Curr Neurol Neurosci Rep (2015) 15: 23
DOI 10.1007/s11910-015-0541-5

BEHAVIOR (HS KIRSHNER, SECTION EDITOR)

The Clinical Presentation of Chronic Traumatic Encephalopathy

Michael W. Lenihan · Barry D. Jordan

Published online: 15 March 2015

Abstract Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disorder attributed to repetitive mild traumatic brain injury. The diagnosis in a living individual can be challenging and can be made definitively only at autopsy. The symptoms are often nonspecific and overlap with neurodegenerative disorders such as Alzheimer's disease (AD) and frontotemporal dementia (FTD). Higher exposure to repetitive head trauma increases the risk of CTE. Genetic risk factors such as presence of an apolipoprotein E ε4 allele may be important. Individuals have varying degrees of cognitive, behavioral, and motor decline. Limitations in the manner in which data have been obtained over the years have led to different clinical descriptions of CTE. At present, there are no biomarkers to assist in the diagnosis. Standard neuroimaging may show nonspecific atrophic changes; however, newer imaging modalities such as positron emission tomography (PET) and diffusion tensor imaging (DTI) show promise. Neuropsychological testing may be helpful in determining the pattern of cognitive or behavioral decline.

Keywords Chronic traumatic encephalopathy · CTE · Dementia pugilistica · Punch drunk · Pugilistic parkinsonism · Postconcussion syndrome · Football · Soccer · Boxers · Biomarkers · Concussion · Subconcussion

This article is part of the Topical Collection on *Behavior*

M. W. Lenihan
Adirondack Neurology Associates, 420 Glen St, Glens Falls, NY 12801, USA
e-mail: mlenihan@nycap.rr.com

B. D. Jordan (✉)
Burke Rehabilitation Hospital, 785 Mamaroneck Ave, White Plains, NY 10605, USA
e-mail: bjordan@burke.org

Introduction

The high-profile deaths of several athletes over the past few years have drawn considerable media attention to chronic traumatic encephalopathy (CTE), a disease described in boxers under various other names since 1928 [1]. It has been identified in participants of contact sports, war veterans, and victims of physical abuse [2]. Fear of permanent neurologic injury may be causing a decline in participation in contact sports.

Despite over 86 years of medical literature, the syndrome remains diagnostically elusive and somewhat controversial. Exposure to repetitive mild traumatic brain injuries is believed to precipitate varying degrees of cognitive, behavioral, and/or motor impairment supported by a specific pattern of tau deposition and neurodegeneration found on autopsy of the brains of affected individuals [2, 3]. There is considerable focus on concussion as a putative risk factor; however, multiple subconcussions are also important [4]. Despite the associations of repetitive head trauma and CTE, there are currently no carefully controlled studies documenting sports-related repetitive head trauma as a cause of late-life cognitive or neuropsychiatric impairment [5].

Diagnosing CTE in a living individual is challenging. This paper will review the evolution of the concept of CTE, clinicopathological presentation, and neurodiagnostic studies. We will also point out limitations to the current model of CTE.

Definition

CTE is a progressive neurodegenerative disorder presumably caused by multiple mild traumatic brain injuries [2, 3, 6]. It is been described in boxing, American football, soccer, ice hockey, professional wrestling, rugby, and baseball [7••]. It has also been described in war veterans, victims of domestic abuse,

epileptics, and a circus clown [2, 8]. Individuals present with a variety of cognitive, behavioral, and motor symptoms.

The syndrome is often difficult to identify clinically due to a broad range of often nonspecific signs and symptoms as well as multiple overlapping disorders. Individuals who sustain a concussion often have transient symptoms following the injury lasting days or weeks. These symptoms may include the following: headache, fatigue, depression, cognitive slowing, and poor concentration. In 80–90 % of individuals, these symptoms resolve spontaneously in 7 to 10 days [9–11]. A minority of individuals will have persistence of these symptoms, referred to as postconcussion syndrome (PCS). Defining the time that symptoms of concussion become PCS has been debated. DSM IV defines PCS as at least 3-month duration of three or more of the following symptoms: fatigue, disordered sleep, headache, vertigo/dizziness, anxiety or depression, personality changes, and/or apathy [12, 13]. Although the vast majority of individuals recover within 1 year, it is estimated that 10–15 % of individuals (nonathletes) have symptoms persisting greater than 1 year after injury [14, 15]. It is suggested that secondary gain, premorbid depression, and posttraumatic stress disorder may account for some of this persistence [16, 17].

Chronic postconcussion syndrome (CPCS) is used to describe the uncommon phenomenon in which these symptoms do not resolve [3]. The incidence of CPCS due to athletic injuries is unknown. Investigations into the incidence of individuals with postconcussive symptoms lasting more than a year have not been limited to athletes [16, 17]. CPCS can be distinguished clinically from CTE by history. CPCS has an acute onset related to a single concussive event whereas CTE is more indolent and may begin years after retirement [3]. Those individuals with a static encephalopathy due to a single severe traumatic brain injury do not have the latent period although later progression later progression may be seen [18].

History

In 1928, Harrison Martland drew attention to a syndrome of cognitive and motor decline that was well known in the boxing community [1]. In his article "Punch drunk," he described the typical course beginning with slight mental confusion and motor slowing progressing to more severe motor disability and mental deterioration, at times necessitating commitment to an asylum. The term punch drunk was one of many unflattering terms used by the boxing community at the time to describe afflicted individuals. The terminology has evolved since then. In 1934, Parker [20] used the term "traumatic encephalopathy" while Millspaugh coined the term "dementia pugilistica" in 1937 [21]. In 1957, Critchley suggested "chronic progressive traumatic encephalopathy" [22]. Later, "chronic traumatic encephalopathy" was used, as progression was not always clear [23].

Most of the early literature centered on CTE in boxers. Typical publications were case reports and case series using clinical and historical descriptions of former boxers given the diagnosis of CTE. At least one large cross-sectional study was published [19]. Pathologic correlation was limited. Corsellis published the neuropathological findings of the brains of 15 ex-boxers in 1973; however, clinical information was obtained postmortem [24].

It was suspected that CTE was not an isolated syndrome in boxers. Studies on former Norwegian professional soccer players revealed neuropsychological impairment, cerebral atrophy on CT, and EEG abnormalities [25–27]. Neurocognitive dysfunction was also found in professional and amateur soccer players in the Netherlands [28, 29].

In 2005, Omalu published the first case of CTE in a former National Football League (NFL) player [30]. Since then, there have been a multitude of reports and pathologic series of former American football players as well as athletes from other contact sports, war veterans, and others subjected to repetitive head trauma diagnosed with CTE based on pathologic findings [2, 3, 31, 32•]. Unlike many of the earlier reports on boxers [19–23], clinical information in the pathology articles was gathered retrospectively (postmortem) from family interviews and, in some cases, medical record reviews, imparting a substantial risk of recall bias. The older literature, on the other hand, is hindered by lack of pathologic confirmation.

Epidemiology

The incidence of CTE in sports is unknown and cannot be determined based on the available literature. In 1969, Roberts randomly selected 250 of 16,781 professional boxers who were licensed to box from 1929 to 1955. They were able to examine 224 fighters. From this sample, the estimated prevalence of CTE was 17 % [19]. Clausen suggested that this prevalence may be an overestimation in current boxers, as exposure has decreased considerably since the 1920s and 1930s. Between the years 1900–1955, the average boxing career length decreased from 19 to 5 years in 2002. At the same time, the number of bouts decreased from an average of 336.5 to 13.3 [33]. Conversely, diagnostic criteria in Roberts' study were not clearly defined and may have been more rigid than the current definition. In addition, more attention was paid to motor signs than to behavioral or cognitive changes, which may miss those with a milder syndrome, leaving open the possibility of underestimation.

The prevalence of CTE in retired athletes in other contact sports has not been determined, and large population-based studies are needed. An Olmsted County cohort of 438 male students who played football from 1946 to 1956 was compared with 140 nonfootball playing male classmates. By chart review, there was no increased risk of dementia, Parkinson

disease, or amyotrophic lateral sclerosis [34]. However, in contrast, Lehman et al. reported a higher mortality rate from AD and motor neuron disease (MND) among retired professional football players compared to the US population [35].

The primary risk factor appears to be exposure to repetitive concussive and subconcussive blows. In boxers, those with longer careers are at greater risk. Those who retired after the age of 28 had career durations greater than 10 years, and those who had more than 150 bouts were at greater risk [19]. Higher weight classes [19] and poor technique [22] are also risk factors.

Exposure may be a risk in American football as well. Of former players who responded to questionnaires, those who reported three or more concussions were more likely to have been diagnosed with depression or have self-reported memory impairment [36–38]. Career length in football players was positively correlated with pathologic CTE stage at postmortem examination [7••].

Genetic risk factors in the development of CTE are not clearly delineated. The presence of the apolipoprotein E (APOE) ε4 allele may increase the risk of chronic traumatic brain injury (CTBI) in athletes. In boxers with >12 professional fights, those subjects with at least one APO E ε4 allele had significantly more neurological impairment. Subjects with <12 fights had significantly less neurological impairment, regardless of APOE genotype. In addition, all boxers with severe impairment had at least one APO ε4 allele [39]. In a study of 53 active professional football players, older players with an APO ε4 allele had lower cognitive performance than comparably experienced players without an APO ε4 allele [40]. This association is not as well established in pathologic series. In a large series of pathologically confirmed CTE, the proportion carrying 1 APOE ε4 did not differ from the general population [7••]. In a subset of that same series, however, the proportion of APOE ε4 homozygotes were higher than expected in the general population. In addition, the proportion was higher in those who presented with cognitive dysfunction compared to those who presented with behavioral or mood dysfunction [41••].

Clinicopathological Presentation

The clinical description of CTE has evolved since Martland published his report in 1928. Earlier publications contained more severely affected boxers [1, 19, 20, 22]. More recent reports describe individuals from a broader athletic background who may not be as severely affected [7••, 32•]. The term dementia pugilistica may still be used for severe dementia that following a long boxing career [3, 18, 42].

On review of the literature to date, it is clear that the clinical presentation can be quite variable. Behavioral and mood symptoms are often early signs and often occur earlier than cognitive decline [41••]. These may be difficult to distinguish from premorbid personality traits, as well as more commonly occurring affective disorders found in young adults. In early CTE, affective disturbances including euphoria and hypomania may predominate [43]. As this progresses, disinhibition, paranoia, irritability, and violent outbursts may occur [35]. Substance abuse and morbid jealousy are seen [42]. In a study of impulsiveness in professional boxers and mixed martial arts fighters, there was an increase in impulsiveness scores with greater fight exposure [44].

Suicide is a frequent cause for presentation to pathologic study. In the series of McKee [7••], the cause of death was listed as suicide in 7 of 51 subjects (13.2 %) who had pathologic findings supporting CTE. Six additional subjects expressed suicidal ideation at some point in their lives. In 6 of the 51 subjects (11.8 %), the cause of death was listed as overdose. In those subjects without CTE, the cause of death was suicide in 7 of 35 (20 %) and drug overdose in 3 of 35 (8.5 %). Series of Omalu [32•] reported 5 of 11 (45.5 %) of their subjects with CTE committed suicide while 3 of 11 (27.2 %) died from drug overdose. Of six subjects who did not have CTE, one each presented with suicide and drug overdose (16.7 %). This may reflect an ascertainment bias in which those who die by these means are more likely to be referred for study. Suicide was not a cause of death in the study of Robert [19]. Of 16,781 professional boxers registered in England, Scotland, and Wales from 1929 to 1955, 16 died by the time the data were collected. None of those subjects died from suicide or drug overdose. In a study regarding cardiovascular deaths related to body mass index, it was noted that the death rate due to suicide in former NFL players was 41 % of the expected rate based on the general population [45]. Wortzel and colleagues performed a recent review of the literature regarding the relationship between CTE and suicide [46]. Only two studies met inclusion criteria with a total of 5 of 17 subjects dying by suicide. These were both uncontrolled case series, and overall quality of evidence was graded as low. Current objective support for a relationship between CTE and suicide is limited.

Cognitive deterioration may present at a later age [41••] although inattention and declining concentration may be initial symptoms [47]. Most areas of cognition may be involved including memory impairment, executive dysfunction, decreased attention and concentration, language impairment, and visuospatial difficulties. With progressive deterioration, frank dementia may occur [42].

Early reports indicate a preponderance of motor symptoms which may start during the athlete's career [19, 42]. Motor signs and symptoms are not as prominent in later reports; however most of the later reports are pathologic studies wherein clinical information was obtained retrospectively from family members and, in some instances, by chart review [2, 7••, 24, 30, 31, 32•, 41••]. Initial motor impairment may include dysarthria with mild imbalance. As this progresses, there may be varying degrees of gait or limb ataxia, spasticity, and parkinsonism [42].

Two distinct presentations were described by Stern and colleagues [41••]. In their study, 36 subjects had neuropathologically confirmed CTE without other comorbid neurodegenerative disorders and had next of kin available for interview. Retrospective histories were obtained from next of kin, and 23 had medical records available for review. From this information, two major initial presentations were apparent. One is a behavioral/mood variant presenting in younger individuals (age of death 51.4±18.5), and the other is a cognitive variant presenting in older individuals (age of death 69.2±21.8). Motor signs were not well described in this study. The clusters of symptoms were not exclusive to each. The majority of subjects presenting with behavioral or mood dysfunction developed cognitive dysfunction at some point. Behavioral symptoms were less common in the cognitive group. The cognitive group was more likely to present with a more severe pathologic stage and was more likely to be homozygous for the APO ε4 allele.

Recent reviews distinguish "classic" CTE from "modern" CTE [5, 10, 48•]. Gardner described the clinical and pathologic features of classic vs. modern CTE based on an extensive review of the literature [48]. Descriptions of classic CTE come from clinical case reports and case series, largely involving boxers with limited pathologic correlation. The largest study was a cross-sectional study by Roberts previously described in this paper [19]. They described two clinical syndromes. The first is a nonprogressive disorder with dysarthria, pyramidal dysfunction, and cognitive deficits seen in approximately 70 %. The second comprising 30 % involves progressive dysarthria and pyramidal dysfunction without cognitive deterioration. One shortcoming of this study is that it is cross-sectional and not prospective, which limits any description of natural history.

Information regarding modern CTE is largely gathered from pathologic studies with retrospective collection of clinical data [2, 7••, 32•]. These studies involve a broader range of subjects, including those from other contact sports, veterans, and nonathletes subjected to repetitive head trauma. The subjects with classic CTE were typically older, with longer careers and greater exposure to head trauma. Motor involvement is described earlier in classic CTE, with a later onset of memory problems, whereas subjects with modern CTE had more prominent neuropsychiatric and behavioral symptoms [48•]. This differentiation between classic and modern CTE likely represents a broader spectrum of disease rather than separate disease entities. It may also reflect differences in the way that the data were obtained.

Headache is frequently described in pathologic series when clinical information is obtained retrospectively [7••, 32•]. Headache was not a presenting complaint in those subjects with the most severe pathologic phase (stage IV) CTE in the series of McKee. It was not a common complaint in earlier, clinically based studies and may reflect an overlap with CPCS or recall bias.

Parkinsonism has commonly been described in CTE, especially in the older literature [1, 19, 20]. Corsellis reported a substantial loss of pigmented cells in the substantia nigra. Lewy bodies were absent, but neurofibrillary tangles were common, distinguishing post traumatic Parkinsonism from idiopathic Parkinson disease [24]. Omalu described similar findings in the substantia nigra as well as the locus coeruleus [32•]. McKee reported increasing degrees of depigmentation of the substantia nigra and locus coeruleus with higher pathologic stages [7••]. Isolated Parkinsonism due to repetitive head trauma, also referred to as pugilistic Parkinsonism, is rarely described [49]. Distinguishing posttraumatic Parkinsonism from idiopathic Parkinson disease is difficult. The former is described as being more slowly progressive and less responsive to L-dopa [50]. Turjanski compared F-dopa positron emission tomography (PET) in six subjects with a history of repetitive head injury (five boxers and one jockey) to age-matched controls with idiopathic Parkinson disease. There was a relative decrease of uptake in caudate nucleus and increased uptake in the putamen in the subjects with repetitive head injury. This reliably distinguished them from the control subjects with idiopathic Parkinson disease [50]. This distinction was not found in a similar study on retired Thai traditional boxers [51]. Former athletes with isolated parkinsonism may coincidentally have idiopathic Parkinson disease or multisystem atrophy. Earlier presentations may be due to earlier drop-out of dopaminergic neurons in those susceptible to Parkinson disease.

McKee and colleagues reported pathologic findings of motor neuron disease (MND) in the spinal cords of three subjects with CTE [52]. These subjects were reported to have a clinical history of progressive weakness, atrophy, fasciculations, and spasticity. These findings were not present in five subjects with CTE but without MND or in controls. Similar findings were present when compared with sporadic cases with amyotrophic lateral sclerosis (ALS). In a subsequent paper, 8 out of 68 subjects had pathologic findings of MND in their spinal cords. Sixty-three percent of these subjects reportedly presented with symptoms of MND and developed cognitive or behavioral symptoms later [7••]. The relationship between ALS/MND and head trauma remains controversial. Reports of higher than expected rates of ALS in Italian soccer players prompted the suggestion that multiple repetitive head traumas may predispose to ALS [53, 54]. Three evidence-based reviews by the same author found class II and III studies that indicated that the association between head trauma and ALS did not exceed what might be expected by chance alone. Evidence supporting a link was rated class IV. The reports concluded that trauma and physical activity are probably not risk factors for ALS [55–57]. The findings of MND in 8 of 68 individuals with CTE are intriguing; however, several have argued that declaring a connection between the two disorders is premature, based on the current literature [57, 58].

Evaluation

The clinical assessment of an athlete or veteran with suspected early CTE can be challenging. As noted above, early signs and symptoms may be nonspecific, and there are multiple other overlapping syndromes such as CPCS, posttraumatic stress disorder, and depression. Thorough history and neurologic exam are of utmost importance. Later stages may be easier to identify; however, these individuals may be difficult to distinguish from those with other neurodegenerative diseases not associated with trauma. Thirty-seven percent of subjects of McKee with CTE had other concomitant neurodegenerative diseases [7••]. In an autopsy series on six former Canadian Football League players with suspected CTE, Hazrati et al. found that only three had pathologic findings consistent with CTE. Other diagnoses included Alzheimer's disease (AD), ALS, and Parkinson disease. Each of the three CTE cases had additional comorbid disease including dementia with Lewy bodies, vascular disease, and AD [59•].

A premorbid history of repetitive head trauma is fundamental for the diagnosis. Social factors such as baseline education, employment status, and substance abuse may obscure the picture. Motor findings involving the cerebellar, extrapyramidal, and/or pyramidal systems support the diagnosis [3].

Neuropsychology

Most studies on the neuropsychology of CTE involve boxers. Mendez reviewed EIGHT neuropsychological studies involving professional boxers. Deficits were present in the following: memory, information processing speed, finger tapping speed, complex attentional tasks, sequencing abilities, and frontal-executive functions [42]. In a study comparing 20 amateur boxers to a control group of orthopedic patients with limb fractures, neuropsychological testing was found to be more sensitive than clinical examination, EEG, and CT in finding neurologic abnormalities in the boxing group. Verbal and visual memory, attention, and four-choice reaction time were more affected. However, these impairments were present in a minority of the boxers [60]. The reliability of neuropsychological testing may be limited when no baseline data are available. In general, neuropsychological testing can identify patterns of cognitive and behavioral impairments which may assist in the differential diagnosis of chronic neurodegenerative disorders.

Imaging

Imaging may help in the workup of individuals with suspected CTE. Findings on the traditional structural imaging studies of brain CT and MRI tend to be nonspecific. Diffuse atrophy with ventricular enlargement, thinning of the corpus callosum, and a cavum septum pellucidum have been well described in the gross pathology of CTE [2, 24]. In a study of 33 retired soccer players from the National Football Team of Norway, one third were found to have central cerebral atrophy on brain CT and 6 % had a cavum septum pellucidum [26]. These findings, although nonspecific, may reflect exposure to repetitive traumatic brain insults.

Nonspecific T2 and fluid-attenuated inversion recovery (FLAIR) MRI white matter changes are of uncertain significance. There was a higher volume of nonspecific white matter changes on FLAIR sequences on former NFL players with cognitive deficits than with age-matched controls. No significant difference, however, was found between cognitively impaired and unimpaired former NFL players [61].

Diffusion tensor imaging (DTI) offers a sensitive measure of axonal injury [62]. This procedure detects Brownian motion of water molecules in brain tissue. Microstructure of the brain interferes with this motion, and injury would increase diffusion [63]. Fractional anisotropy (FA) is a measure of white matter integrity [64]. In studies on professional boxers, there was increased whole brain apparent diffusion coefficient (ADC) [63]. In addition, decreased FA was found in the corpus callosum, internal capsule, deep white matter, and cortical gray matter compared to controls [62, 64, 65]. In a study on retired NFL players, decrease FA was present in bilateral frontal and parietal lobes, left temporal lobe, and corpus callosum in subjects with cognitive or mood impairment compared to age-matched control. These differences were not present in asymptomatic athletes [61]. In a study on Division III football players, decreased FA was associated with the degree of repetitive helmet impacts when compared to preseason studies. These changes persisted 6 months after the end of the season [66]. Depressive symptoms have been correlated with decreased FA in retired NFL players with a history of concussion. In a study on 25 retired NFL athletes, decreased FA in the forceps minor had 100 % sensitivity and 95 % specificity in identifying subjects with depression [63].

Other imaging modalities under investigation include functional MRI [61], magnetic resonance spectroscopy [67], and PET. In one study, 5 retired NFL players with a history of mood and cognitive symptoms underwent studies with 2-(1-{6-[(2-[[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl}-ethylidene)malononitrile (FDDNP)-PET. FDDNP is a tracer that binds both amyloid plaques and tau deposits. The FDDNP signal was higher in subjects compared to that in five controls [68]. More recently, Mitsis et al. have utilized amyloid and tau PET imaging in an attempt to diagnose CTE [69].

Biomarkers

To date, no biomarkers have demonstrated the ability to predict the presence of CTE. Two studies on amateur boxers

Table 1 Clinical criteria for chronic traumatic encephalopathy [3]

Classification	Definition	Clinical example
Definite	Any neurologic process consistent with the clinical presentation of CTE along with pathologic confirmation	Cognitive, behavioral, and/or motor dysfunction
Probable	Any neurological process characterized by two or more of the following conditions: cognitive and/or behavioral impairment, cerebellar dysfunction, pyramidal tract disease or extrapyramidal disease, clinically distinguishable from any known disease process, and consistent with the clinical description of CTE	Cognitive impairment and extrapyramidal dysfunction suggestive of parkinsonism. Cerebellar dysfunction that is inconsistent with parkinsonism
Possible	Any neurologic process that is consistent with the clinical description of CTE but can be potentially explained by other known neurologic disorders	Primary dementia such as Alzheimer disease, primary cerebellar degeneration, Wernicke-Korsakoff syndrome, and ALS.
Improbable	Any neurologic process that is inconsistent with the clinical description of CTE and can be explained by a pathophysiologic process unrelated to brain trauma.	Cerebrovascular disease, multiple sclerosis, brain neoplasm, or other inherited neurologic disorders

revealed elevated levels of CSF neurofilament light protein (NFL) and glial fibrillary acidic protein (GFAP) when drawn within 7 to 10 days after a bout in one study and 1 to 6 days after a bout in the second. The degree of elevation correlated with exposure to head trauma. NFL and GFAP remained elevated at 14 days; however, only NFL remained elevated at 3 months, although it had decreased from the initial value [70, 71]. In a similar study, plasma tau was elevated 1–6 days after a bout but returned to normal after a rest period of at least 14 days [72]. These proteins appear to be markers of acute injury; however, any relationship to the development of CTE has yet to be determined.

Conclusion

CTE affects an unknown percent of individuals with a history of recurrent mild traumatic brain injury. The causative link between repetitive head trauma and CTE has not been well established. Also, not known is the reason that some individuals develop CTE while others with a similar history of head trauma do not. APOE genotype may impart increased risk of CTBI to individuals exposed to repetitive brain injury [3]; however, other genetic risk factors are possible but have yet to be discovered. Identifying CTE in a living individual is challenging. Symptoms can be nonspecific, and there may be overlap with other neurodegenerative diseases. Criteria for the clinical diagnosis of CTE have been described [3] (Table 1). There are no biomarkers to confirm the diagnosis of CTE. Radiologic studies offer only nonspecific findings that may support the diagnosis.

Changes in investigational methods appear to have produced two different pictures of CTE. Earlier classic reports of CTE involved clinical descriptions of older subjects afflicted with a more severe disease and motor manifestations. The more recent autopsy case studies of modern CTE have included subjects with milder disease and a broader background of other contact sports and nonathletic repetitive head trauma. These studies are limited by selective referral patterns and retrospective clinical data collection. The subjects with "classic" CTE may fit the clinical description of subjects with pathologic stage IV of McKee [7••, 41••].

Defining the true nature of CTE may depend on large prospective studies that include detailed neurocognitive examination, precise neurodiagnostic testing, and, ultimately, autopsy. The Professional Fighters Brain Health Study will attempt to prospectively follow more than 400 boxers over 5 years with serial imaging studies, computerized cognitive assessments, genotyping, and exploratory blood biomarkers [73]. An ultimate goal would be to identify individuals early in the disease and remove from continued exposure. It is not known, however, if early recognition and intervention would be effective.

Compliance with Ethics Guidelines

Conflict of Interest Michael W. Lenihan and Barry D. Jordan declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Martland HS. Punch drunk. JAMA. 1928;15:1103–7.
2. McKee AC, Cantu RC, Nowinski CJ, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. J Neuropathol Exp Neurol. 2009;68:709–35.

3. Jordan BD. The clinical spectrum of sports-related traumatic brain injury. Nat Rev Neurol. 2013;9:222–30.
4. Bailes JE, Petraglia AL, Omalu BI, et al. Role of subconcussion in repetitive mild traumatic brain injury. J Neurosurg. 2013;119:1235–45.
5. Karantzoulis S, Randolph C. Modern chronic traumatic encephalopathy in retired athletes: what is the evidence? Neuropsychol Rev. 2013;23:350–60.
6. Saulle M, Greenwald BD. Chronic traumatic encephalopathy: a review. Rehabil Res Pract. 2012;2012:1–9.
7.•• McKee AC, Stein TD, Nowinski CJ, et al. The spectrum of disease in chronic traumatic encephalopathy. Brain. 2013;136:43–64. *This is the largest, most complete pathologic study of subjects with CTE. 4 stages of CTE are identified and correlated with retrospective histories*.
8. Omalu B, Hammers JL, Bailes J, et al. Chronic traumatic encephalopathy in an Iraqi war veteran with posttraumatic stress disorder who committed suicide. Neurosurg Focus. 2011;31:E3.
9. McCrea M, Guskiewicz KM, Marshall SW, et al. Acute effects and recovery time following concussion in collegiate football players the NCAA concussion study. JAMA. 2003;290:2556–63.
10. McCrory P, Meeuwisse WH, Kutcher JS, et al. What is the evidence for chronic concussion-related changes in retired athletes: behavioural, pathological and clinical outcomes? Br J Sports Med. 2013;47:327–30.
11. McClincy MP, Lovell MR, Pardini J, et al. Recovery from sports concussion in high school and collegiate athletes. Brain Inj. 2006;20:33–9.
12. Halstead ME, Walter KD, The Council on Sports Medicine and Fitness. Clinical report—sports-related concussion in children and adolescents. Pediatrics. 2010;126:597–611.
13. American Psychiatric Association. Postconcussional disorder. In: Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Test Revision. Washington: American Psychiatric Association; 2000. p. 760–2.
14. Stern RA, Riley DO, Daneshvar DH, et al. Long-term consequences of repetitive brain trauma: chronic traumatic encephalopathy. PM R. 2011;3:s460–7.
15. Alexander MP. Mild traumatic brain injury: pathophysiology, natural history, and clinical management. Neurology. 1995;45:1253–60.
16. Carroll LJ, Cassidy JD, Peloso PM, et al. Prognosis for mild traumatic brain injury: results of the WHO collaborating centre task force on mild traumatic brain injury. J Rehabil Med. 2004;43:s84–105.
17. King NS, Kirwilliam S. Permanent post-concussion symptoms after mild head injury. Brain Inj. 2011;25:462–70.
18. Chauhan NB. Chronic neurodegenerative consequences of traumatic brain injury. Restor Neurol Neurosci. 2014;32:337–65.
19. Roberts AH. Brain damage in boxers. London: Pitman Publishing; 1969.
20. Parker HL. Traumatic encephalopathy('punch drunk') of professional pugilists. J Neurol Psychopathol. 1934;15:20–8.
21. Millspaugh J. Dementia pugilistica. US Nav Med Bull. 1937;35:297–303.
22. Critchley M. Medical aspects of boxing particularly from a neurologic standpoint. Br Med J. 1957;1:357–62.
23. Johnson J. Organic psychosyndromes due to boxing. Brit J Psychiatry. 1969;115:45–53.
24. Corsellis JAN, Bruton CJ, Freeman-Browne D. The aftermath of boxing. Psychol Med. 1973;3:270–303.
25. Tysvaer AT, Lochen EA. Soccer injuries to the brain. A neuropsychological study of former soccer players. Am J Sports Med. 1991;19:56–60.
26. Sortland O, Tysvaer AT. Brain damage in former association football players: an evaluation by cerebral computed tomography. Neuroradiology. 1989;31:44–8.
27. Tysvaer AT, Storli O, Bachen NI. Soccer injuries to the brain: a neurologic and electro-encephalographic study of former players. Acta Neurol Scand. 1989;80:151–6.
28. Matser JT, Kessels AGH, Jordan BD. Chronic traumatic brain injury in professional soccer players. Neurology. 1998;51:791–6.
29. Matser JT, Kessels AGH, Lezak MD, et al. Neuropsychological impairment in amateur soccer players. JAMA. 1999;282:971–3.
30. Omalu BI, DeKosky ST, Minster RL, et al. Chronic traumatic encephalopathy in a national football league player. Neurosurgery. 2005;57:128–34.
31. Omalu BI, DeKosky ST, Hamilton RL, et al. Chronic traumatic encephalopathy in a national football league player: part II. Neurosurgery. 2006;59:1086–93.
32.• Omalu BI, Bailes J, Hamilton RL, et al. Emerging histomorphologic phenotypes of chronic traumatic encephalopathy in American athletes. Neurosurgery. 2011;69:173–93. *Omalu et al. represents the second largest pathologic series in CTE. A syndromic profile of CTE positive cases is described.*
33. Clausen H, McCrory P, Anderson V. The risk of chronic traumatic brain injury in professional boxing: change in exposure variables over the past century. Br J Sports Med. 2005;39:661–4.
34. Savica R, Parisi JE, Wold LE, et al. High school football and risk of neurodegeneration: a community-based study. Mayo Clin Proc. 2012;87:335–40.
35. Lehman EJ, Heion MJ, Baron SL, et al. Neurodegenerative causes of death among retired National Football League players. Neurology. 2012;79:1970–4.
36. Guskiewicz KM, Marshall SW, Bailes J, et al. Association between recurrent concussion and late-life cognitive impairment in retired professional football players. Neurosurgery. 2005;57:719–26.
37. Guskiewicz KM, Marshall SW, Bailes J, et al. Recurrent concussion and risk of depression in retired professional football players. Med Sci Sports Exerc. 2007;39:903–9.
38. Kerr ZY, Marshall SW, Harding HP, Guskiewicz KM. Nine-year risk of depression diagnosis increases with increasing self-reported concussions in retired professional football players. Am J Sports Med. 2011;40:2206–12.
39. Jordan BJ, Relkin NR, Ravdin LD, et al. Apolipoprotein E ε4 associated with chronic traumatic brain injury in boxing. JAMA. 1997;279:136–40.
40. Kutner KC, Erlanger DM, Tsai J, et al. Lower cognitive performance of older football players possessing apolipoprotein E ε4. Neurosurgery. 2000;47:651–7.
41.•• Stern RA, Daneshvar DH, Seichepine DR, et al. Clinical presentation of chronic traumatic encephalopathy. Neurology. 2013;81:1122–9. *Stern et al. provides more extensive history on a subset of subjects in McKee's 2013 series. They found 2 patterns of presentation: younger onset of behavioral dysfunction and older onset cognitive dysfunction*.
42. Mendez MF. The neuropsychiatric aspects of boxing. Int J Psychiatry Med. 1995;25:249–62.
43. Guterman A, Smith RW. Neurological sequelae of boxing. Sports Med. 1987;4:194–210.
44. Banks SJ, Mayer B, Obuchowski N, et al. Impulsiveness in professional fighters. J Neuropsychiatry Clin Neurosci. 2014;26:44–50.
45. Baron SL, Hein MJ, Lehman E, Gersic CM. Body mass index, playing position, race and the cardiovascular mortality of retired professional football players. Am J Cardiol. 2012;109:889–96.
46. Wortzel HS. Chronic traumatic encephalopathy and suicide: a systematic review. Biomed Res Int. 2013;2013:424280.
47. Lakhan SE, Kirchgessner A. Chronic traumatic encephalopathy: the dangers of getting "dinged". Springerplus. 2012;1:2.

48.• Gardener A, Iverson GL, McCrory P. Chronic traumatic encephalopathy in sport: a systematic review. Br J Sports Med. 2014;48:84–90. *This article illustrates the differences in reports of* "*classic*" *CTE vs* "*modern*" *CTE.*

49. DeKosky ST, Blennow K, Ikonovovic MD, Gandy S. Acute and chronic traumatic encephalopathies: pathogenesis and biomarkers. Nat Rev Neurol. 2013;9:192–200.

50. Turjanski N, Lees AJ, Brooks DJ. Dopaminergic function in patients with posttraumatic parkinsonism: an ^{18}F-dopa PET study. Neurology. 1997;49:183–9.

51. Bhidayasiri R, Chotipanich C, Joutsa J, et al. Boxing and Parkinson disease: a link or a myth? An 18F-FDOPA PET/CT study in retired Thai traditional boxers. Parkinsonism Relat Disord. 2012;18:694–6.

52. McKee AC, Gavett BE, Stern RA, et al. TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. J Neuropathol Exp Neurol. 2010;69:918–29.

53. Chi A, Benzi G, Dossena M, et al. Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. Brain. 2005;128:472–6.

54. Belli S, Vanacore N. Proportionate mortality of Italian soccer players: is amyotrophic lateral sclerosis an occupational disease? Eur J Epidemiol. 2005;20:237–42.

55. Armon C. An evidence-based medicine approach to the evaluation of the role of exogenous risk factors in sporatic amyotrophic lateral sclerosis. Neuroepidemiology. 2003;22:217–28.

56. Armon C. Sports trauma in amyotrophic lateral sclerosis revisited. J Neurol Sci. 2007;262:45–53.

57. Armon C, Nelson LM. Is head trauma a risk factor for amyotrophic lateral sclerosis? An evidence based review. Amyotroph Lateral Scler. 2011;13:351–6.

58. Bedlack RS, Genge A, Amato AA, et al. Correspondence regarding: TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. J Neuropathol Exp Neurol. 2011;70:96–7. *J Neuropatho Exp Neurol. 2010;69;918–29.*

59.• Hazrati LN, Tartaglia MC, Diamandis P, et al. Absence of chronic traumatic encephalopathy in retired football players with multiple concussions and neurological symptomatology. Front Hum Neurosci. 2013;7:222. *A small series of 6 subjects with suspected CTE. All 6 had other neurodegenerative diseases. 3 had concomitant CTE. This series illustrates the challenge of premorbid diagnosis of CTE.*

60. McLatchie G, Brooks N, Galbraith S, et al. Clinical neurological examination, neuropsychology, electroencephalography and computed tomographic head scanning in active amateur boxers. J Neurol Neurosurg Psychiatry. 1987;50:96–9.

61. Hart J, Kraut MA, Womack KB, et al. Neuroimaging of cognitive dysfunction and depression in aging retired National Football League players: a cross-sectional study. JAMA Neurol. 2013;70:326–35.

62. Zhang L, Heier LA, Zimmerman RD, et al. Diffusion anisotropy changes in the brains of professional boxers. Am J Neuroradiol. 2006;27:2000–4.

63. Zhang L, Ravdin LD, Relkin N, et al. Increased diffusion in the brain of professional boxers: a preclinical sign of traumatic brain injury? Am J Neuroradiol. 2003;24:52–7.

64. Strain J, Didenbani N, Cullum CM, et al. Depressive symptoms and white matter dysfunction in retired NFL players with concussion history. Neurology. 2013;81:25–32.

65. Chappell MH, Uluğ AM, Zhang L, et al. Distribution of microstructural damage in the brains of professional boxers: a diffusion MRI study. J Magn Reson Imaging. 2006;24:537–42.

66. Bazarian JJ, Zhu T, Zhong J, et al. Persistent, long-term cerebral white matter changes after sports-related repetitive head impacts. PLoS ONE. 2014;9:e94734.

67. Dean PJ, Otaduy MC, Harris LM, et al. Monitoring long-term effects of mild traumatic brain injury with magnetic resonance spectroscopy: a pilot study. Neuroreport. 2013;24:677–81.

68. Small GW, Vladimir K, Siddarth P, et al. PET scanning of brain tau in retired National Football League players: preliminary findings. Am J Geriatr Psychiatr. 2013;21:138–44.

69. Mitsis EM, Riggio S, Kostakoglu L, et al. Tauopathy PET and amyloid PET in the diagnosis of chronic traumatic encephalopathies: studies of a retired NFL player and a man with FTD and a severe head injury. Transl Psychiatry. 2014 (in press)

70. Zetterberg H, Hietala A, Jonsson M, et al. Neurochemical aftermath of amateur boxing. Arch Neurol. 2006;63:1277–80.

71. Neselius S, Brisby H, Theodorsson A, et al. CSF-biomarkers in Olympic boxing: diagnosis and effects of repetitive head trauma. PLoS ONE. 2012;7:e33606.

72. Neselius S, Zetterberg H, Blennow K, et al. Olympic boxing is associated with elevated levels of the neuronal protein tau in plasma. Brain Inj. 2013;27:425–33.

73. Bernick C, Banks S, Phillips M, et al. Professional fighters brain health study: rationale and methods. Am J Epidemiol. 2013;178:280–6.