MINI-SYMPOSIUM: The Study and Consequences of Repetitive Traumatic Brain Injury

Clinical Features of Repetitive Traumatic Brain Injury and Chronic Traumatic Encephalopathy

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Abstract
Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease characterized by a distinct pattern of hyperphosphorylated tau (p-tau). Thought to be caused by repetitive concussive and subconcussive injuries, CTE is considered largely preventable. The majority of neuropathologically confirmed cases have occurred in professional contact sport athletes (eg, boxing, football). A recent post-mortem case series has magnified concerns for the public’s health following its identification in six high school level athletes. CTE is diagnosed with certainty only following a post-mortem autopsy. Efforts to define the etiology and clinical progression during life are ongoing. The goal of this article is to characterize the clinical concepts associated with short- and long-term effects of repetitive traumatic brain injury, with a special emphasis on new clinical diagnostic criteria for CTE.

Differences in cerebellar pathology in CTE confirmed cases in boxing and football are discussed.

INTRODUCTION
Participating in contact sports is thought to increase an individual’s risk for later-life impairments and neurodegeneration. Both active and retired athletes who report multiple concussions are significantly more likely to have problems with depression, emotional liability, executive function, attention and memory. In a study commissioned by the National Football League (NFL), it was reported that retired players were 20 times more likely than age-matched controls to receive a diagnosis of dementia, Alzheimer’s disease (AD), cognitive impairment or related memory impairment disorders (93). Lehman et al, for the National Institute for Occupational Safety and Health, found that neurodegeneration was listed as the cause of death three times more often in NFL players than in the general US population (46,47). Mounting evidence suggests chronic traumatic encephalopathy (CTE) may be the major underlying etiology in these reports. In fact, a recent study with the National Alzheimer’s Coordinating Center Uniform Data Set reported an atypical, tau predominant pathology in cases of suspected AD after grouping participants with significant traumatic brain injury (TBI) histories (73). Mounting evidence suggests chronic traumatic encephalopathy (CTE) may be the major underlying etiology in these reports. In fact, a recent study with the National Alzheimer’s Coordinating Center Uniform Data Set reported an atypical, tau predominant pathology in cases of suspected AD after grouping participants with significant traumatic brain injury (TBI) histories (73). Recently, the Chronic Traumatic Encephalopathy Center (CTEC) added 68 new cases of CTE to the literature (52), which doubled the number of cases reported in the world’s literature. Of the 68 new cases, it is particularly concerning that six cases of neuropathologically confirmed CTE were identified in high school level athletes (17). As a result, the National Institutes of Health and the National Institute of Neurological Disorders and Stroke (NINDS) have teamed up with investigators to provide financial support for multicenter and multidisciplinary investigations into this condition. The purpose of this article is to review (i) the acute effects of sports-related TBI, including clinical criteria for concussions, post-concussion syndrome (PCS); second impact syndrome (SIS) (ii); the chronic effects of sports-related TBI, including CTE (iii); review new clinical diagnostic criteria for CTE; and (iv) provide clinical and pathological details from two cases of neuropathologically confirmed CTE from a professional football player and a professional boxer.

TBI
Concussion
The word “concussion” derives from the Latin concutere, meaning “to shake violently.” Concussions are just that—a shaking of the brain inside the skull, which alters the alertness of the injured person or produces symptoms that fall into four major categories:

(i) Somatic: headaches, nausea, vomiting, balance and/or visual problems, dizzy spells and issues such as sensitivity to light and noise.
(ii) Emotional: sadness to the point of depression (even suicide), nervousness and irritability.

(iii) Sleep disturbance: sleeping more or less than usual and trouble falling asleep.

(iv) Cognitive: difficulty concentrating, troubles with memory, feeling mentally slow or as if in a fog that will not lift.

Changes in alertness can be relatively mild (slightly dazed) or profound (unconscious), yet both situations fall within the definition of concussion. Although concussion is often classified as a form of mild TBI (MTBI), when the profound potential effects are considered, many clinicians do not view a concussion as a necessarily mild injury. It is, however, generally agreed that:

(i) Both direct and indirect head trauma produce linear and rotational forces on the brain, with rotational forces being the most injurious (14).

(ii) Concussions do not typically cause structural changes seen on routine imaging studies, such as computed tomography (CT) and magnetic resonance imaging (MRI) scan, but rather exert their pathological changes at the microscopic and biomechanical levels from the brain being shaken within in the skull (13).

(iii) Following a concussive event, there is a destructive pathophysiological and biomechanical response that initiates a chain of neurometabolic and neurochemical reactions that include (79):

- Activation of inflammatory response.
- Imbalance of ionic concentrations.
- Increase in the excitatory amino acids.
- Dysregulation of neurotransmitter release and synthesis.
- Imbalance of mitochondrial functions and energy metabolism.
- Productions of free radicals.

(iv) While an individual prognosis cannot be determined, all concussions are initially managed with both cognitive and physical rest (12, 15, 31).

(v) Following a concussive event, even after resolution of all symptoms, there may be long-lasting, ultrastructural and functional brain alteration as shown by (79):

- Susceptibility weighted imaging MRI.
- Diffusion tensor imaging (DTI) MRI.
- Functional MRI.
- Magnetic resonance spectroscopy MRI.
- Positron emission tomography MRI.

(vi) Because of the unique features of the maturing brain, young athletes are more vulnerable to the effects of a concussion than adults (32, 76).

PCS

While there are two well-recognized definitions of PCS (2, 65) (Tables 1 and 2), most clinicians recognize PCS as the persistence of concussion symptoms lasting beyond a month.

Individuals at increased risk for this condition include athletes with multiple concussions, those with concussions in close proximity to each other and athletes subjected to a double hit such as a direct helmet-to-helmet hit and then the head hitting the ground as the athlete falls (18). At even higher risk is an athlete that experiences additional head trauma while they are symptomatic from a prior concussion through the course of the same game or match. PCS is usually very debilitating, but it typically clears up in a matter of months. Although rare, there are reports where post-concussion symptoms take as long as 5 years to clear up after trauma (18). For those who are able to recover from PCS, especially those with shorter courses, many are able to safely return to competitive sports. For those who do not recover, it is presently not possible to rule out incipient CTE.

SIS

The most concerning concussion-related problem is SIS. Autoregulation, the process by which our brain normally maintain a constant blood flow, is the basis of this serious condition. When the brain’s blood pressure rises, there is a concurrent restriction in the diameter of arterioles. When the blood pressure falls, the opposite occurs: arterioles dilate, or relax, to maintain constant blood flow (Figure 1A–C).

SIS disrupts autoregulation (Figure 1D). Instead of constricting when blood pressure is normal or elevated, arterioles dilate and allow blood to rush through. The result: a massive inflow of blood to the brain accompanied by an equally dramatic increase in intracranial pressure—a highly dangerous situation, which often leads to brain herniation and death. The patients who survive are almost always severely disabled.

Each year, a few athletes lose their lives to SIS, although the exact number is unclear. Since 1987, the senior author of this paper has been involved in a research study that tracks catastrophic injuries causing death, permanent brain injury or spinal cord damage among high school and college football players in the

<table>
<thead>
<tr>
<th>Table 1. International classification for diseases 10th revision clinical criteria for post-concussion syndrome.</th>
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<tbody>
<tr>
<td>A. Head injury usually severe enough to cause loss of consciousness within 4 weeks of symptom onset</td>
</tr>
<tr>
<td>B. Preoccupation with symptoms and fear of brain damage with hypochondrial concern and adaptation of sick role</td>
</tr>
<tr>
<td>C. Three from below</td>
</tr>
<tr>
<td>Headache, dizziness, malaise, fatigue, noise intolerance</td>
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<tr>
<td>Irritability, depression, anxiety, emotional lability</td>
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<tr>
<td>Concentration, memory or intellectual deficit without neuropsychological evidence of deficit</td>
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<td>Insomnia</td>
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<td>Reduced alcohol intolerance</td>
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<th>Table 2. Diagnostic and statistical manual of mental disorders fourth edition criteria for post-concussion syndrome.</th>
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<tr>
<td>A. History of severe concussion</td>
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<tr>
<td>B. Neuropsychological evidence of attention or memory impairment</td>
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<td>C. At least three of the following occurring shortly after injury lasting for 3 months</td>
</tr>
<tr>
<td>Fatigue</td>
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<tr>
<td>Sleep impairment</td>
</tr>
<tr>
<td>Irritability or aggression</td>
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<tr>
<td>Anxiety, depression or labile affect</td>
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<td>Headache</td>
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<td>Dizziness</td>
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<td>Personality change</td>
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United States. During a 13-year interval, 15 cases of SIS were identified out of 94 cases of catastrophic head injury (9). In that study, approximately 40% of athletes were kept on the field despite having concussion symptoms. With a greater commitment to keeping players with concussion symptoms off the field, deaths from SIS could be drastically reduced or eliminated.

Subconcussive brain trauma

A concussion is well recognized as an etiological factor for a spectrum of neurological conditions, including PCS and risk for developing CTE, a neurodegenerative disorder occurring later in life. The role of subconcussive head trauma, defined as head trauma that does not result in recognized concussion symptoms or signs, is not well known. In our published work from the Center for the Study of Traumatic Encephalopathy at Boston University Medical School, we have seen cases of CTE in deceased athletes who never had a recognized concussion. These athletes had, however, sustained many thousands, often more than 10 000 subconcussive blows during their athletic career (53). For athletes who have sustained concussions, our experience tells us that the risk of CTE occurrence correlates best with total head trauma, including both concussive and subconcussive blows (52).

Recent publications clearly point to the damaging effects of repetitive subconcussive trauma in male contact sport athletes when compared with age-matched male noncontact sport athletes (16). Significant abnormal changes in DTI MRI, including fractional anisotropy (FA) and mean diffusivity, were observed in contact sport athletes. Abnormalities were most robust in the corpus callosum, external capsule and inferior fronto-occipital fasciculus areas of the brain containing long myelinated axonal fiber tracts. These abnormal findings were not only seen preseason in the contact vs. noncontact groups, but increased when the groups were compared with preseason to postseason. An alarming finding, this preseason-postseason difference suggests long-term effects from the repeated head trauma associated with playing just one season of a contact sport. A study of 50 Division I football players compared with 25 matched controls found that the volume of the hippocampus (part of the brain important for memory) was reduced by 15%–25% in the football players (77). This diminished brain volume reflected neuronal loss and was correlated with decreased cognitive activity and reaction time. The study further found hippocampus size to be inversely correlated with an athlete’s total years of play. These findings suggested that subconcussive hits have a harmful effect on young brains.

These data validate the idea that brain injury can occur from the repetitive impacts sustained in contact sports, even in the absence of clinically apparent TBI. These subconcussive hits still impart resultant linear and rotational accelerations on the brain as it violently shakes inside the skull.

What makes the author’s findings so compelling and concerning is that in the last year alone, multiple reports in peer-reviewed journals have shown significant differences in preseason vs. postseason values in contact sport athletes using a variety of tests. These findings have included metabolic brain function as measured by functional MRI (87), neurocognitive testing (ImPACT) (87) and structural breakdown of the blood–brain barrier as manifested by S100B protein in the blood (50) structural changes seen on DTI imaging (46). While the majority of these studies have involved American football players, some have included soccer and hockey athletes.

Figure 1. Autoregulation of brain arterioles and pathophysiology. Baseline (A): When blood pressure is normal, brain arteriole blood vessels are neither constricted nor dilated. Increased blood pressure (B): The brain seeks to maintain a constant blood flow. The brain arteriole blood vessels constrict. Decreased blood pressure (C): As pressure falls, brain arteriole dilation occurs. Blood flow to the brain remains unchanged. Dysautoregulation or second impact syndrome (D): A serious disruption occurs. The brain acts as if blood pressure is low when it is not low; it is normal or may be elevated. Brain arteriole blood vessels dilate and blood rushes into the brain and results in a massive rise in intracranial pressure. Within minutes, the brain can herniate, resulting in coma.
This demonstrates that all head trauma, even at the subconcussive level, can result in brain damage in susceptible individuals. It can be argued that the subconcussive group may have included some unrecognized concussions. It is necessary to carry out additional studies beyond the immediate postseason, up to 3, 6 or 12 months, to see in what percentage the abnormalities have included some unrecognized concussions.

Cumulative exposure

In those exposed to repetitive head trauma, there are several possible long-term outcomes that may occur: (i) none, that is, there is no appreciable neurological signs or symptoms; (ii) static deficits that are a result of the head trauma but do not progress; and (iii) a neurodegenerative process, with the repetitive head trauma as either a risk factor (eg, AD) or cause of, for example, CTE. To characterize the clinical features associated with repetitive head trauma, there may be no better groups to examine than football players and boxers. These athletes, particularly those who make it to the professional level, are exposed to thousands of blows to the head over the course of many years. Quantifying such exposure is among the major challenges in the field of TBI. Research efforts are underway to define “clinically practical” measurements of blows to the head among contact sport athletes. For now, the “gold standard” for determining a lifetime history of TBI is retrospective self-reports or proxy reports obtained in a structured interview. These include the NINDS common data elements and recommendations from the Center for Disease Control and Prevention (23, 24, 34). The researchers at the CTEC developed novel questionnaires to obtain athletes’ athletic and concussion histories and to provide meaningful and accurate estimates of overall repetitive TBI (RTBI) exposure (5, 6, 70). While there are inherent limitations of retrospective self-reports, numerous studies have demonstrated their usefulness in evaluating the association between long-term RTBI exposure and latent impairments with an acceptable level of reliability (23, 45). For example, the CTEC recently reported a link between previous football experience and executive dysfunction in older retired football players (74). In their study, 64 retired college and professional football players were compared with healthy adults. Subjects were administered the Behavior Rating Inventory of Executive Function, adult version, to evaluate nine areas of executive functioning with scores compared with published age-corrected normative scores for healthy adults. Relative to healthy adults, the football players indicated significantly more problems overall, as well as on seven of the nine clinical scales, including inhibit, shift, emotional control, initiate, working memory, plan/organize and task monitor. These symptoms were greater in athletes aged 40 and older, indicating that although RTBI experienced by football players is associated with both short-term and long-term self-reported executive dysfunction, these symptoms may develop or worsen in the fifth decade of life.

In the absence of a direct measure of a subject’s cumulative trauma exposure, there are several potential surrogates, such as number of fights, fights per year, number of knockouts and years of fighting, that have been utilized in studies with boxers. Among football players, the total number of seasons, primary position and level achieved (high school, college, professional) have been utilized as well. However, each of these variables may actually have a slightly different influence on the development of long-term impairments and underlying neuropathology, including CTE. Number of fights, for example, may act as a proxy for amount of training. Some have postulated that the effects of repeated blows to the head—even at a subconcussive level—that occur during sparring may play an important role in causing cumulative brain injury as the boxing match itself. Investigations using electroencephalography (EEG) and CT in professional boxers reported a stronger association between total number of years/bouts fought than to the total number of knockouts (KOs), implicating cumulative subconcussive effects (19, 72). Frequency of fighting may be a complementary variable that requires consideration; fighting more frequently may reduce the time the brain has to fully recover from prior trauma and be a risk factor that interacts with number of fights. On the other hand, when the period of unconsciousness exceeds 1 minute, KO may reflect the more severe end of the spectrum of MTBI. However, in the majority of cases where loss of consciousness (LOC) is only seconds, LOC is not correlated with a severe MTBI. While the number of KOs sustained in sanctioned professional fights can be tracked from commonly available records, KOs that may have occurred at other times are harder to trace.

Aside from the specific aspects of RTBI exposures (eg, severity, location and frequency), the timing of exposure in relation to brain maturation may also influence long-term outcomes. Recently, Cantu and Hyman hypothesized that the age at which an individual is first exposed to RTBI could play a major role in the pathological cascade that leads to CTE (13). In the book “Concussions and Our Kids (13),” the authors provide a theoretical groundwork for why certain developmental ages are particularly vulnerable to the effects of RTBI. Experimental evidence to support this hypothesis first appeared in a study of amateur boxers in 1971 (39). In this study, Jedliňskی et al demonstrated a stronger correlation between neurological presentations and pathological EEG (r = 0.47), and psychiatric findings (r = 0.60) in boxers who began their fighting careers at age 15, 16 or 17, showing a stepwise change in the association with each year (39). Since this publication, there has been little additional research into the subject of “age at first contact sport exposure.” Having identified this gap (13), a new study lead by Julie Stamm (83) demonstrated similar findings in American style football players. In this study, an association was made between participation in tackle football prior to age 12 and a greater cognitive impairment later in life; this was determined based on objective neuropsychological tests in a sample of 41 former NFL players (ages 40–69).

In a another recent study group of 730 National Collegiate Athletic Association Division I Football Championship Series athletes, it was demonstrated that while there were no significant differences between position groups in the number of diagnosed concussions, there were significant differences between position groups in the number of undiagnosed concussions (P = 0.008) and “dings” (P < 0.001), with offensive linemen reporting significantly greater numbers than any other positions (3). It is therefore reasonable to suggest that positions with greater risk of concussion have a greater likelihood for cumulative and latent neurodegeneration. Indeed, Lehman et al attempted to subgroup NFL players into “speed” and a “nonspeed” groups for analysis, but were limited by the available sample size (48). To date, no method has been shown to reliably predict which athletes are likely to develop late-life impairments and CTE disease, other than to roughly classify risk as involvement in contact sports (47).
A contemporary study designed to better understand the effect of repetitive head trauma on clinical and subclinical outcomes is the Professional Fighters Brain Health Study (PFBHS). The PFBHS is a longitudinal study of active professional fighters (boxers and mixed martial arts), retired professional fighters and age-/education-matched controls (6). The main objective of the PFBHS is to determine the relationships between measures of head trauma exposure, along with other potential modifiers and changes in brain imaging and neurological/behavioral function over time. Initial results from the PFBHS indicate that increased exposure to head trauma, as measured either by number of professional fights or years of professional fighting, is associated with imaging and performance findings. Because of its ability to potentially reflect white matter integrity, MRI-based DTI has been studied in many different groups exposed to repetitive head trauma. In the PFBHS, a relationship was found between number of KOs and DTI measures in several white matter and subcortical grey matter regions (75). Moreover, striking changes were seen in transcallosal motor pathways. These fibers transverse a long distance, and given the torsional movement of the brain that can occur with head trauma, may be particularly susceptible to injury. Specifically, in 17 active fighters—scanned two times with approximately 1-year interval—transverse diffusivity ($P = 0.055$) and FA ($P = 0.018$) in a motor pathway, defined by DTI tracking from the left M1 seed, were significantly related to number of professional fights over a period of a year (see Figure 2).

While findings have been reported in a variety of sports and military settings, there is no uniform method for DTI analysis that can be applied at an individual level on differing MRI equipment. Measurement of MRI volumes may be a more practical tool, as methods for automated volumetrics are commercially available. Cross-sectional analysis of over 200 active fighters have shown significant correlations between higher number of fights or years of fighting and lower volumes of the thalamus and caudate (see Figure 3) (5).

Overall, these findings cannot be interpreted as being indicative of risk for any specific long-term outcome (ie, CTE). However, additional research examining the relationship between different potential RTBI exposure variables (ie, age of first exposure, subconcussions, years of fighting) and neuropathologically confirmed CTE lesions is warranted.

**CTE**

**Historical context**

As a result of its early discovery in boxers, CTE has been variously referred to as “cumulative encephalopathy of the boxer (20),” “chronic progressive traumatic encephalopathy (27)” and “chronic traumatic encephalopathy (26, 62)” to reflect its trauma etiology and clinical presentation. In the earlier half of the 20th century, it was suggested that the punch-drunk condition was unique to the sport of boxing. The first neuropathologically characterized case of CTE was reported by Brandenberg and Hallervorden in 1954 (10). As additional cases appeared (21, 33), an association formed between the blows endured from boxing and the subsequent development of neurofibrillary tangle predominant dementia. Augustus Thorndike MD, a Massachusetts General Hospital with the Harvard University Athletic Department (1952) declared in the New England Journal of Medicine: “The college health authorities are conscious of the pathology of the ‘punch-drunk’ boxer. Just how much one should permit recurrence of cerebral concussion in college athletes is a matter of opinion (p. 556) (88).” New research shows that CTE is more common in former contact sport athletes than previously realized. Interest in this condition has grown considerably since 2005, following the first post-mortem autopsy report characterizing the pathological hallmarks of CTE in a professional football player (64). Additional neuropathological evidence of CTE has been reported in many sports other than...
professional boxing and football, including professional soccer, mixed martial arts, rugby, ice hockey, wrestling and baseball (52, 53, 84).

**CTE with motor neuron disease (MND)**

MND has been reported in a subset of cases with CTE (54, 57). It is not yet clear whether the pathology in these cases represents a variant of CTE or CTE with overlapping comorbid disease. Recent data suggest that professional American football players have more than four times the risk of dying from amyotrophic lateral sclerosis (ALS) MND than age- and gender-matched controls (47). Our recent review of the world’s literature (61) uncovered the first case of CTE MND ever reported (57) with pathological evidence to support the link between sport-related RTBI and atypical ALS. Meyers et al. reported clinical and neuropathological findings from a 41-year-old retired professional boxer who presented clinically with signs of progressive motor weakness (57). The subject had a significant boxing history, with a career that began at age 14 and included only two known KOs, which were verified by the Pennsylvania Boxing Commission. This case is historically important because the findings reported by Meyers et al. corroborate the findings reported in our more recent case series (52, 54). In 2010, the members of the CTEC reported the first case series with neuropathologically confirmed CTE and ALS in two football players and one boxer (54). Among our recent series of 68 cases, approximately 11% demonstrated pathological evidence of MND (52). The predominant presentation (63%) involved motor weakness, atrophy and fasciculations in addition to cognitive and behavioral symptoms.

**Preclinical CTE**

Analogous to other neurodegenerative diseases, there were neuropathologically confirmed CTE cases in our sample that lacked overt clinical symptoms or impairment (52, 81). As is the case in preclinical AD, developing methods to identify persons at this early stage of CTE disease is crucial for investigating preventative methods and treatments. Additionally, preclinical cases could provide invaluable information about the etiology and development of symptoms in living individuals. Several studies in boxers and football players support the interpretation that asymptomatic head trauma can cause long-term brain damage that may only become apparent once the normal aging process has contributed to neuronal degeneration (89).

**Clinical symptoms of CTE**

The symptoms associated with CTE pathology typically manifest in one of four clinical domains: (i) cognitive, (ii) behavior, (iii) mood and (iv) motor (61, 86).

Table 3 summarizes the clinical symptoms identified in our recent systematic review of 202 previously published cases of male athletes with histories of RTBI that met review criteria for possible, probable and neuropathologically confirmed CTE (61). The sample included 141 boxers, 54 American football players, 5 ice hockey players and 2 professional wrestlers, making this the largest pooled case review of the clinical features in CTE to date. Progression was identified in 137 cases (68%), most often reported in cognitive symptoms, resulting in dementia. The cases described as “stable” were notably younger in age. Symptoms typically manifest 8–10 years after initial RTBI. The clinical course of CTE is slow, much slower than AD or Frontotemporal dementia, with a progression rate estimated at 11–14 years between pathological stages (52).

**Clinical subtypes of CTE**

Similar to other neurodegenerative conditions, the clinical features in CTE are heterogeneous. Stern et al., identified two relatively

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**Table 3. Symptoms of chronic traumatic encephalopathy.**

<table>
<thead>
<tr>
<th>Cognitive features</th>
<th>Behavioral features</th>
<th>Mood features</th>
<th>Motor features</th>
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<tbody>
<tr>
<td>Memory impairment</td>
<td>Physical violence</td>
<td>Depression</td>
<td>Ataxia</td>
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<tr>
<td>Executive dysfunction</td>
<td>Verbal violence</td>
<td>Hopelessness</td>
<td>Dyssarhria</td>
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<tr>
<td>Impaired attention</td>
<td>Explosivity</td>
<td>Suicidality</td>
<td>Parkinsonism</td>
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<tr>
<td>Dysgraphia</td>
<td>Loss of control</td>
<td>Anxiety</td>
<td>Gait</td>
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<tr>
<td>Lack of insight</td>
<td>Short fuse</td>
<td>Fearfulness</td>
<td>Tremor</td>
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<tr>
<td>Perseveration</td>
<td>Impulsivity</td>
<td>Irritability</td>
<td>Masked facies</td>
</tr>
<tr>
<td>Language difficulties</td>
<td>Paranoid delusions</td>
<td>Apathy</td>
<td>Rigidity</td>
</tr>
<tr>
<td>Dementia</td>
<td>Aggression</td>
<td>Loss of interest</td>
<td>Weakness</td>
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<tr>
<td>Alogia</td>
<td>Rage</td>
<td>Labile emotions</td>
<td>Spasticity</td>
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<tr>
<td>Visuospatial difficulties</td>
<td>Inappropriate speech</td>
<td>Fatigue</td>
<td>Clonus</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Boastfulness</td>
<td>Flat affect</td>
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<tr>
<td>Reduced intelligence</td>
<td>Childish behavior</td>
<td>Insomnia</td>
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<td></td>
<td>Socially inappropriate behavior</td>
<td>Mania</td>
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<td></td>
<td>Disinhibited behavior</td>
<td>Euphoria</td>
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<td></td>
<td>Personality changes</td>
<td>Mood swings</td>
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<td>Psychosis</td>
<td>Prolx</td>
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<td></td>
<td>Social isolation</td>
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*Core diagnostic clinical feature, defined as any feature that appeared in 70% or more of the neuropathologically confirmed chronic traumatic encephalopathy (CTE) cases without comorbid disease.*

*Supportive diagnostic feature, defined as any feature that appeared in neuropathologically confirmed CTE cases without comorbid disease.

Table adapted from Montenegro et al. (61) with permission.
distinct clinical presentations: one consisting of behavioral and mood symptoms with an earlier age at onset [mean age at onset 34.5 standard deviation (SD) = 11.6] and another consisting of cognitive impairment with a later age at onset (mean age at onset 58.5, SD = 17.7) (86). Among cases with initial behavioral and mood symptoms, 86% progressed to include cognitive symptoms whereas only 46% of cognitive cases developed behavior and mood symptoms. In addition to the two subtypes described in Stern et al., Montenigro et al identified an additional “mixed subtype” (mean age at onset 43.0, SD = 14.0) in neuropathologically confirmed cases where the predominant presentation was neither behavioral-mood or cognitive, but rather a combination of the two (61). Consistent with recent subtype descriptions (61, 86), earlier studies in boxers also reported having identified recurring subtypes in the presentation of CTE. Classifications identified in the earlier literature (61) were based on various clinical features, including initial presentation, progression, age at onset and occurrence of dementia. For example, Ernst Jokl (founder of the American College of Sports Medicine) distinguished between the two types of chronic impairment in punch-drunk boxers, namely a “behavioral-psychopathic” type and a “neurological-psychiatric” one (60). The former involved cases with presentations involving “viciousness,” “murder committed from jealousy” and “delinquency.” Research involving these subtypes represents an opportunity to refine risk-factor definitions, develop targeted prevention strategies and someday assess treatment responsiveness.

Clinical diagnostic criteria

To date, the only definitive means of diagnosing CTE is through post-mortem autopsy. However, the ability to diagnose CTE during life is critical to conduct epidemiologic studies on CTE and to eventually plan treatment trials. To address this gap, Montenigro et al proposed new clinical research diagnostic criteria for CTE (61) that overcome the limitations identified (49, 58) in the previous criteria (40, 43, 44, 92). The new criteria are based on a systematic review of the previous literature, as well as on the clinical features reported in neuropathologically confirmed cases of CTE without comorbid disease (52, 53, 86). The proposed diagnostic criteria include five general criteria, three core clinical features and nine supportive features to identify the “traumatic encephalopathy syndrome” (TES). The term TES is used to describe the “syndrome” of clinical features that comprise this condition when the underlying pathology is speculative (Table 4). Criteria for the behavioral/mood variant, cognitive variant, mixed variant and TES dementia phenotypes are also provided (Table 5).

Additional biomarker evidence is required to indicate the likelihood that the etiology underlying TES is caused by the CTE pathology. Several potential biomarkers for “probable CTE,” “possible CTE” and “unlikely CTE” are proposed based on recent and ongoing biomarker research (Table 6) (4, 59, 80). Additional research is needed to validate the usefulness of the proposed biomarkers for CTE. Efforts to validate the utility of the proposed clinical criteria (61) are currently underway (Table 4–6).

Treatment and disease management

The treatment of CTE is currently theoretical and remains to be validated with prospective treatment trials. Treatment and manage-
and lecithin (42). Additionally, there are no known preventative interventions for CTE, although it has been suggested that treatments demonstrating effectiveness for AD and TBI might also show promise for CTE (49). For example, one candidate is amantadine, which is considered to be a safe and effective treatment for severe TBI (68). Recent preliminary investigations have suggested that nonpharmacological interventions may benefit contact sport athletes. Studies of professional football players report statistically significant improvements in neurocognitive function for up to 6 months with dietary supplementation (e.g., omega-3 fatty acids) (1, 78). Additional research is needed to determine whether or not reported improvements were maintained in the long term (49). Because of the severe behavioral mood manifestations of this disease, counseling and cognitive behavioral therapy may also help to mitigate the aberrant behavioral and mood manifestations of this disease (49).

Table 5. Criteria for diagnostic subtypes with modifiers (61).

<table>
<thead>
<tr>
<th>A. Traumatic encephalopathy syndrome diagnostic variants</th>
<th>Select one</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Cognitive” Cognitive core features without behavioral/mood.</td>
<td>“Cognitive”</td>
</tr>
<tr>
<td>“Behavioral/mood” Behavioral/mood core features without cognitive.</td>
<td>“Behavioral/mood”</td>
</tr>
<tr>
<td>“Mixed” Both cognitive and behavioral/mood core features.</td>
<td>“Mixed”</td>
</tr>
<tr>
<td>“Dementia” Progressive cognitive core and functional impairment.</td>
<td>“Dementia”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. “With motor features” modifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>“With motor features” Dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait change, falls and/or other features of parkinsonism.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Clinical course modifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Select one</td>
</tr>
<tr>
<td>“Stable” History or tests indicate little if any change.</td>
</tr>
<tr>
<td>“Progressive” Clear indication of progression over 2 years.</td>
</tr>
<tr>
<td>“Unknown/inconsistent” Unknown or inconsistent information</td>
</tr>
</tbody>
</table>

CTE then and now

Recently, certain authors have made a distinction between “classic” and “modern” descriptions of CTE (30, 51). The “classic” entity, proposed by McCrory et al., is defined by the cases reported by Roberts and Corsellis et al in their boxing subjects (25, 71). This particular description highlighted early cases that had prominent motor features, including dysarthria, difficulties with gait and pyramidal problems. It was noted that early reports in boxers identified progression in “the physical signs and problems, but not the cognitive deficits” (p. 2) (30), which is the distinguishing factor from what are considered to be “modern” CTE cases. Alternatively, “modern” cases (i.e., cases published after 2004) are characterized by prominent mood, behavior and progressive cognitive features, but with a reduced frequency of motor symptoms. Our assessment of the evidence suggests that this distinction between “classic” and “modern” CTE presentations is largely an artifact of review bias. The first source of this bias involves the “classic CTE” article by Roberts, who writes: “more attention has been paid, intentionally, to the clinical signs which indicate lesions of cerebellar, pyramidal and extra-pyramidal systems, than to the evidence of dementia or personality change . . . (for) lesions in these systems are readily comparable . . . Leaving aside for later consideration the question of dementia and psychiatric disturbance, which undoubtedly occurs” (p. 47) (71). This methodological limitation prevents any reasonable inferences about the frequency of behavior, mood and cognitive symptoms in classic cases. Although, “in the first case described,” Roberts emphasized that in addition to motor features “dementia had clearly progressed over the years” with “development of a paranoid illness” (p. 44) (71). This evidence does not support the definition of “classic” CTE, rather it suggests that some of the perceived differences in symptoms reported in earlier cases were caused by the methodological limitations and biased review. For instance, the distinction between “classic” and “modern” presentations also does not account for possible group effects related to different sport exposures, that is, the “classic” presentation is derived from boxers while the “modern” presentation is predominantly derived from American football players (61). It is our hypothesis that sport-specific differences in exposure alter the course and severity of certain clinical manifestations in CTE. In the sections that follow, we explore our hypothesis by re-examining the CTE case evidence in boxers and football players previously reported by McKee et al (52, 53) and provide two detailed clinical and pathological case reports from two professional level athletes, a former US professional lightweight boxing champion and an American NFL player.

Table 6. Chronic traumatic encephalopathy (CTE) likelihood criteria (61).

<table>
<thead>
<tr>
<th>“Probable CTE”</th>
<th>Does not satisfy criteria for another disorder more consistently</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meets classification for any TES variant.</td>
<td></td>
</tr>
<tr>
<td>At least one positive “potential biomarker”</td>
<td></td>
</tr>
<tr>
<td>Positive PET tau imaging.</td>
<td></td>
</tr>
<tr>
<td>Negative PET amyloid imaging.</td>
<td></td>
</tr>
<tr>
<td>Normal beta-amyloid CSF levels.</td>
<td></td>
</tr>
<tr>
<td>Elevated CSF p-tau/tau ratio.</td>
<td></td>
</tr>
<tr>
<td>Cavum septum pellucidum.</td>
<td></td>
</tr>
<tr>
<td>Cortical thinning or atrophy.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>“Possible CTE”</th>
<th>May satisfy diagnostic criteria another disorder.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meets classification for any TES variant.</td>
<td></td>
</tr>
<tr>
<td>Progressive course.</td>
<td></td>
</tr>
<tr>
<td>No testing or one negative biomarker except for PET tau.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>“Unlikely CTE”</th>
<th>Does not meet general criteria (1–5) for TES.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Or has had negative PET tau imaging.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CSF = cerebrospinal fluid; PET = positron emission tomography; TES = traumatic encephalopathy syndrome.

BOXING AND AMERICAN FOOTBALL

Trauma risk factors for CTE

All reported neuropathologically confirmed CTE cases have a significant history of brain trauma, usually repetitive, which suggests that RTBI is a necessary factor in acquisition of CTE degenerative pathology. Not every case of CTE has a history of concussions, leading to the belief that subconcussive impacts may be sufficient to induce neuronal degeneration and subsequent neurodegeneration. Alternately, not every individual that is exposed...
to RTBI, either concussive or subconcussive, necessarily develops CTE (37). It is not known what specific aspect of exposure (sport, age, level, position, severity, frequency and mechanics) influences the risk of acquiring CTE. The threshold of damage required for induction and progression of tau pathology is likely multifactorial and may incorporate genetic, environmental and/or nutritional factors (85). Most of what we know about CTE comes from limited information provided in post-mortem case series. Investigations with confirmed cases have identified factors that influence the severity (52) and phenotype (86) of CTE pathology. In American football players with neuropathologically confirmed CTE, there is a positive correlation with the severity of pathology and the total number of years played (Spearman’s test, $r = 0.805, P < 0.0001$), as well as years since retirement (Spearman’s test, $r = 0.753, P < 0.0001$) and age at death (Spearman’s test, $r = 0.806, P < 0.0001$) (52). Conversely, informant-reported number of concussions (Spearman’s test, $r = 0.259, P = 0.184$), years of education (Spearman’s test, $r = 0.258, P = 0.134$) and lifetime steroid use (Wilcoxon–Mann–Whitney test, $P = 0.731$) were not significantly correlated. In boxers with neuropathologically confirmed CTE, the severity of the tau pathology appears to correlate with the total number of years exposed (53).

**Impact type and biomechanics**

The types of impacts athletes endure differ by sport. However, each impact is composed of both linear and rotational forces (13, 14).

Rotational acceleration (Figure 4A,B) occurs when a force is eccentric or tangential to the center of gravity of the head. In boxing, when a punch is directed toward the lateral side of an opponent’s face (ie, “hook punch”) or chin (ie, “upper cut”), the force of the impact will cause the head to twist and rotate outward along the fixed spinal axis (Figure 4A) (13, 38). The sudden rotational acceleration of the skull and hyperextension of the neck causes brain deformation at mechanically rigid inflection points, such as the cerebellopontine angle (Figure 4B). Regions of the brain that are composed of multiple tissue types with different tensile strengths near rigid boney structures, such as the midbrain, are particularly vulnerable to shearing forces that stretch and injure vessels, axons and glia. The greatest risk a boxer faces for concussion is the result of impacts that generate rotational accelerations, such as the hook punch (8). Linear acceleration (Figure 4C,D) occurs when a force is applied directly through the center of gravity of the head, such as in the anterior to posterior direction (14, 67). Investigations with accelerometers placed in helmets have shown that the majority of impacts in American-style football occur from helmet-to-helmet impacts at the top-front of the helmet (Figure 4C). This is true of all levels (ie, youth and professional) and positions, with the exception being the quarterback position. The forces generated in this type of impact are absorbed at the point of origin, which is nearest the frontal lobes (anterior), and transmitted through the brain, down to the brainstem and cerebellum (-posterior) (Figure 4D). The helmet-to-helmet impacts in American football generate a larger net linear
acceleration experienced by the frontal lobes, when compared with the net rotational acceleration generated by the hook punch in boxing (91). The significance of impact differences between sports on long-term consequences and neurodegeneration is not yet known. Cumulative exposure to different impact types has the potential to influence the onset, type, location, severity and progression of underlying neuropathology.

CTE in boxers and American football players

As the types of impact and predominant forces differ between sports (Figure 4), it was hypothesized (61) that the phenotype of CTE would also differ with the type of sport exposure. Some authors question whether the underlying pathology between CTE in American football players and boxers is really the same (8, 30, 51, 63). To explore this issue and to test our hypothesis, we compared the frequency and severity of motor symptoms in addition to cerebellar pathology in professional boxers and professional American football players with neuropathologically confirmed CTE previously described by McKee et al (52). Because of the spectrum of pathology in CTE stages I through IV, cases were grouped into early CTE (stages I and II) and late CTE (stages III and IV). In CTE, neurofibrillary tangle (NFT) lesions progress from a multifocal state (stage II) to a widespread state (stage III) (55). This grouping allowed us to be reasonably confident that any significant difference between groups was caused by the differences in sport exposure and not the natural progression of CTE disease (Table 7).

Our analysis found that the proportion of boxers with motor symptoms (parkinsonism, gait changes and dysarthria) was significantly greater (Table 7, \( P < 0.05 \), Fisher’s exact test) than the proportion in American football players. The proportion of boxers identified with NFT pathology in their cerebellum dentate (71%) was also greater than American football players (57%), although this trend did not quite reach significance. However, we also compared the proportion of cases that had severe (++++) NFT pathology in the cerebellum dentate and found that boxers had significantly more severe NFT deposition (Table 7, \( P < 0.05 \), Fisher’s exact test) than American football players. The lack of significance in frequency of cerebellar involvement between the two sports suggests either one of two possibilities: (i) our sample size was too small to detect the difference or (ii) the severe NFT deposition in the cerebellum dentate of boxers reached clinical thresholds for motor symptoms, whereas in football players it did not. In summary, the results of our secondary analysis (Table 7) of previously reported CTE cases (52) supports the hypothesis that impacts in boxing cause greater strain to the midbrain and cerebellum (Figure 4B) than and therefore having a greater frequency of motor symptoms in boxers with confirmed CTE than football players. This was also evidenced by the severity of CTE NFT pathology in the cerebellum dentate. Although preliminary, these results suggest that different biomechanic exposure profiles influence the risk for specific CTE phenotypes and alter the underlying pathological severity.

Illustrative case studies

The history and clinical presentation of the following cases were obtained through post-mortem telephone interviews with family members while the interviewer remained blind to neuropathological diagnosis and apolipoprotein E status. Semi-structured interviews and well-characterized informant questionnaires were utilized in combination with medical records. For a detailed description of the methods used, see Stern et al (86). Post-mortem pathological analysis and diagnosis methods are described in McKee et al (52).

NFL player, case 1

Clinical history: 56-year-old Caucasian male with a history of high blood pressure and a basal ganglia cerebral vascular accident at 54 and death from a myocardial infarction at age 56. He participated in American football for a total of 17 years, beginning at age 12, and played for 7 years in the NFL at the running back and full back positions. He endured approximately 20 concussions, 10 in the NFL level and five in college. Two concussions resulted in loss of consciousness. At 54, he awoke with symptoms of leg weakness and an MRI demonstrated “a small lacunar infarct to the basal ganglia.” Post-stroke changes were mild and stable, with slowness in movement and complaints of fatigue. After 3 months of rest, he returned to his work as a bank vice president and did well. Around the time that he retired from the NFL, he began to experience recurring posterior headaches, with onset at age 32. Family informants reported that his mood changed in his mid-30s and indicated that he struggled with feelings of sadness and depression. His depression was further supplemented with Wellbutrin. In the year prior to death, he was prescribed with Wellbutrin. In the year prior to death, he was prescribed with Wellbutrin. In the year prior to death, he was prescribed with Wellbutrin. In the year prior to death, he was prescribed with Wellbutrin. In the year prior to death, he was prescribed with Wellbutrin. In the year prior to death, he was prescribed with Wellbutrin. In the year prior to death, he was prescribed with Wellbutrin. In the year prior to death, he was prescribed with Wellbutrin. In the year prior to death, he was prescribed with Wellbutrin. In the year prior to death, he was prescribed with Wellbutrin. In the year prior to death, he was prescribed with Wellbutrin. In the year prior to death, he was prescribed with Wellbutrin. In the year prior to death, he was prescribed with Wellbutrin. In the year prior to death, he was prescribed with Wellbutrin. In the year prior to death, he was prescribed with Wellbutrin. In the year prior to death, he was prescribed with Wellbutrin. In the year prior to death, he was prescribed with Wellbutrin. In t
improvement in *motor* symptoms and family informants reported no new symptoms in the time leading up to his death. A change in his *cognitive* function was observed by family informants during the 5 years leading up to his death. The family version of the cognitive difficulties scale identified mild to moderate cognitive difficulties in short-term memory, attention and concentration and language (28, 82). Several of these changes were reported to have occurred prior to his stroke and with progression. In contrast, results on the functional activities questionnaire (total score = 0) and the modified AD8 informant interview for dementia (total score = 1) did not indicate significant functional impairment or dementia (29, 69). He did not serve in the military nor did he receive a diagnosis related to dementia, parkinsonism or AD.

Clinical diagnosis (61): TES mixed variant; progressive course; possible CTE.

Pathological findings: brain weight was 1550 g. *Gross* findings include a corpus callosum that is thinned throughout its extent, ventricular enlargement, pallor of the substantia nigra and pallor of the locus coeruleus. *Microscopic* (Figure 5A–D) findings were diagnostic of CTE (52) and included numerous tau-immunoreactive NFTs, neurites and astrocytic tangles in the perivascular, sulcal depth, superficial cortical, subpial and glial distribution. No beta-amyloid protein was found.

Pathology diagnoses (52): CTE stage III/IV; vascular disease.

**Boxer, case 2**

Clinical history: 61-year-old Caucasian male with a history of hepatitis C virus and significant liver cirrhosis that led to a transplant at age 58. The subject died from liver failure and complications of pneumonia. He was a former professional boxer and a US lightweight boxing champion. His boxing career began when he was 8, lasting a total of 26 years. He went on to win the Golden Gloves championship and was ranked the top US lightweight boxing champion for several years, with a total of 36 professional bouts in his 12 years at the professional level. He retired at age 34. Over the course of his career, he reported that he had suffered multiple concussions with only one with loss of consciousness, although the specific number of concussions he experienced is not known. He was also involved in one motor vehicle accident at the age of 56, at which time he experienced headaches, backache and signs of a concussion. A noncontrast brain CT scan found no acute intracranial process and therefore he “did not require medical care.” His brain CT did, however, discover that his ventricles and sulcal spaces showed prominent “cerebral atrophy,” including decreased attenuation within the periventricular white matter suggestive of small vessel disease, both of “uncertain significance.” There was also evidence of chronic fractures in the nasal and orbital bones. He did not serve in the military nor did he receive a diagnosis related to dementia, parkinsonism or AD. Family informants described him as being violent and hot-headed since childhood, but noted that his *behavior* deteriorated significantly starting at age 30, with onset of impulsivity, spousal abuse, intermittent explosivity and generally being out of control. In his early 50s, his *mood* was depressed and he developed feelings of hopelessness and worthlessness. At age 55, *cognitive* symptoms related to executive dysfunction became apparent to the family. At age 56, an altercation with his daughter lead to a formal psychiatric consultation, which
noted he had “increased memory problems (frequently) forgets placement of personal items and previous conversations,” as well as worsening dysphoria, irritability and paranoid delusions that his girlfriend was attempting to kill him. He also suggested that the boxing association had officially diagnosed him with “pugilistic dementia.” In his late 50s he reported falling at home from “feeling unsteady and weak.” Motor impairments were obvious in the year prior to his death; he was never diagnosed with parkinsonism or ALS, however, he lost ability to speak, developed dysphagia for food and liquids and his handwriting deteriorated.

Clinical diagnosis (61): TES mixed variant; with motor features; progressive course; probable CTE.

Pathological findings: brain weight was 1230 g. Gross findings include generalized atrophy of the cerebral cortex, atrophy, atrophy of the fornix, cavum septum (1.0 cm), multiple septal fenestrations posteriorly and atrophy of the thalamus and mammillary bodies. There was pallor in the substantia nigra and locus coeruleus. Microscopic (Figure 5E–H) findings were diagnostic of CTE (52) and included numerous tau-immunoreactive NFTs, neurites and astrocytic tangles in the perivascular, sulcal depth, superficial cortical, subpial and glial distribution. No beta-amyloid protein was found. The tau pathology in the substantia nigra, basis pontis and cerebellum was particularly severe. There was mild proliferation of protoplasmic astrocytes consistent with hepatic disease.

Pathological diagnosis (52): CTE with classic microscopic of stage III/IV with mild transactive response DNA binding protein (TDP-43) proteinopathy.

CONCLUSIONS AND FUTURE DIRECTIONS

Participating in a contact sport is now thought to increase an individual’s risk for later-life impairment and possibly developing CTE. CTE has been diagnosed in a wide range of individuals with a history of head trauma, including American football players, soccer and hockey players, boxers, wrestlers and soldiers who have received battlefield injuries. It has even been reported in athletes as young as 17, who only played sports in high school or college. Given the wide range of people that are diagnosed and the recent increase in reported cases, CTE is likely more prevalent than previously thought. To date, the only definitive means to diagnose CTE is through post-mortem autopsy. The neuropathological features of CTE are increasingly well-characterized, yet the clinical aspects of CTE require further elucidation. There is an urgent need for methods that can reliably diagnose CTE during life. To address this gap, new clinical research diagnostic criteria for CTE were proposed and studies to validate its utility are ongoing.

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REFERENCES

Chronic traumatic encephalopathy in boxers vs. football players