Chronic Traumatic Encephalopathy

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Introduction

The effect of repetitive head trauma on athletes participating in contact sports has become a highly publicized and controversial topic. But, just how serious a risk concussive (and even subconcussive or asymptomatic) cerebral trauma is in the long-term relative to other risk factors facing professional athletes remains uncertain. Media reports on the "concussion epidemic" and the potential link between repetitive brain injury and long-term cognitive and emotional problems in the brains of former athletes from contact sports have certainly generated much public fear and anxiety on the topic.

Although the concept of dementia resulting from sports competition might be thought provoking, the public fear on this topic has *far* outpaced the scientific evidence supporting its existence and the scope of its occurrence. To the best of our knowledge, the data supporting the presence of brain disorders resulting from contact sports participation has been based thus far on reports from a skewed sample of athletes in the absence of any reliable or objective means to diagnose the condition or any population-based parameters to determine its prevalence or incidence. To date, there is no proven mechanism for its cause.

The term chronic traumatic encephalopathy (CTE) is currently used widely to describe a condition that is alleged to be a specific form of tauopathy resulting from repetitive brain injury that purportedly leads to a distinct clinical profile of cognitive, behavioral, and motor symptoms. It is claimed that these symptoms are ultimately caused by a form of neuropathology that is distinct from what is encountered in other more common forms of neurodegenerative disease, such as Alzheimer's (AD) or Parkinson's disease (PD) [1].

While forms of dementia have been described in relation to participation in combative sports, such as boxing, for nearly 100 years, the type of dementia that is most publicized today has been extended to include participants from professional American football, ice hockey, wrestlers, and soccer players and even nonathletes (e.g., a circus clown, a self-injurer, and a patient with epilepsy) [2]. It has also been associated with cerebral trauma from blast exposure in soldiers [3]. The condition currently characterized as CTE is believed by its proponents to be progressive and incurable with associations to both aggressive and suicidal behaviors, extending to what might amount to as a public health crisis.

This chapter provides a critical review of the evidence-based literature examining the risks of

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repetitive brain injury on the cognitive and mental health outcome of professional athletes, with a particular focus on studies of American football. The topic is clearly one that remains provocative, confusing, and disturbing. As with the non-sports arena, research regarding the association between concussion and the likelihood of developing late-life cognitive and psychiatric conditions is beset by numerous methodological problems, including reliance on retrospective report of injury characteristics by the athlete or others, failure to control for confounding variables, and a tendency to generalize from the literature involving *moderate to severe* traumatic brain injuries (TBI) to those with *mild* traumatic brain injuries (MTBI) or concussion. The goal is to highlight the numerous methodological issues besetting the research on CTE while making recommendations for future studies.

Dementia Pugilistica

For over a century, it has been believed that repetitive blows to the head sustained in sport are linked with cognitive and behavioral impairments occurring later in life. One of the first formal scientific descriptions of this topic was provided in a 1928 paper by Martland, a New Jersey pathologist and medical examiner, who reported a cluster of characteristic signs and symptoms, including confusion, bradykinesia, tremors, and gait disturbance, which were hypothesized to have followed repetitive boxing-induced TBI, a condition that he termed "punch drunk" [4, 5].

In 1937, Millspaugh coined the more formal term *dementia pugilistica* (DP) to describe a disease marked by motor deficits and cognitive dysfunction observed primarily in boxers [6]. By the 1970s, a sufficient number of boxers believed to have DP had been studied pathologically, leading to the popular belief that this form of neurodegeneration was similar to, but distinguishable from, other causes of neurodegenerative disease, like AD.

Symptoms of DP were reported to manifest long after (anywhere from 7 to 35 years) the start of a boxer's career [7, 8]. In terms of its incidence, the condition was initially observed in 17% of retired professional boxers. Risk factors included retirement after age 28, participation in boxing for more than 10 years, fighting in more than 150 bouts, and greater sparring exposure. Additionally, the probability of developing DP is believed to be increased for boxers with a history of technical knockout or knockout [9], in "sluggers" rather than more "stylish boxers" [10], and in those with the *APOE* e4 allele [11]. The risk of DP in amateur boxers is noted to be substantially lower than those participating in the sport on a professional basis [12].

The defining neuropathological features of DP, as later described by Corsellis and colleagues [13], included (a) abnormalities (cavum, fenestrations) of the septum pellucidum (a thin, triangular, vertical membrane separating the anterior horns of the left and right lateral ventricles); (b) scarring on the inferior surface of the lateral cerebellar lobes (primarily in the tonsillar region), with loss of Purkinje cells in these areas; (c) degeneration of the substantia nigra with loss of pigmentation, neurofibrillary changes, and the absence of Lewy bodies; and (d) diffuse neurofibrillary tangles in the cerebral cortex (primarily medial temporal) and brain stem, with very few, if any, senile plaques. It was from this study that Corsellis and his colleagues concluded that DP pathology was generally similar to AD but because plaques were not observed in all cases (seen in 11/15 cases) that DP likely represented a *unique* form of pathology.

Neuropathological examination of the brains of former boxers with DP has also resulted in different findings over the years. In a review study of 11,173 boxers, McCown indicated that he did not find a single case of "punch drunk syndrome" [14]. While he did not dismiss the possibility that boxing can potentially injure the brain, he did not support the idea that there was a *distinct* neurological syndrome unique to former boxers. In a more idiopathic view of the condition, he believed that the clinical changes observed in former boxers were likely due more to factors inherent in the person rather than in the occupation itself.

Evolution of Modern Day CTE

CTE is essentially the newest term used to describe DP, popularized largely by the efforts of two groups of investigators. Dr. Bennett Omalu, a Nigerian-born neuropathologist, is often cited as the first to identify CTE pathology in an athlete retired from the National Football League (NFL). The second group includes members of the Boston Center for the Study of Traumatic Encephalopathy (BU CTSE), led by Dr. Ann McKee, a neuropathologist who has made many highly publicized proclamations on the clinical characteristics of CTE based on select postmortem case reports or studies from small samples of brain specimens obtained from autopsies of retired athletes.

Formal inquiry into the relationship between head injury and late-life changes in mood and cognition actually began with a series of questionnaire studies performed by Guskiewicz and colleagues [15]. This group analyzed data regarding memory changes from a general health questionnaire sent to 3729 retired professional NFL players in 2001. Based on the retirees' responses, it was found that those players with three or more concussions were five times as likely to have a clinical diagnosis of mild cognitive impairment (MCI) and three times as likely to have more significant memory problems as compared to retirees without a history of concussion. A trend toward earlier onset of AD was also noted along with observations of a higher disease prevalence in younger cohorts, relative to the general population. Although compelling, these data were limited by design as a cross-sectional retrospective self-report study [15].

As stated, Omalu and his colleagues, performing neuropathological studies on autopsy material, described the first cases of CTE in retired NFL players in 2005 and 2006 [16, 17]. Medical history in the first two patients included symptoms of cognitive impairment, mood disorder, and Parkinsonism after retirement. There was no family history of AD noted or other head trauma incurred outside of football. In the first case, a neuropathological examination was performed after approximately 12 years following retirement. On autopsy, the brain showed no cortical atrophy, contusions, or infarcts. There was mild neuronal cell loss noted in the frontal, parietal, and temporal neocortex. CTE was reported to be evident by the demonstration of tau in the form of neurofibrillary tangles in the hippocampus [17].

The second reported case of autopsy-confirmed CTE in a retired professional football player displayed neuropathological features that *differed* from the first reported case [16]. This case had a 14-year span of play in organized football starting at age 18. The athlete was diagnosed with major depressive disorder without psychotic features after retirement from professional football and, after several failed attempts, committed suicide. Upon examination, the postmortem brain was also noted to demonstrate evidence of tau-positive neurofibrillary tangles and neuropil threads, but contrary to the first case, amyloid plaques were completely absent. Reasons for the contrasting neuropathological features of these two cases have never been made clear.

The clinical and neuropathological profile of CTE described by McKee and her colleagues in Boston was based initially on a collection of case reports and a review of the existing literature [2]. The characteristics of CTE, as reported by that group, are described in terms of a progressive tauopathy, which follows a sequence of clinical changes and associated neuropathological changes. The reported cause of these changes is alleged to be repetitive closed head injury, which can occur in a variety of contact sports, non-sport-related accidents, or in the setting of military service. Interestingly, analysis of a case series from a convenience sample of 202 football players showed neuropathological features of CTE as defined by this group in the vast majority (87%) of its players coming to their center in Boston at autopsy [18].

The researchers from Boston argue that the neuropathological changes associated with CTE are distinct from those found in other forms of dementia [1, 19]. They describe a long list of changes, which may or may not be present. Gross changes include anterior cavum septum

pellucidum and typically posterior fenestrations. Enlargement of the lateral and third ventricles is also common. Additional gross features include atrophy of the frontal and temporal cortices, atrophy of the medial temporal lobe, thinning of the hypothalamic floor, shrinkage of the mammillary bodies, pallor of the substantia nigra, and hippocampal sclerosis. Microscopic changes include an abundance of neurofibrillary inclusions, in the forms of neurofibrillary tangles, neuropil threads, and glial tangles.

In 2013, Stern and colleagues [20] described two major clinical variants of CTE – one variant has predominant behavioral and mood features developing at a relatively early age, while the other variant exhibits predominant cognitive disturbance with a later age of onset. Impulsivity, explosiveness, and violence are some of the most compelling and highly publicized symptoms that have been associated with CTE, and these are the features that have been alleged to have caused premature deaths in an alarmingly high number of individuals included in the Boston autopsy series. More recent published work from the Boston group describes a wider array of clinical presentations of CTE, including groups characterized by specific behavioral, mood, and cognitive symptoms, in addition to those with presentations characterized by dementia with and without motor symptoms [21].

Based on their ongoing work, the Boston group has concluded that clinical and pathological changes in CTE evolve in a progressive manner along a spectrum where the neuropathology ranges in severity from focal perivascular epicenters of neurofibrillary tangles (Stage I) to a severe tauopathy affecting widespread brain regions (Stage IV) [1]. The group also hypothesizes that the neuropathological spectrum of changes is accompanied by parallel changes in overt clinical symptoms, ranging from initial features of headache and attentional disturbance (Stage I) to a full-blown dementia associated with word finding difficulty and aggression (Stage IV).

Their view is that CTE is distinguishable from AD, other age-related changes, and other neurodegenerative tauopathies because of differing distributions of tau pathology. While the clinical symptoms of CTE are acknowledged by this group to overlap with those of other neurodegenerative conditions, they claim that a number of historical and symptomatic features distinguish CTE from other conditions [20]. For one, there is the claim that those presenting with CTE are known to have a history of exposure to repetitive brain injury with a profile of symptoms that distinguish them from individuals experiencing prolonged forms of post-concussion syndrome. Secondly, those with CTE often exhibit an earlier age of onset as compared to those with dementia due to AD and have a less rapid course of progression than non-AD conditions such as the behavioral variant of frontal temporal lobar degeneration (FTL-bv). There are, however, no reliable blood, cerebrospinal fluid, or neuroimaging biomarkers yet identified to distinguish CTE from a large list of other similar neurodegenerative conditions with overlapping symptoms and pathology.

Methodological Challenges to the Study of CTE

Ongoing and extensive media coverage has provided the public with an impression that much is now well-understood about CTE, including its clinical characteristics and its causes. However, this is far from the truth. The facts are that, from a scientific standpoint, the study of CTE is still in a preliminary stage with much that remains to be learned. Critically important is that, at this point in time, it is unknown how many athletes truly exhibit the reported signs and symptoms of CTE (i.e., beyond the number of brains examined postmortem by the Boston group). Also, yet to be identified is exactly who is prone to developing the condition? While the onset of CTE has been linked to repetitive head injury, that association has *not* been demonstrated scientifically nor is there an established neurophysiological mechanism. Additionally, while stories of many athletes diagnosed with CTE are publicized, there are, as of yet, *no* established clinical criteria for making the diagnosis in living subjects. A brief review of the state of the science and existing challenges is provided in the paragraphs below.

Epidemiology

A review of the published literature on CTE reveals that the rate reported in some groups has been alarmingly high, with one recent report demonstrating CTE pathology in 110 of the 111 players (99%) who had formerly played in the NFL [18]. A closer look at these data, however, reveals that these figures are not based on randomly acquired samples nor are they compared to any existing control group. An athlete's entry into this study and similar investigations is influenced by highly biased recruiting methods, based on public responses to press releases and media reports – meaning that those athletes and families who are more likely to be experiencing some of the cognitive, mood, and behavioral changes described as associated with CTE are more likely to participate or become available for study at high-profile research sites. At the same time, those retired players who do not experience any of these reported changes prior to death are not counted as "negative" cases. This highlights the classic "denominator problem" – focusing on positive cases while ignoring negative cases, a problem that has long affected all levels of behavioral research in TBI and other neurological and medical conditions [22].

Another major issue is that studies examining the relationship between the more general category of TBI and dementia have produced mixed results over the years. Some have suggested an association between TBI occurring over the lifetime and an increased risk of AD in later life [23]. However, those associations have not been observed in more recent studies using both prospective and retrospective methods [24]. In fact, investigations into the relationship between MTBI and late-life dementia from systematic reviews and other carefully conducted reports have found this relationship to be negative or inconclusive [25, 26].

Efforts to study rates of dementia in retired athletes have produced mixed results thus far. One study demonstrated that, while the general death rate in retired NFL players was lower than what is observed in men from the general population, the rate of death associated with neurodegenerative disease such as AD, PD, or amyotrophic lateral sclerosis (ALS) was nearly three times higher. However, this study is limited by its reliance on a relatively limited number of deaths attributed to neurodegenerative causes (N = 17) and no conclusive link between these conditions and head trauma [27]. It is noted that this type of relationship was not found in a study of retired players from the Canadian Football League, raising questions about the generalizability of the findings [28]. Since that time, a range of pathologies have been reported in yet another small sample of retired professional soccer players (N = 14) [29]. There is clearly a need for more controlled studies using a larger sample of athletes before any firm conclusions can be made.

Interesting results have arisen from a brain bank study examining neuropathological changes in 1721 men reviewed for history of past brain injury or participation in contact sports [30]. The results showed the presence of tau pathology associated with CTE in 21 of 66 former athletes with none of these same changes in 198 individuals without any association with contact sports, including 33 individuals with documented single-incident TBI. While these findings raise a suspicion that CTE might exist in approximately 30% of those individuals exposed to contact sports, the study did not establish any link between the pathology and any cognitive or behavioral changes in those individuals. The findings also contrast reports of two studies demonstrating no increase in neurodegenerative disease later in life in those individuals participating in football many years earlier in life relative to control groups who did not play football [31, 32].

In light of the many discrepancies in published studies, it comes as no surprise that the prevalence of CTE remains unknown with estimated rates ranging widely, from 4% to 87%, depending on the source and sample of interest [18, 33]. Taking a commonsense view, one might ask, "could CTE really be affecting 99% of those men who formerly played in the NFL?" The answer is clearly no, as is well understood by anyone who has ever witnessed lucid and insightful discussions of the sport and other related topics

involving retired NFL players via sports broadcasts or by other means. Unfortunately, the publicity that has surrounded CTE has trumped many of the pivotal contributions that former NFL players have offered to fields of business and economics, politics, and the law.

It is also entertaining to extend the argument to examine the much larger population of former high school football players. Published estimates suggest that over 6 million males participated in the sport between 1970 and 1988, resulting in a cohort that is currently in the 45–60-year age group [34]. If one were to extend the 90% prevalence estimates to that number, memory clinics nationwide would be inundated with the need to treat cognitive, mood, and behavioral changes in over 5 million men given their prior participation in football alone – this is something that is certainly not happening. The lack of any current epidemic of former football players presenting to clinics with these overt behavioral presentations is yet further support for the fact that there really is no current public health crisis and that great strides need to be made for any real estimates of the true prevalence of CTE in football and all other contact sports can be made.

Causal Mechanisms

There is an assumption among laypersons, members of the media, and healthcare professionals of a strong link between CTE and concussions. This is, as repeatedly pointed out so far, not yet established. In fact, there is no clear link between history of discrete concussions and the development of any type of dementia, including CTE that has yet to be identified. Rather, there is a hypothesized link between CTE and brain injury in retired athletes and others propagated almost exclusively by one group of researchers that is based on cumulative exposure to repetitive injury, rather than any direct association to concussion, occurring either as a single event or through multiple occurrences. Some of the most highly publicized cases of CTE (approximately 20%) were not known to have sustained any concussions at all during the course of their football careers, although it is certainly possible that injuries that these players sustained were not reported [35].

Establishing a scientifically validated link between repetitive brain injury and CTE requires a specification of what type of injury is sufficient to cause the damage and how many injuries are needed to cause a recognizable pattern of symptoms and associated neuropathology. In response to this question, one must define what constitutes a "subconcussive blow," while specifying how this type of blow can be differentiated, on one hand, from the level of impact that causes a true concussion and, on the other hand, a totally benign blow to the head [36]. Use of the term subconcussive to describe the impact implies that we are already able to identify the occurrence of concussion in an accurate manner and understand the lower boundary threshold for development of its symptoms, which is clearly not the case [37].

At one point, there had been hope that questions about the physical and biomechanical characteristics of injury impacts would be answered through the use of helmet-based sensors. Such sensors could be used to characterize the kinematic features of concussive impacts and the number of head-impact exposures sustained by athletes during the course of routine sports participation. While the results from initial studies using this methodology provided valuable data regarding the range of severity and number of head impacts sustained by athletes in various settings, investigators were unable to establish a clear threshold of impact for concussive injury and therefore, by definition, what constitutes a subconcussive blow [38]. More recently, questions about the reliability of the data acquired from these devices and their oversensitivity to registration of other types of body movements have curtailed their use to a large degree, as evidenced by the NFL's decision to discontinue studies using these methods in 2015.

Another question that arises is whether results obtained from basic neuroscience research have provided a neurophysiological mechanism that establishes a link between repetitive brain injury and tauopathy in animal samples. While several studies have attempted to use traditional brain

injury paradigms to study CTE in animals, there has been variable success in replicating the profile of tau phosphorylation and progressive behavioral deficits that has been associated with the disorder [39]. While some interesting results are reported from one recent study [40], there has been little success, to date, in replicating a staged progression of tau pathology, beginning in superficial cortex and spreading to other regions, including the hippocampus, nor has there been any controlled laboratory production of TDP-43 immunoreactive nuclear inclusions in response to repetitive head impact, as hypothesized by the CTE proponents [1].

The issue of exposure is central to any theory linking repetitive brain injury sustained in contact sports to the development of neurodegenerative changes. However, it is clear that the issue of exposure is not simple, as is evident from the existence of autopsy-defined cases of CTE documented in an 18-year-old athlete with exposure limited to participation in high school football, to retired NFL players, aged 80 or older, who had played the game for many years. There are also cases of CTE pathology in individuals who had never played contact sports in addition to a lack of identified pathology in some retired athletes with many years of sustained competition at the professional level [41–43].

Studies of exposure to repetitive head impact can take two basic forms, with one focusing on the exposure resulting from positional play (e.g., running back versus offensive lineman) and the other cumulative exposure resulting from the total number of years of participation in the sport. The results from existing studies demonstrate that quarterbacks, running backs, and defensive backs are the players most susceptible to concussions, while offensive line is the position that is exposed to the most number of repetitive head blows during the course of a football season [44–46]. However, the relative risk of CTE occurring in linemen versus other players remains unknown. One study has attempted to combine exposure variables to compute a "cumulative head impact index" (CHII) with results showing that the index was effective in predicting subjective ratings for a number of individual clinical symptoms [47].

There has been some suggestion that NFL players who began their football careers through youth leagues before the age of 12 years exhibit greater levels of cognitive dysfunction and impaired neuropsychiatric functioning, although the studies have received criticism on methodological grounds [48–50]. At the current time, many more studies need to be performed before we can make any firm conclusions about any negative effects of exposure to contact sports.

Clinical Symptoms and Neurodiagnostic Findings

Nowadays, it is not uncommon to encounter media coverage of a retired athlete struggling with mental health and associated social issues that are attributed to a reported diagnosis of CTE. These accounts should come as a surprise to those who are aware of the current status of the science, as it is clear that the scientific study of CTE remains in its early stages, raising questions about the source and validity of the reported diagnoses. While there is some reported consensus on the neuropathological criteria used to make the diagnosis in postmortem brains, there remains no accepted diagnostic standard or consensus criteria for making a clinical diagnosis of CTE, based on symptoms or neurodiagnostic tests, in a living patient. Any efforts to establish a reliable set of symptoms will encounter obstacles in differentiating symptoms from those observed in overlapping conditions, bias from retrospective reporting of symptoms, lack of an established cause, and excluding psychosocial effects associated with substance abuse, marital discord, and employment-related factors.

The clinical presentation of CTE has been associated with a broad spectrum of cognitive, mood, behavioral, and motor symptoms that are believed to appear in advance of similar changes known to occur in a variety of other neurodegenerative conditions [20, 21]. The diagnostic challenge in these cases is to develop a reliable method for successfully distinguishing them from other known neuropsychiatric and neurodegenerative conditions, including AD, PD, ALS,

depression, and frontotemporal dementia (FTD), with some of these conditions having relatively high prevalence rates in the general population [51, 52]. There is clearly a need for establishing and validating a set of characteristic clinical symptoms and other features that would distinguish an individual with CTE from experiencing any of these other conditions with a high level of reliability and specificity.

There have been several attempts over the past several years to establish standardized clinical and research criteria for making a diagnosis of CTE. In 2013, Victoroff, for example, examined 436 published cases of CTE to establish criteria for "traumatic encephalopathy" [53]. He enumerated a number of critical signs and symptoms associated with the condition. Another set of clinical criteria emphasize classification into definite, probable, possible, and improbable CTE groups [54].

Two independent groups developed criteria for diagnosis of traumatic encephalopathy syndrome (TES), which comprise the reported clinical features of CTE. Both groups emphasized prior exposure to head injury in the context of outlining a set of more general symptoms [21, 55]. Efforts are currently being made to validate at least one set of these criteria in relation to other neuropathological and neurodiagnostic criteria [56]. In the meantime, there remain no established symptom-based criteria for making a diagnosis of CTE based on these or any other clinical criteria.

There has been much interest in establishing a biomarker that is effective for making a diagnosis of a neurodegenerative disorder, considered by many to be the "holy grail" of clinical neuroscience. To date, there has been little success in establishing any single reliable biomarker; limited gains have been made in the study of AD [57]. There has been no progress in developing a biomarker for CTE over and above what is used for other neurodegenerative disorders. Blood and cerebrospinal fluid candidate markers for tau pathology and inflammatory processes have been identified, although the study of these markers is in a very early stage [58]. There has also been some interest in structural imaging features, such as a cavum septum pellucidum, for aiding diagnosis of CTE [59], although that finding has been shown to lack sensitivity and specificity [60]. Another avenue of interest involves functional imaging techniques such as positron emission tomography (PET), using compounds sensitive to tau or amyloid deposition. While there have been preliminary reports of identified tau abnormalities in small samples [61, 62], there is a long way to go in establishing the specificity of those findings with the ability to distinguish CTE from other neurodegenerative conditions.

Accuracy of the Neuropathological Diagnosis

The practice of establishing a definitive diagnosis of neurodegenerative disease dates back to the nineteenth century and has been based on postmortem analysis with neuropathology – this has been considered the gold standard by which to gauge all other diagnostic tests. In the modern study of CTE, the earliest information in support of this condition came from the identification of unexpected neuropathological changes with known associations to other dementing conditions but in younger individuals with a history of exposure to contact sports. There continues to be controversies and criticisms regarding the specificity of the observed neuropathological changes associated with CTE.

In light of continued scientific advances, there is now some question regarding the accuracy of neuropathological diagnosis and its use as the gold standard for diagnosis [63]. The results from a recent large-scale study found that the specificity of the neuropathological diagnosis of AD, based on neuritic plaque densities and Braak neurofibrillary stages, ranged in various datasets from 44% to 70% compared to other clinical diagnoses, including FTD, Lewy body disease, cerebrovascular disease, and hippocampal sclerosis [64]. In another report, results from a survey of practicing neuropathologists showed that the majority feel unable to make a neuropathological diagnosis of AD without clinical data and only one in four reported using standardized diagnostic criteria on a regular basis [65].

In the study of CTE, the emphasis has been on identifying a pattern of tau deposition in the brain that is different from the pattern observed in other neurodegenerative conditions [1]. The more recent characterization of CTE suggests that symptoms progress along a spectrum and that the profile of tau deposition in younger individuals with mild symptoms (Stage I) differs in nature from normal age-related patterns of tau deposition, while the pathology observed in more chronic stages of illness (Stage IV) can be distinguished on reliable basis from AD and other advanced stage neurodegenerative conditions. Questions naturally arise on the reliability of the clinical symptoms documented in these cases, as most are based on retrospective reports from relatives with a strong potential to be influenced by hindsight bias. Criticisms are also made on the purity of the pathology obtained in many of the cases that have studied as most did not die as a result of the end stage of a neurodegenerative disease but rather from a range of other causes (e.g., hanging, gunshot wound, or drug overdose) [66].

Some have suggested that the focus on tau and its relation to the emergence of CTE symptoms is premature, given that the pathology has not been established as the cause of the symptoms [67]. Questions have also arisen as to whether the neuropathological features of CTE are necessary or sufficient for one to exhibit the clinical and symptomatic features of the disorder. In one summary analysis of neuropathological reports from some of the earliest published autopsy cases, it was found that only 20% of the cases demonstrated "pure" CTE pathology, while 23% of the cases with clinical symptoms exhibited no signs of neurodegenerative pathology [42]. An additional 5% of the studied cases exhibited signs of CTE neuropathology and no clinical symptoms, a finding that has been replicated in more recent studies demonstrating similar forms of pathology in 12% of older adults exhibiting no symptoms of neurodegenerative disorder [29, 41].

Research on CTE has also been limited by the lack of consistency in the neuropathological criteria that have been used to diagnose the disorder. As mentioned above, the relative patterns of amyloid and tau appearing in more recently reported cases of retired football players and others are reported to differ from what was described in earlier reports on retired boxers [42]. There have also been differences in the neuropathological characteristics reported by the modern CTE advocates. For example, in cases reported by Omalu and colleagues, there was more of a lobar cortical distribution of pathology [17], whereas the cases reported by McKee and colleagues were focused more on perivascular spaces and the depths of the sulci [1]. Additionally, the Boston group has described the spectrum of clinical and pathological changes in CTE, while Omalu and colleagues have focused more on a definition of four separate CTE phenotypes [68].

In 2016, a report was published which summarized results of a consensus panel of 7 neuropathologists who evaluated digitized images of neuropathological specimens from 25 cases of CTE and other tauopathies, concluding that CTE could be reliably distinguished from those other conditions [69]. However, when one looks more closely at the data, one finds that the reported agreement among reviewers was clearly not spectacular (Kappa = 0.78). Alzheimer's changes were reported by consensus members in 8 of 10 CTE cases, while CTE findings were identified in 8 of 15 cases without clinical features of CTE. In the end, while the consensus findings are commonly invoked to establish the validity of the neuropathological diagnosis of CTE, the data actually raise doubts about the specificity of the diagnoses made within the sample. There clearly needs to be continuing analysis of the accuracy and generalizability of the consensus study findings before those criteria can be used as the "gold standard" for CTE research.

Alternative Perspectives on CTE

As stated throughout this chapter, CTE is characterized as a progressive tauopathy that occurs as a consequence of repetitive mild traumatic brain injury. As a clinical syndrome, the cognitive impairment and many complex behaviors associated with CTE, including aggression and suicide, result from specific neuropathological

changes that are proposed to be distinct from those changes seen in other clinical conditions, including AD, FTD, and depression. Many of the assumptions associated with the clinical presentation of CTE might appear a little odd or extreme, to clinicians and social scientists, who typically consider a number of alternative medical and psychosocial factors before attributing the emergence of complex behavioral symptoms to the direct effects of neuropathology.

Much of what is described about CTE as a syndrome comes from neuropathological studies. This is not surprising given the leading and early role of neuropathologists in published work on CTE. However, with this focus on autopsy data, less (if any) attention is paid to critically important clinical data that other clinicians routinely consider. Skilled neuropsychologists, for example, routinely view complex behavioral symptoms in the overall context of a person's life and not as isolated symptoms. The aim of this section of the chapter is to provide alternative perspectives to the topic of CTE as a clinical condition, as demonstrated through results of neuropsychological studies and application of the biopsychosocial model.

Neuropsychological Studies

Neuropsychologists in clinical practice are often asked to evaluate cognitive and behavioral changes in older men with the aim of determining whether their presenting symptoms are representative of normal aging, neurodegenerative disorder, or other clinical condition(s). When one considers published base rates, the lifetime risk of developing dementia is 15% in older males from the general population and 10% in males reaching age of 45 years [70, 71]. This value is often ignored when estimating the prevalence of CTE in retired athletes. Overall rates of dementia are commonly reported in retired athletes – however, they are rarely viewed in the context of the existing base rates, where it must be demonstrated that the rate of dementia in this select population of retired athletes exceeds the rate that would be expected in individuals who were not theoretically exposed to the same risk factors for development of CTE. In other words, demonstrating that dementia develops in one of six NFL players actually tells us nothing, as that is the same rate expected over the course of any man's lifetime.

Based on a typical neuropsychologist's clinical knowledge and training, the primary aim when performing an evaluation of cognitive and behavioral changes in retired football players would be to rule out the presence of the most likely clinical conditions in this age group, which would be MCI or AD. In fact, as mentioned earlier in this chapter, it had been demonstrated through survey studies of retired football players that those athletes with multiple concussions were more likely to be diagnosed with MCI than those without a reported history of concussion with a trend toward earlier onset of AD in the multiple concussion group [15]. Perhaps the most important factors to consider with the clinical presentation of CTE are that cognitive and behavioral changes are being reported in individuals that are much younger than individuals who typically present to memory disorder clinics. This requires an explanation of why conditions such as MCI or AD would be presenting earlier in these individuals.

Based on these survey data and the availability of emerging data from accelerometer studies, Randolph and Kirkwood were among the first investigators to suggest that many years of repetitive head trauma from playing sports could result in diminished "cognitive reserve" [72], employing a concept developed by Yaakov Stern in the study of aging and dementia [73]. Using cognitive reserve as guiding concept, it was hypothesized that retired athletes are less able to compensate for normal age-related brain changes, as a result of cumulative head injury exposure, and are therefore more likely to exhibit cognitive changes earlier than would otherwise be expected for their age. If this were true, one would expect the early emergence of these clinical symptoms to resemble the changes associated with more prevalent conditions, such as MCI or AD, rather than any newly emerging clinical syndrome, such as CTE.

In the first published study employing neuropsychological tests to study retired professional football players, the resulting test profile was found to be very similar to what was observed in a control group of patients diagnosed with MCI [74]. The retired athletes were also significantly younger and somewhat less impaired overall in terms of their neurocognitive status. Furthermore, approximately 35% of the players' spouses provided subjective ratings of their husbands' behavior that were above the published figure associated with possible dementia (scores of >2 on a dementia screening index). Although these data were considered preliminary, they did support the hypothesis that repetitive head trauma from many years of playing football may lead to the earlier expression of late-life cognitive disorders that are similar in characteristics to what is more commonly observed in conditions such as MCI and AD. Since that time, other published studies have also provided data supporting the hypothesis that cognitive reserve mediates the clinical expression of CTE [18].

Additional studies using neuropsychological test batteries with retired NFL players have reported objective evidence of cognitive impairment (e.g., problems with memory and naming) and mood symptoms considered to be more consistent with diagnoses of MCI or depression than CTE. For example, in a study by Hart and colleagues [75], cognitive findings were associated with white matter abnormalities and regional cerebral blood flow differences demonstrated on neuroimaging, which is common among individuals with depression as well as MCI. In another study, this same group of researchers reported that concussion history in NFL athletes was associated with reduced hippocampal volume and lower verbal memory performance, which is typical of individuals with MCI [76]. Not surprisingly, the clinical profile observed in those athletes was attributed to MCI rather than CTE.

Results from another study of 42 former NFL players reported that players who had initiated their football playing careers before the age of 12 exhibited more evidence of late-life cognitive impairment on neuropsychological tests [50]. The findings were observed primarily on tests of executive functioning, memory recall, and estimated verbal intellectual functioning. The results of that study were criticized on several factors, including an emphasis on retrospective findings and a failure to control for premorbid cognitive differences in the two groups. In a similar neuropsychological study involving a different sample of NFL players [77], the data did not show greater impairment in NFL players who participated in youth football; importantly, the data were controlled for a number of clinical variables, and appropriate statistical corrections were applied.

Neurobiopsychosocial Perspectives

Over 40 years ago, there was a call to arms in medicine for increased recognition of the influence that social, psychological, and behavioral factors play in the development and manifestation of disease through development of a biopsychosocial model [78]. With the increasing focus on identifying diagnostic biomarkers, neuropsychologists have become increasingly vocal in their support for a more updated approach to that model, incorporating advances in imaging and neurobiology, through development of a neuropsychobiological perspective for assessing and treating the effects of concussion and its long-term consequences [79]. Several have criticized the degree to which existing studies and theories of CTE have failed to account for the influence that biopsychosocial factors are likely to exert on the presentation of symptoms in NFL retirees [51, 80–82].

In a critical review of the CTE literature, Asken and colleagues reviewed different factors that may potentially affect an athlete's risk for developing CTE, many of which are not recognized or controlled for, in most of the existing studies of CTE [80]. Prominent among these factors are biopsychosocial variables including developmental factors, demographics, drug/alcohol abuse, adjustment to retirement, and ongoing sleep difficulties. In the following paragraphs, we will further highlight the degree to which biopsychosocial factors potentially

influence complex behaviors including depression, suicide, and violence, which are considered among the most critical and highly publicized features of CTE.

There has been increased study of the mental health of elite athletes with an emphasis on depression and its relationship to concussion history [83]. Guskiewicz and colleagues were the first to demonstrate a relationship between concussion frequency and the emergence of depressive symptoms in retired NFL players, and this finding has been supported in research performed by this group and others [84–86]. However, there are other studies demonstrating increased rates of depression in NFL retirees arising from a host of other medical and psychosocial factors [87]. This group hypothesizes that chronic pain induced by musculoskeletal difficulties affects the retirees' physical activity and fitness levels to a degree that increases the risk for depression. The authors highlight the degree to which these factors interact with problems arising from employment issues, financial status, marital relations, and decreased social support. Other factors can result from retired players transition from a socially visible individual to a point of relative anonymity during retirement, with adjustment to retirement noted to be a significant predictor of many of the behavioral and emotional symptoms commonly attributed to CTE [81, 88]. What clearly emerges is a very complex interaction between health issues and a number of other important psychosocial factors when evaluating the occurrence of these behaviors in retired professional athletes.

Turning to the controversial topic of suicide and CTE, it is clear to most seasoned clinicians that suicidal ideation and associated behaviors are symptoms of depression and are typically not included among the diagnostic criteria associated with traditional neurodegenerative disorders, such as AD or PD. It is therefore disconcerting to see that suicidality is now included among the diagnostic features of TES without recognizing its primary link to depression [21, 55]. There is an overrepresentation of suicide as the cause of death for many of the younger postmortem cases that have been studied and found to have neuropathological evidence of CTE [68]. Some have hypothesized that impaired neurotransmitter homeostasis in the brain may explain the overrepresentation of suicides in studies of CTE [89], but this is with no apparent recognition of the undoubtedly large number of *other* possible factors that might have been responsible for suicides in those subjects.

Public health statistics show that across the nation there has been an increase in suicides over the past 20 years, with the greatest increase observed in males between the ages of 40–64 years. Job, financial, and legal problems are cited as the most common circumstances surrounding the suicides occurring in that age group [90]. One might notice that this is the same age group that characterizes the retired NFL players who have been included in CTE studies. While it might appear at first glance that former NFL players are at risk for suicide, the results of research investigations examining this topic have actually found that these players are at a lower risk for suicide than other males from their age group [91, 92].

Modern research has demonstrated that suicidal behaviors are heterogeneous in nature and result from a complex interaction of physical and social causes [93]. In detailed discussions of the relationship between suicide and CTE, Iverson concluded that there is no proven connection between CTE and suicide with observation that there are multiple underlying biopsychosocial causes for suicide and a belief that any conceptualization of suicide as a result of a progressive tauopathy as scientifically premature and potentially fatalistic [94, 95]. A recent study found that most professional football players who committed suicide in recent years suffered from multiple life stressors secondary to social, economic, and mental health factors [96].

There are many serious dangers of associating suicide and CTE. One can only imagine the many negative consequences that can result from informing an individual that their symptoms, including suicidal ideation, are the result of a progressive and "incurable" condition such as CTE, as opposed to a very treatable condition such as depression. Given the potential for contagion effects secondary to suicide reporting

in the media [97], it is very important that clinicians, scientists, and journalists seriously consider the continued reporting of a link between CTE and suicide, given the current status of the science and the potential to circulate misinformation rapidly through social media.

There has also been much attention placed on reports of violent behaviors in NFL players and retirees. Information obtained from media investigations has indicated that, while NFL players exhibit lower rates of arrest and violent crimes in comparison to the general population, there is a general increased rate of domestic violence arrests in this group, when controlling for other factors [98]. CTE researchers include agitation, explosivity, loss of control, and short fuse among the behavioral features associated with TES [21, 55]. Based on the proposed association between CTE and aggression, it has been easy for some to speculate that the domestic violence rates in NFL players might be due to an early expression of the neuropathological effects of that condition. As one might imagine, explaining this type of violence as the result of abnormal brain functioning resulting from head injury could have significant legal and societal implications [99].

As seen in studies of other complex behaviors, the research on domestic violence has clearly demonstrated that there is combination of psychobiological and sociocultural determinants underlying these behaviors [100]. While there might be many biological factors that render males more prone to aggressive behaviors in general, it is clear that domestic violence stems from a number of complex sociocultural factors that extend well beyond any pattern of hormonal expression or the effects of abnormal tau deposition in the brain.

One should remember that, to begin with, football is a violent sport, and those who excel in the sport might succeed because of their ability to express or channel aggression through the sport. Recent reviews have supported the notion that there are higher rates of violence in athletes, which is believed to be the result of a number of factors including masculine culture and social norms attached to certain sports [101]. Unfortunately, much of the macho culture associated with football and other sports includes negative impressions of women and glorification of some antisocial behaviors, including illicit drug use. The hope is that future attempts to curtail these behaviors will be focused more on rectifying the social contributions of violence as opposed to becoming distracted by any attempts to treat violence as a sole consequence of the underlying neurobiology.

Conclusion

Over the past 10–15 years, CTE has become one of the most highly publicized and controversial topics encountered in medicine and the clinical neurosciences. As reviewed in this chapter, the study of this condition started nearly 100 years ago with observations of cognitive, behavioral, and motor changes in professional boxers. Since that time, with the help of modern informational technology and social networking, a modern form of CTE has now been described, based on findings from autopsy studies performed primarily on retirees from professional contact sports. With this newer form of the condition, there has been emphasis on a more expanded list of behavioral changes, including high-profile behaviors such as suicide and violence and an accompanying pattern of underlying neuropathological changes that are proposed to be distinct from the original form of the condition seen in boxers and from changes associated with more prevalent conditions, including AD and PD.

It is unfortunate that the media coverage of CTE has extended well beyond the results of scientific studies, which remain preliminary, but has led the public nonetheless to have a false sense of what is known about CTE. As a result, there has been an outcry for changes in the sport with some calling for an outright ban on tackle football in younger athletes. While some of the proposed changes for football have been appropriate and have made the sport safer, many questions still need to be addressed before making any more radical changes. With all the enthusiasm for banning these sports, many are forgetting what might become unintended consequences of reducing

youth activities, including the potential for an even greater increase in childhood obesity and rises in associated conditions like early type II diabetes and hypertension. In the end, the increased risk for development of neurodegenerative disorders secondary to cerebrovascular factors could outweigh whatever risks were associated with participation in contact sports.

As summarized in this chapter, there remain several serious methodological flaws in existing studies of CTE, which continue to limit conclusions one can currently make about the incidence, cause, and characteristics of the condition. To date, there is no knowledge of the true frequency of CTE in the general population or any sense of who might be most affected. Existing studies have been based on autopsy series that have been limited through biased sampling methods and variable methods for defining the clinical symptoms and pathology found in the participants. At this point, while it is assumed that CTE is caused by exposure to repetitive head injury, that causal relationship has not been established scientifically. There also remains no validated method for diagnosing CTE in living subjects or distinguishing it from other neurodegenerative conditions, using clinical symptoms, neuroimaging, or neurobiological markers. While there has been an emphasis on the definition of a distinct pattern of neuropathological changes in CTE subjects, a closer look indicates that the ability to distinguish the condition from other neurodegenerative diseases is not as strong as advertised.

It is also becoming increasingly clear that there will remain a cost to limiting explanations of the clinical presentation of CTE to the effects of neuropathology without fully considering or exploring the degree to which other neurobiopsychosocial factors might be playing a causative role. The results of neuropsychological studies have focused more on conceptualizing cognitive and behavioral changes observed in NFL retirees in terms of an early expression of MCI or AD rather than as an effect of any newly emerging neuropathological condition. There has also been a focus on the role that depression plays in the manifestation of the changes reported in this population. It will be necessary to consider the full range of sociological and cultural factors influencing complex conditions and behaviors such as depression, suicide, and violence in order to make advances in our understanding of these conditions and any relation they might have to participation in contact sports. The good news is that neuropsychologists are well equipped, through their knowledge and combined use of neurobiological and psychosocial methodologies, to provide valuable insights and advances in the study of CTE. The hope is that neuropsychologists play a larger role in shaping the direction of CTE research in the future with results of a more balanced account of its characteristics and its causes.

Clinical Pearls

- Media coverage of CTE has extended well beyond the results of scientific studies, which remain preliminary and has led the public to have a false sense of what is known about CTE.
- The study of CTE is still in a preliminary stage with much that remains to be learned. At the current time, many more studies need to be performed before we can make any firm conclusions about any negative effects of exposure to contact sports.
- Estimates of the prevalence of CTE in retired athletes should be considered in the context of published base rates for dementia. The lifetime risk for developing dementia is 15% in older males from the general population and 10% in males above age 45. The questions should be whether the rate in retired athletes exceeds the rate that would be expected in individuals who were not theoretically exposed to the same risk factors for development of CTE.
- To date, there is no clear link between history of discrete concussions and the development of any type of dementia, including CTE, that has yet to be identified.
- While there is some reported consensus on the neuropathological criteria used to make the

diagnosis in postmortem brains, there remains no accepted diagnostic standard or consensus criteria for making a clinical diagnosis of CTE, based on symptoms or neurodiagnostic tests, in a living patient.

- While initial studies using helmet sensors provided valuable data regarding the range of severity and number of head impacts sustained by athletes, questions about the reliability of the data acquired from these devices and their oversensitivity to registration of other types of body movements have curtailed their use to a large degree.
- Neuropsychological studies have focused more on conceptualizing cognitive and behavioral changes observed in terms of an early expression of MCI or AD rather than as an effect of any newly emerging neuropathological condition. There has also been a focus on the role that depression plays in the manifestation of the changes reported in this population.
- Thus far, explanations of the clinical presentation of CTE have been limited to the effects of neuropathology without fully considering or exploring the degree to which other neurobiopsychosocial factors might be playing a causative role.
- Neuropsychologists are well equipped, through their knowledge and combined use of neurobiological and psychosocial methodologies, to provide valuable insights and advances in the study of CTE.

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