Does a Unique Neuropsychiatric Profile Currently Exist for Chronic Traumatic Encephalopathy?

Faith M. Hanlon, PhD[1]; Christopher A. McGrew, MD, FACSM[2,3]; and Andrew R. Mayer, PhD[1,4,5]

Abstract

There is evidence that repetitive mild traumatic brain injury leads to specific patterns of neuropathological findings, labeled chronic traumatic encephalopathy (CTE). However, questions remain about whether these neuropathological changes produce changes in behavior, cognition, and emotional status that are associated with a *unique* neuropsychiatric profile that can be assessed using currently available clinical tools. Our review of the literature indicates that insufficient evidence currently exists to suggest a distinct neuropsychiatric profile for CTE. Major limitations to the field presently include the relatively nascent nature of the topic, reliance on retrospective next-of-kin reporting, the lack of prospective studies, and similarities in neuropsychiatric symptoms between CTE, other neurodegenerative disorders and forms of psychopathology. Clinicians and researchers alike have a responsibility to adopt a cautious and balanced approach for antemortem assessments to minimize the potential unintended negative consequences of both overdiagnosing and underdiagnosing a clinical entity that has yet to be clearly established.

Introduction

Recently, there has been increasing public concern that mild traumatic brain injury (mTBI), especially when repetitive in nature, can lead to neurodegenerative changes, labeled chronic traumatic encephalopathy (CTE; for a review see 38). Similar to most neurodegenerative disorders, it is critical to note that CTE can only be definitively diagnosed at autopsy, with no specific in-life biomarkers currently available (37). Moreover, there is growing alarm that these specific histological changes may be associated with long-term neurobehavioral sequelae that manifest as a unique neuropsychiatric profile. Conversely, others have expressed skepticism that CTE represents a distinct clinical entity, suggesting the need for prospective studies with appropriate epidemiologic design involving case controls that can more causally link clinical symptoms (assessed in life) with pathological findings (23,45).

Our review focuses on the spectrum of neuropsychiatric symptoms that have been associated with CTE, as well as published CTE research and diagnostic clinical criteria. We also compare the proposed profile with other behavioral disorders, neurodegenerative diseases, and comorbidities to critically evaluate whether current published evidence supports the existence of a distinct neuropsychiatric profile for CTE. The determination of a unique neuropsychiatric profile has enormous clinical, research, and general health implications. Specifically, CTE has no known treatments and currently implies a uniformly poor prognosis. The potential dangers of premature clinical diagnoses are best illustrated by the suicide of a patient who incorrectly assumed they had CTE, as recently reported in the popular press (4). Importantly, this tragedy also needs to be balanced against premature conclusions that repetitive mTBI does not lead to any long-term neuropsychiatric changes (43) given the suffering that these symptoms cause for both the patient and their loved ones. The review begins with a brief historical summary of the development of CTE as a neurodegenerative disease to provide the necessary background for our fundamental question.

There have been several attempts to identify the neuropathological criteria (8,29), phenotypes (40), and stages (31) of CTE. Historically, mental alterations, emotional deterioration, and motor abnormalities displayed among some professional boxers was first labeled as "punch-drunk" (27) syndrome in the medical literature. Other early labels for this condition included "traumatic encephalopathy" (42) and "dementia pugilistica" (34). Bowman and Blau (3) appear to have been

[1]The Mind Research Network/Lovelace Biomedical and Environmental Research Institute, Albuquerque, NM; [2]Department of Family and Community Medicine, University of New Mexico School of Medicine, Albuquerque, NM; [3]Department of Orthopedics and Rehabilitation, Sports Medicine Division, University of New Mexico School of Medicine, Albuquerque, NM; [4]Departments of Neurology and Psychiatry, University of New Mexico School of Medicine, Albuquerque, NM; [5]Department of Psychology, University of New Mexico, Albuquerque, NM

Address for correspondence: Andrew R. Mayer, PhD, The Mind Research Network, Pete & Nancy Domenici Hall, 1101 Yale Blvd. NE, Albuquerque, NM 87106; E-mail: amayer@mrn.org.

the first to label childish behavior, depression, paranoia, aggression, poor orientation, insight, and short-term memory in a boxer as CTE of pugilists, with Critchley (9) later adopting the label of CTE to describe similar clinical phenomena in a series of case studies. Corsellis et al. (8) was the first to describe gross and microscopic neuropathology in 15 fighters, differentiating it from other neurodegenerative disorders and defining the syndrome with four major neuropathological criterion.

However, it was not until 2005, when Bennet Omalu reported hyperphosphorylated tau protein (p-tau) accumulation in the brain of a retired National Football League (NFL) player that CTE became more widely recognized (41). This increase in public awareness was primarily driven by the perception that the prevalence of CTE could be much greater than previously expected, rather than being limited to martial combatants. Omalu et al. (40) subsequently furthered his work to identify four phenotypes based on neuropathological features. In the largest study to date examining CTE neuropathology, McKee et al. (31) identified 68 (80.0% of sample) of 85 patients with a history of repetitive mTBI as having CTE. Moreover, 43 of 68 brains showed evidence of CTE only, whereas eight patients also exhibited motor neuron disease (MND), seven had Alzheimer's disease (AD), 11 had Lewy body disease, and four had frontotemporal degeneration (FTD). Based on these results, McKee and colleagues developed staging criteria that differentiated CTE from other tauopathies.

In a more recent study utilizing a brain bank for neurodegenerative disorders, the presence of CTE pathology was investigated in persons with and without a history of contact sports participation (2). There was no evidence of CTE in the 198 participants who did not report a history of contact sports, whereas 21 (31.8% of sample) of the 66 contact athletes exhibited signs of CTE. Finally, the provisional neuropathological criteria for CTE (30,31) were recently used to evaluate and diagnose 25 pathological cases that included other tauopathies by a blinded panel (29). The panel achieved very good agreement for the overall diagnosis of all tauopathies and even higher agreement for CTE, resulting in a consensus statement about neuropathological criteria necessary for a definitive diagnosis of CTE (29).

In summary, this brief review highlights the nascent nature of the field of CTE, with relatively few published reports before the start of 21st century compared to other neurodegenerative disorders. Although the neuropathological characterization of CTE represents the most advanced arm of the field, a definitive cause and effect relationship has yet to be established through prospective studies. Moreover, multiple biological, genetic, environmental and lifestyle factors likely contribute to the final disease profile (i.e., not all athletes with a history of repeated brain trauma will definitively develop CTE (19,45)). The neuropathological characterization of CTE is beyond the scope of the current review, and the interested reader is referred to other sources that discuss gross and microscopic pathologies currently associated with repetitive head trauma (8,24,26,31).

Clinical Symptoms

An examination of the purported clinical presentation of CTE (composed of physical, behavioral, emotional, and cognitive symptoms) is the focus of the current review. These clinical symptoms are typically not present immediately after head trauma, begin subtly, and exhibit a progressive, insidious deterioration (12). In an extensive review of the literature, Montenigro et al. (36) list the most common clinical features thought to be associated with the presentation of CTE. The first physical symptoms of CTE are typically headaches. In more advanced stages, a proportion of patients develop frank motor signs, such as parkinsonism, tremor, dysarthria, gait disturbance, coordination difficulties, masked facies, rigidity, muscle weakness, spasticity, clonus, and ataxia (31,36). Commonly reported mood features include depression, hopelessness, suicidality, anxiety, fearfulness, irritability, labile emotions, apathy, loss of interest, fatigue, flat affect, insomnia, mania, euphoria, mood swings, and prolix (36).

From a behavioral perspective, inhibitory deficits and aggressive tendencies are typically reported first, with other frontal-like symptoms emerging with disease progression. These include, but are not limited to, explosivity, loss of control, impulsivity, rage, physical and verbal violence, inappropriate and disinhibited speech, boastfulness, childish behavior, social inappropriateness and isolation, paranoid delusions, personality changes, and even psychosis (36). The term "general cognitive impairment" has been used in many studies to describe the progressive cognitive decline observed in patients with CTE, as well as AD (36). More specific cognitive deficits retrospectively reported in CTE cases include memory impairment (short-term and episodic, with eventual dementia), executive dysfunction, lack of insight, perseveration, impaired attention and concentration, language difficulties, dysgraphia, alogia, and visuospatial deficits (36,54).

Research conducted on the clinical symptomatology associated with post-mortem diagnosis of CTE has typically been based on retrospective reports from next-of-kin informants. This retrospective reporting approach has raised validity concerns in other settings (18), and some of the critical flaws associated with this methodology are reviewed in the sections that follow. In one retrospective study, Omalu et al. (40) interviewed next-of-kin and other family members regarding their recall of the clinical symptoms reported by deceased patients with postmortem diagnoses of CTE. Typically, recounted cognitive deficits included loss of memory, language, and executive functioning, which are common across other neurodegenerative conditions and behavioral disorders.

In another retrospective study, McKee et al. (31) outlined a progression of cognitive deficits hypothesized to be linked with the neuropathology observed at each of their suggested stages of CTE. Stage I clinical symptoms included headache, loss of attention and concentration, with a few patients also reporting short-term memory deficits, aggressive tendencies, and depression. Stage II symptoms additionally included mood swings, explosivity, and short-term memory loss. Stage III was also characterized by executive dysfunction and visuospatial difficulties, with 75% of the sample reporting cognitive impairment. Stage IV patients further suffered from language difficulties, paranoia, and gait difficulties, with all patients exhibiting severe memory loss with dementia.

Stern et al. (54) used the same four staging criteria to categorize 36 patients with neuropathological findings of

CTE from a brain bank without the use of case controls. Next-of-kin informants, blind to the neuropathologic findings, provided retrospective reports of the subjects' histories and clinical symptoms. Eleven of the patients were reported to have initial cognitive deficits (*i.e.*, episodic memory and executive function). Thirteen had initial behavioral symptoms (*i.e.*, explosivity, impulsivity, and violence), and nine had initial mood changes (*i.e.*, depression and hopelessness). The final three were reported to be asymptomatic. The patients with initial mood and behavioral symptoms had similar age of onset (34.5 ± 11.6 yr), death, and neuropathological stage (stages II and III), which differed from the group initially presenting with cognitive impairment (58.5 ± 17.7 yr old) at stages III and IV. Stern et al. (54) therefore suggested that their results were consistent with earlier studies of boxers (*e.g.*, 8) that reported two distinct clinical subtypes of CTE. The first subtype exhibits initial features of mood/behavioral symptoms at a younger age of onset, whereas the second exhibits initial features of cognitive impairment at an older age of onset. Most of the patients with mood and behavioral impairments developed cognitive impairments later in the disease course, possibly suggesting a chronology of symptom progression from early behavioral changes to cognitive decline when more pronounced neuropathological deficits occur.

More recently, several studies have used neuropsychological testing and advanced neuroimaging techniques to investigate cognitive functioning in living, retired NFL players (5,15,17,39,46). In a very large cohort of retired NFL players, 61% had at least one concussion and 24% sustained three or more concussions (15). Those with multiple concussions were more likely to suffer from mild cognitive impairment and memory problems. Hart et al. (17) examined retired NFL players as well, with most sustaining a prior concussion. They found cognitive deficits in 41% of the players, with cognitively impaired patients showing worse performance on tests of naming, word finding, and visual/verbal episodic memory compared to players with no cognitive deficits and normal controls. A subset had neuroimaging data, which was suggestive of both white matter and regional blood flow abnormalities in the cognitively impaired patients.

In another study examining retired NFL players, Casson et al. (5) reported cognitive impairments in a smaller subset of players (24%), with none of the retired players exhibiting frank dementia. Interestingly, they found mean fractional anisotropy (FA) measured with diffusion tensor imaging to be negatively associated with the number of concussions sustained in the NFL. Finally, Multani et al. (39) also examined retired professional football players from the Canadian Football League, all of whom had sustained multiple concussions. These players were found to have white-matter tract abnormalities and suffered from memory, executive functioning, language, and sensory deficits, along with behavioral changes, constitutional issues, and headaches. It is important to note that to date there are no available confirmatory autopsy evaluations for these studies.

Solomon et al. (51) reviewed outcomes across specific neuropsychological tests from some of the above literature (13 studies including NFL draft picks, active players, or retirees) with the goal of developing normative neurocognitive data. In contrast to the positive findings from individual studies, combining data across studies for individual neuropsychological tests showed similar scores to the general population norms for retired NFL players (51). The negative findings in the Solomon review could speak to the heterogeneity of symptom presentation or could be the result of a failure to control for such things as concussion history or exposure to subconcussive blows that the different NFL players sustained. For example, in a large sample of former high school and college football players, a cumulative head impact index predicted later-life cognitive impairment, executive dysfunction, depression, apathy, and behavioral dysregulation (35).

As a result of these studies, several clinical (21,22,48) and research (36,56) diagnostic criteria have been developed. For example, Montenigro et al. (36) proposed diagnostic research criteria for the clinical condition they term "traumatic encephalopathy syndrome" (TES) that may be associated with CTE, as well as other potential long-term effects of repetitive head impacts. These criteria include clinical features that were reported in at least 70% of the cases reviewed by Stern et al. (54). They propose five criterion to evaluate TES: 1) history of repetitive head trauma; 2) no other neurological disorder; 3) clinical features for at least 12 months; 4) alterations in at least one of the core clinical features (*i.e.*, cognitive, behavioral, or mood); and 5) at least two supportive features (*e.g.*, documented decline and delayed onset). They also identify four subtypes (TES behavioral/mood variant, TES cognitive variant, TES mixed variant, and TES dementia) and include a three-tiered classification system for underlying CTE (probable CTE, possible CTE, and unlikely CTE). Victoroff (56) also developed provisional research diagnostic criteria for assessing clinically probable traumatic encephalopathy (TE) and clinically possible TE based on clinical features that were reported in at least 7% of their reviewed published cases. These criteria were not intended to determine underlying CTE neuropathology.

Jordan (21,22) has proposed diagnostic criteria to evaluate the probability of underlying CTE neuropathology for clinical purposes, outlining four classifications: 1) definite CTE (diagnosed with pathological confirmation at autopsy); 2) probable CTE; 3) possible CTE; and 4) improbable CTE. Jordan's classification is based on a clinical evaluation that includes clinical history, physical and neurologic examination, neuroimaging, neuropsychological and laboratory testing. In contrast, Reams et al. (48) propose evolving criteria for a clinical diagnosis of TES which are not intended to be used to diagnose underlying CTE. They define CTE as the neuropathological tauopathy disease and TES as the clinical progressive neurodegenerative disease that may occur after repetitive head trauma. Based on their required features (cognitive decline for at least two yr, exclusion of any other neurologic disorder, history of repetitive head trauma, evidence of a delayed symptom onset that has a progressive course) and supportive features (emotional, behavioral, and motor disturbances), patients can be diagnosed with probable, possible, or unlikely TES. Given the evolving nature of CTE and TES research, the researchers indicate that these working criteria will be updated over time.

The Question of Differential Diagnosis

The previous section discussed the various lines of evidence, research, and diagnostic criteria that have been developed to describe a clinical syndrome associated with

CTE pathology and/or repetitive head trauma (21,22,36,48,56). Although research criteria are critical for the continued examination and understanding of CTE, it is important to ask whether such a neuropsychiatric profile can *currently* help identify CTE as a *unique* syndrome based on in-life clinical and neuropsychological evidence alone (*i.e.*, differential diagnosis). A neuropsychiatric profile can be defined as a specific grouping of cognitive, motor, and behavioral characteristics that reliably identifies a disorder. They serve important roles in research, clinical care, medicolegal assessment, and health education of the general population at large.

To date, no studies have causally linked clinical findings with neuropathology. Thus, the differential diagnosis of CTE based on clinical evidence alone is currently unvalidated. Randolph (45) concluded that the clinical symptoms associated with CTE are broad and common to a variety of neurological diseases. Therefore, Randolph suggests that it may be difficult to define a unique clinical syndrome associated with CTE. Randolph and colleagues also have questioned the neuropathological diagnosis of CTE on the basis of methodological flaws. Predominant critiques raised included that recently published evidence of CTE was primarily based on postmortem brain samples of convenience (donated by concerned family members), biased retrospective reports, inconsistent neuropathological findings, and lack of prospective, longitudinal and case-controlled studies (23). Some of these initial concerns have subsequently been addressed by the consensus study (29) and by replication studies in non–CTE-specific brain banks (2,49). However, questions about sample bias, individual differences, prevalence, and lack of prospective case controls remain.

There are several additional methodological and mechanistic reasons why it may be difficult to identify a unique neuropsychiatric profile for CTE relative to a unique neuropathological profile (29). Foremost, the majority of studies to date are based on retrospective interviews from other people or based on the clinical profiles of repetitively injured individuals (*e.g.*, retired collision sport athletes) who have not yet been diagnosed and may never develop CTE. Retrospective corroborative reports are biased not only by the informants' differing perspectives and memories of the patient, but also by the increased media attention that CTE has been receiving. Second, similar to other neurodegenerative disorders, the clinical disambiguation of disease states becomes more difficult as the disease progresses and symptoms worsen, suggesting that unique profiles may only be present earlier in disease onset. Third, it is possible that repetitive TBI may initiate a variety of differing protein abnormalities resulting in different neurodegenerative diseases (*e.g.*, CTE, AD, FTD, and Lewy body disease). Yet if they affect the same brain regions, then clinical symptoms would remain similar (31).

There are other risk factors that potentially interact with TBI as well, increasing the likelihood of clinical signs of dementia and potentially contributing to frank neuropathology. As previously noted, several nonspecific factors, such as normal aging, psychiatric illness, and opiate abuse have all been found to be associated with abnormal tau protein at autopsy (52). Several of these potentially confounding comorbidities may be more prevalent in populations with a high exposure to repetitive trauma either due to pain issues (*e.g.*, opiate abuse) or the linking of personality traits (an increased tendency for risk-taking activities). Biological sex (11), as well as the APOE-e4 genotype (7), also have been suggested to affect outcomes after brain injury. Thus, with no current methods for noninvasively tracking disease progression, researchers have justified caution when making the assumption of a causal relationship between repetitive head injury and a unique neuropsychiatric profile relative to other neurodegenerative conditions (6,23,28,32).

An alternative theory to CTE as a unique clinical disorder suggests that repetitive head injuries initiate a cascade of neurotoxic events that diminishes cerebral reserve, which in turn leads to an earlier clinical presentation of age-related neurodegenerative diseases (*e.g.*, AD, FTD, Parkinson's disease, or mild cognitive impairment) that are not distinct from CTE (25,46,47). For example, Randolph et al. (46) reported possible cognitive impairment in 35.1% of a relatively young sample of retired NFL players, which was similar to patients with a diagnosis of mild cognitive impairment due to AD. The authors concluded that the increased cognitive impairment in their retired NFL player sample may be caused by diminished cerebral reserve. Based on an extensive review, Lye and Shores (25) provide evidence for a strong connection between TBI and risk for developing AD, providing further evidence that TBI diminishes cerebral reserve, which in turn increases the risk of a dementia. Along these lines, in a large study investigating 188,764 U.S. veterans, those with a history of TBI at baseline had an increased likelihood (odds ratio, 1.6) for developing different types of dementia (AD, vascular dementia, FTD, Lewy Body disease, dementia not otherwise specified) over a 9-yr follow-up period relative to those with no history of TBI (1). Similarly, other studies suggest a potential link between TBI and an increased risk of Parkinson's disease (20).

From a methodological standpoint, it is critical to differentiate the effects of single or multiple isolated TBIs from the repetitive injuries that stereotypically occur during collision sports. Although it has been suggested that neurodegenerative changes may manifest even after a single TBI event (i.e. blast injury in military or simulated blast in lab animals; 14), a more prevalent view is that multiple injuries are necessary for development of progressive neurodegenerative changes. Several lines of evidence demonstrate that the extent of risk for dementia subsequent to TBI follows a dose-response curve model, with more severe injury and greater numbers of repetitive traumas leading to greater risk (50). The relevance of these risk factors increases if the repetitive head injuries occurred in close temporal proximity, occurred early in life, or occurred over an extended period of time (53,55,57). Thus, the populations thought by CTE researchers to be most at risk for CTE are those patients who were previously involved in high impact sports (*e.g.*, boxing, mixed-martial arts, American football, ice hockey, lacrosse) and potentially military personnel. In the Unites States, American football is associated with the highest number of TBIs and also is played by the most individuals (see 10, for frequency and rates of concussion for a variety of sports), rendering it an important consideration during differential diagnosis (2).

To date, there have been few studies that have tried to disambiguate TBI-induced dementias from non-TBI dementias in well-controlled studies. Some report that clinical

symptoms manifest earlier in CTE (~30 and 65 yr; 33) relative to AD (52), whereas others have not observed this difference (49). Similarly, it has been suggested that the clinical symptoms of CTE have a more gradual onset and prolonged progression relative to both AD and FTD (12,33). From a purely clinical perspective, it has been suggested that patients with mild AD typically do not exhibit the behavioral symptoms associated with CTE (33). Others note that disinhibition, inappropriateness, and apathy, which are common in the behavioral variant of FTD (44), are observed less frequently in CTE (54). In contrast, those with the behavioral variant of FTD do not exhibit the memory deficit that is common in CTE. Studies also have reported that dementia patients with a history of TBI more frequently report symptoms of depression, anxiety, irritability, and motor disturbances relative to patients without a TBI history, with memory loss a less prominent complaint at disease onset relative to patients with probable AD (49). Patients in later stages of CTE display signs of parkinsonism, which is atypical for AD but consistent with the classical clinical presentation of Lewy body dementia. However, several behavioral traits reported to be central to CTE (*e.g.*, explosivity and aggression) are not typically associated with Lewy Body dementia (16,33).

Finally, it also has been reported that different sports may produce diverse cognitive impairment profiles due to the type of impact (*i.e.*, hook punch in boxing vs. helmet-to-helmet contact in American football; (37)). For example, boxers may exhibit more prominent motor symptoms (parkinsonism, gait disturbances, and dysarthria) than American football players, possibly due to boxers having more pathology in their midbrain and cerebellum. Some researchers have even made a distinction between "classic CTE" (more prominent motor features) versus "modern CTE" (mood/behavioral symptoms, with progressive cognitive deficits; (13,28)). This distinction, however, could simply be an artifact of earlier retrospective studies focusing mostly on motor symptoms in boxers (38) and clearly requires additional study.

Conclusions

In summary, a critical review of the literature suggests that insufficient evidence currently exists to conclude that there is a unique neuropsychiatric profile associated with CTE. Major limitations to the field presently include the early reliance on retrospective next-of-kin reporting about clinical symptoms and the lack of data causally linking clinical symptoms with neuropathology at autopsy (*i.e.*, large, prospective studies). The currently proposed neuropsychiatric presentations of the CTE syndrome are quite similar to other known neurodegenerative disorders, as well as other forms of psychopathology. Notably, this last critique is not unique to CTE, but rather is shared across most neurodegenerative disorders, especially in the later stages of disease progression.

These critiques may be a result of the nascent nature of the field or could suggest that CTE is not a distinct clinical entity. Although CTE has been described in various forms for approximately a century, it has only received more widespread study within the last decade, especially for clinical features. We emphasize that ongoing research on the proposed clinical features of CTE is critical and should be actively pursued. However, given the current lack of evidence provided by high-quality prospective research studies, clinicians have a responsibility to adopt a cautious and balanced approach for antemortem *clinical* evaluations when considering the potential long-term neuropsychiatric effects of head trauma. This is especially true given the lack of any known treatments for CTE relative to evidence of efficacy for other treatable symptoms (*e.g.*, depression, irritability, etc.) that are not specific to CTE. We believe that a balanced and cautious approach will minimize the potential unintended negative consequences of both overdiagnosing and underdiagnosing a clinical entity which has yet to be clearly established.

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