A Critical Review of the Clinical Features of Chronic Traumatic Encephalopathy

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Summary

Chronic traumatic encephalopathy (CTE) has been described in the literature as a progressive neurodegenerative disease. The microscopic neuropathology described in recent cases of CTE includes: (i) localized neuronal and glial accumulations of phosphorylated tau involving perivascular areas of the cerebral cortex, sulcal depths, and with a preference for neurons within superficial cortical laminae; (ii) multifocal axonal varicosities involving deep cortex and subcortical white matter; (iii) variable and often absent beta-amyloid (Aβ) deposits [generally less than that encountered in Alzheimer’s disease (AD)]; and (iv) TDP-43-positive inclusions and neurites [1, 2]. Some of the described neuropathology may be encountered in other conditions, such as AD, frontotemporal dementia, progressive supranuclear palsy, and aging, but the distribution and localized nature of the p-tau lesions are considered unique and thought to set the tau pathology apart from aging, AD, or other tauopathies1. The clinical features of CTE have been described as chronic psychiatric problems, substance abuse, aggression, and cognitive impairment [1-4]. These clinical features, of course, are not unique to CTE. The described clinical features in recent cases are very similar to how depression manifests in middle-aged men and with frontotemporal dementia as the disease progresses. It has not been established that the described tau pathology, especially in small amounts, can cause complex changes in behavior such as depression, substance abuse, suicidality, personality changes, or cognitive impairment. Future studies will help determine the extent to which the neuropathology is causally related to the diverse clinical features.

1 New Consensus Criteria for the Neuropathology of CTE

The first NIH-supported consensus workshop relating to defining the neuropathological criteria for CTE occurred in Boston on February 26th and 27th of 2015. The initial findings from this consensus group were presented on the NINDS-NIH website as the “Report from the First NIH Consensus Conference to Define the Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy” (www.ninds.nih.gov/research/tbi/ReportFirstNIHConsensusConference.htm; Downloaded March 30, 2015). The neuropathology considered pathognomonic of CTE, and required for diagnosis, is abnormal accumulation of tau in neurons and glia in an irregular, focal, perivascular distribution and at the depths of cortical sulci. Many other neuropathological abnormalities were identified, especially in more severely affected brains, but those abnormalities were not considered unique to CTE.

The consensus group also defined “supportive criteria” for the neuropathological diagnosis of CTE, and noted that these criteria were more likely to be present in severely affected cases: “(i) macroscopic abnormalities such as abnormalities of the septum pellucidum (cavum, fenestration), disproportionate dilatation of the IIIrd ventricle or signs of previous brain injury; (ii) abnormal tau immunoreactive neuronal lesions affecting the neocortex predominantly in superficial layers 2 and 3 as opposed to layers 3 and 5 as in AD; (iii) abnormal tau (or silver-positive) neurofibrillary lesions in the hippocampus, especially in CA2 and CA4 regions, which differs from preferential involvement of CA1 and subiculum in AD; (iv) abnormal tau immunoreactive neuronal and astrocytic lesions in subcortical nuclei, including the mammillary bodies and other hypothalamic nuclei, amygdala, nucleus accumbens, thalamus, midbrain tegmentum and substantia nigra; and (v) tau immunoreactive in thorny astrocytes in subpial periventricular and perivascular locations.” The consensus group also defined, for the first time, neuropathological findings that should be considered exclusions to the primary diagnosis of CTE, as follows: “(i) CA1 predominant neurofibrillary degeneration in the hippocampus in association with amyloid plaques, as seen in AD; (ii) cerebellar dentate cell loss, prominent coiled bodies in oligodendroglia, and tufted astrocytes as seen in PSP; and (iii) severe involvement of striatum and pallidum with astrocytic plaques in cortical and subcortical structures as seen in CBD.”
Ten Things Clinicians Should Know About Chronic Traumatic Encephalopathy

1. Chronic traumatic encephalopathy (CTE) has been poorly understood for more than 80 years. As of the beginning of 2015, there are still no widely accepted and empirically-evaluated diagnostic criteria for either the neuropathology or the clinical features.

2. Originally called “Punch Drunk” [5], it was later called traumatic encephalopathy [6], dementia pugilistica [7], and chronic traumatic encephalopathy (CTE) [8]. Roberts [9] published a book entitled *Brain Damage in Boxers: A Study of the Prevalence of Traumatic Encephalopathy Among Ex-Professional Boxers*. This book provides detailed clinical information on a random sample of 224 retired professional boxers, 11% of whom were deemed to have mild CTE and 6% were considered to have a moderate-to-severe form of the syndrome. Roberts described what appeared to be two syndromes, one appeared static and one progressive.

3. A few years later, Corsellis and colleagues [10] made a large contribution to the literature by carefully describing the gross and microscopic neuropathology believed to be unique to dementia pugilistica in 15 boxers (e.g., neurofibrillary degeneration, neuronal loss, ‘scarring’ of the cerebellar tonsils, and cavum septum pellucidum and septal fenestrations).

4. Those studying and writing about CTE (a.k.a., dementia pugilistica), prior to 2005, struggled with whether it is a distinctly different neurological disease separate from other diseases such as Alzheimer’s disease, Parkinson’s disease, and the frontotemporal dementia.

5. CTE was thought to be found almost entirely in boxers prior to 2005. There were isolated case reports of dementia pugilistica in people who were not boxers, including a battered woman in 1990. Omalu and colleagues reported the first case of a retired National Football League (NFL) player in 2005, and the second case in 2006. There has been a fairly dramatic evolution of both the neuropathology and clinical features of CTE in the past few years, especially as described in American football players. In the past, CTE was diagnosed in some retired boxers who presented with serious problems, such as neuropsychiatric symptoms and Parkinsonism, whereas at present it has been diagnosed in young athletes with no or mild symptoms [11].

6. In 2010, Omalu reported on another case of a former NFL football player. In this article, it was introduced for the first time that suicidality was a prominent clinical feature of CTE [4]. It had been introduced in the media, however, hundreds of times prior to the publication of this article. This conclusion appears to be based on the fact that two of the three cases examined by Omalu and colleagues completed suicide. In their published review of all known cases up to 2009, McKee and colleagues did not consider suicidality to be associated with, or a clinical feature of, CTE. It was not included in their extensive tables as a possible clinical feature or discussed as such in the article. In contrast, suicide is now widely cited in the literature as a clinical feature of CTE.

7. Suicide was not considered a clinical feature in the first 80 years of writing relating to CTE. At present, there are no published cross-sectional, epidemiological, or prospective studies showing a relation between contact sports, CTE, and risk of suicide. In a large-scale retrospective epidemiological study of retired NFL players that examined death rates associated with cardiovascular disease [12], it was noted that former NFL players were less likely to die by suicide than men in the general population (there were only nine reported cases of suicide between 1960 and 2007). Therefore, according to the only published epidemiological data to date, NFL players are at decreased risk, not increased risk, for completed suicide relative to the general population. In two recent reviews of the literature, it was concluded that there is insufficient scientific evidence to conclude that CTE is a risk factor for suicide [13, 14]. That said,
former NFL players might be at increased risk for depression [15, 16], and their rate of chronic pain and opioid use is high [17]. Depression is a well-established risk factor for suicide, but there is also evidence that patients with chronic pain are at increased risk for suicidal ideation [18] and for suicide [19]. Moreover, former NFL players with depression and chronic pain are much more likely to report life stress and financial difficulty than former players without depression [15]. Therefore, factors unrelated to CTE might place certain former athletes at increased risk for suicide.

There is a mature body of evidence suggesting that the causes of suicide are complex, multifactorial, and difficult to predict in individual cases. In general, the rate of suicide in civilians [20] and the military [21] has increased in recent years, and suicide is also a problem that affects athletes in non-contact sports, such as cricket, baseball, power lifting, and track and field throwing events [22-25]. Moreover, concern has been expressed about the rate of suicide in people from specific occupations, such as physicians [26, 27]. In adults from the general population over the age of 50, aggression [28], limited social connectedness [29], poor physical health [30], and depression [31] are associated with increased risk for suicide.

Future studies relating to suicidal ideation, suicide attempts, and completed suicide in former athletes—those with and without a history of repetitive neurotrauma—are needed to determine if repetitive neurotrauma can be added to the list of known risk factors for completed suicide. In addition, given the thousands of media stories relating to contact sports and CTE, it would be interesting to examine whether media coverage has had an adverse psychological effect on retired athletes, and whether repeated exposure to news stories elicits or reinforces suicidal ideation in some athletes.

8. In 2013, McKee and colleagues introduced four neuropathological stages of CTE [11]. For the first time, they reported that CTE could be diagnosed in someone who has no clinical symptoms. Stage 1 CTE can be diagnosed based on having small focal epicenters of p-tau and no clinical symptoms, or symptoms such as headaches and mild depression. This represented a fundamental change in that now a person can be said to have a degenerative neurological disease in the absence of serious physical, cognitive, behavioral, or psychological problems.

9. In 2014, Montenigro and colleagues proposed a new syndrome called Traumatic Encephalopathy Syndrome [32]. This syndrome is extraordinarily broad in scope, encompassing people with depression and those with late-stage dementia. For example, if a person played high school and collegiate sports (for at least 2 years at the college level) and had current problems with depression, anxiety, and headaches, that person would meet criteria for the new Traumatic Encephalopathy Syndrome.

10. Many men identified as having CTE had depression or chronic depression prior to their deaths. CTE researchers have written that the depression was a clinical feature of CTE, implying that it was caused by the tau pathology or other aspects of the neuropathology attributed to CTE. It is essential, however, to appreciate that the causes of depression are diverse and that depression is not uncommon across an adult man’s lifespan. The extent to which the neuropathology attributed to CTE, especially in small amounts, can cause depression de novo or worsen existing depression is currently unknown. It is known, however, that men with depression show the full spectrum of symptoms and problems that have been proposed to represent early-stage CTE clinical features [33-44], so many men with depression, and no history of repetitive neurotrauma, would appear symptomatically to have CTE (if there were established clinical diagnostic criteria for the condition). As illustrated below, depression represents the single most challenging diagnostic and differential diagnostic condition for early stage CTE.

In general, depression is believed to arise from the cumulative impact [45-47] of genetics [48-51], adverse events in childhood [52-55], and ongoing life stressors [56-59]. In addition, people with a variety
of health problems and medical conditions, such as chronic pain [60-63], diabetes [64-66], cardiovascular and cerebrovascular disease [67-71], hypothyroidism [72], low testosterone [73-75], obesity [76], traumatic brain injuries of all severities [77-82], small vessel ischemic disease [83], Parkinson’s disease [84], and Alzheimer’s disease [85] are at increased risk for having depression. Anxiety problems (especially posttraumatic stress disorder [86-89], chronic pain [61, 90-93], and chronic insomnia [94] are all bidirectionally-associated with depression. Chronic headaches are also associated with depression [95-98].

Some of the clinical features of CTE reported in the recent literature are also core diagnostic features of depression, such as sadness, hopelessness, suicidality, and cognitive difficulties. Subjectively-experienced problems with concentration, memory, problem solving, and thinking skills are a cardinal diagnostic feature of major depressive disorder [99]. Cognitive problems associated with depression are likely to significantly impair daily functioning, particularly functioning at work [100]. In a study of outpatients with depression who were employed (N=164), 96% endorsed difficulty with concentration and 93% reported problems with memory; these cognitive symptoms were perceived by 52% of patients to be significantly interfering with their occupational functioning [101].

Interestingly, authors of several lay and academic books suggest that men who are depressed engage in behaviors that are similar to some of the other clinical features of CTE, such as being irritable, angry, and aggressive—as well as engaging in risky behaviors involving sex, alcohol, drugs, and gambling [e.g., 102, 103]. Researchers have also reported that anger [33] and irritability [34, 35] are associated with depression. Winkler and colleagues reported that men with depression scored significantly higher on a measure of irritability, they were more likely to overreact to minor annoyances and have anger attacks, they had lower impulse control, and they were more likely to abuse alcohol and drugs than women with depression [36]. Based on an analysis of the National Comorbidity Survey Replication, Martin and colleagues noted that men reported higher rates of anger attacks/aggression, substance abuse, and risk taking compared with women [37]. Men who engage in domestic violence often have PTSD and/or depression [40-42]. The Diagnostic and Statistical Manual of Mental Disorders-5th Edition notes that many people with depression have considerable problems with irritability (e.g., persistent anger, a tendency to respond to events with angry outbursts or blaming others, and an exaggerated sense of frustration over minor matters), and family members often notice social withdrawal or neglect of pleasurable recreational activities. In a recent large study involving sex differences in depression [104], factors related to depression in men were conduct disorder, drug abuse, childhood sexual abuse, prior history of depression, and stressful life events occurring in the past year (e.g., financial, employment, and legal).

Conclusions

CTE was originally described in boxers. The description of CTE has been expanded to include post-mortem case studies of young athletes, retired athletes, military service members, and veterans. It has been asserted unequivocally that there is focally and regionally unique neuropathology caused by neurotrauma (single or repetitive), and this neuropathology, even in small amounts, causes complex changes in behavior and cognition such as depression, anger dyscontrol, suicidality, and mild cognitive impairment [1, 11, 105-110]. As of 2013, there are now many documented cases of focal and regionally specific tau deposition. However, the mechanisms by which this tau deposition might drive or reflect progressive neurodegeneration or specific clinical features are unclear.

There is an enormous and mature scientific literature on numerous biopsychosocial causes for mental health and cognitive problems in men in the general population. Therefore, there are important expanded and alternative hypotheses to consider. First, repetitive neurotrauma might be associated with reductions in
cerebral reserve resulting in the person being more vulnerable to an earlier expression of late-life neurodegenerative disorders [111-113]. Second, small amounts of tau pathology in specific locations (e.g., depths of sulci or perivascular) might be clinically silent, and people have mental health and cognitive problems that are due to other multifactorial causes similar to what is seen in the general population of adults. Finally, the tau pathology reported to be unique to CTE contributes in a small but meaningful way to the development of mental health problems, personality changes, and/or cognitive difficulties. All three alternative hypotheses might be partially correct, are worthy of study, and have major clinical and societal implications.

Therefore, when we consider the plight of former athletes, civilians, and veterans who present for clinical services with depression or evidence of dementia, it is important to be cautious and circumspect in discussing the possibility that they might have this disease. At present, there are no nationally or internationally agreed upon clinical diagnostic criteria for CTE. Moreover, many of the case studies that have undergone detailed neuropathological examination at autopsy show macroscopic and microscopic pathology consistent with pre-clinical Alzheimer’s disease, frontotemporal dementia, Lewy body disease, cerebrovascular disease, and other neurological conditions—and some of these cases have met full neuropathological criteria for one of those diseases. A tremendous amount of research is needed to better understand if at some point in the natural history there is a unique and reliable relationship between tau pathology and specific clinical symptoms—especially depression and suicidality.

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