diagnosed postmortem at this time. However, unlike AD, CTE research is in its infancy, and there are neither published and validated clinical diagnostic criteria nor biomarkers for the disease. As such, there are many unanswered questions about the development of CTE. Although it is believed that repetitive brain trauma is associated with the neuropathogenesis of the disease, whether CTE can occur following a single traumatic brain injury in at-risk individuals is not yet known. The type, number, and severity of concussive and/or subconcussive hits necessary to trigger the neurodegenerative cascade leading to CTE has yet to be determined. Moreover, other factors, including duration of exposure to head trauma, age at first exposure, gender, age, race, and genetic predisposition, may play a role in the development of CTE, although further research is needed in these areas. Given its potential to impact a broad population of those who have experienced repetitive brain trauma, CTE is an important public health issue. A critical first step is the ability to diagnose CTE during life. Several neuroimaging techniques have the potential to serve as biomarkers for the disease.

Reference