Chronic traumatic encephalopathy

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General information

Often described in retired boxers, chronic traumatic encephalopathy (CTE) encompasses a spectrum of symptoms that range from mild to severe form AKA dementia pugilistica or punch drunk syndrome (among others). Symptoms involve motor, cognitive, and psychiatric systems. CTE is distinct from posttraumatic dementia (which may follow a single closed head injury) or from posttraumatic Alzheimer's syndrome. Although generally accepted, not all authorities agree that repeated concussions have any long-term sequelae.

There are some similarities with Alzheimer's disease (AD), including the presence of neurofibrillary tangles having similar microscopic characteristics (the main difference is that they tend to be more superficial in CTE than in AD) and the development of amyloid angiopathy with the attendant risk of intracerebral hemorrhage.

EEG changes occur in one-third to one-half of professional boxers (diffuse slowing or low-voltage records).

Definition

"Chronic traumatic encephalopathy" (CTE) is described as a slowly progressive neurodegenerative disease believed to result from multiple concussions.

The damaging neurological effects of sports-related repetitive head trauma were described by Harrison S. Martland in 1928 [1]. His clinical description of 'punch drunk syndrome' in a group of former boxers has been extended to include a complex neuropathological and clinical diagnosis known today as Chronic Traumatic Encephalopathy (CTE).

The more generic designation, chronic traumatic encephalopathy (CTE), has been employed since the mid-1900s and has been used in recent years to describe a neurodegenerative disease found not just in boxers but in American football players, other contact sport athletes, military veterans, and others with histories of repetitive brain trauma, including concussions and subconcussive trauma [2].

This has prompted renewed interest and controversy regarding the potential for long-term neurodegenerative changes to occur after concussive and even sub-concussive repetitive or blast wave associated head trauma [3] [4].

There is insufficient evidence to establish causation between sports concussion and CTE. It is likely that many of the cases with neuropathological findings represent the normal aging process, the effects of opiate abuse, or a variant of frontotemporal lobar degeneration. Whether particular genetic

causes may place athletes at greater risk of neurodegenerative disease is yet to be determined [5].

see Chronic traumatic encephalopathy in American football players

Epidemiology

Former American football players are at risk for chronic traumatic encephalopathy (CTE) which may have parkinsonism as a clinical feature.

Thus far CTE research has been limited to selective case reports. There are no published systematic studies incorporating both sport and non-sport related head trauma populations. Based on this lack of data, it is currently impossible to determine the incidence of new cases occurring within contact sport. Additionally, overall prevalence of CTE amongst all cases of head trauma cannot be determined at this time. Finally, due to the fragmented data collected in case reports, no conclusions can be drawn about potential risk factors for developing CTE in contact sports [6].

To date, all pathologically confirmed CTE cases have had a history of head trauma; however, the reported degree of severity, frequency of blows to the head, and documentation of prior concussion is highly variable [7].

Of 153 pathologically confirmed cases of CTE represents the most current and most complete number of confirmed CTE cases in the medical literature. The final number of CTE cases was determined after accounting for 113 duplicate reported cases. Duplicate cases accounted for 43% of all cases of CTE identified in the medical literature by this review. Although Maroon et al. acknowledge the occasional need for re-evaluating former CTE cases in order to further understand CTE findings presented to date, the high rate of re-reporting cases often without explicit notation of previous documentation has led to an erroneous, inflated impression of the number of CTE cases reported. The 153 CTE cases described in the review also include four unique cases of CTE found in media reports which were substantiated by cross confirmation from multiple sources including quotes from CTE investigators.

Of the 153 unique pathologically confirmed cases of CTE, six major mTBI subgroups were identified: former boxers, former football players, former hockey players, former military veterans, former professional wrestlers, and other miscellaneous causes of head trauma. Former boxers and football players made up the majority of all cases (86.2%). This observation is consistent with the long standing history of CTE research in the sport of boxing and the recent focus on former football players [8].

Pathophysiology

Traditionally, concussions were considered benign events and although most people recover fully, about 10% develop a post-concussive syndrome with persisting neurological, cognitive and neuropsychiatric symptoms. CTE was once thought to be unique to boxers, but it has now been observed in many different athletes having suffered multiple concussions as well as in military personal after repeated blast injuries. Much remains unknown about the development of CTE but its pathological substrate is usually tau protein, similar to that seen in Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD).

There is an urgent need for understanding the relationship between concussion and the development of CTE as it may provide a window into the development of a proteinopathy and thus new avenues for treatment [9].

Chronic traumatic encephalopathy is characterized by a unique pattern of accumulation of hyperphosphorylated tau in neurons and astrocytes. The tau abnormalities begin focally and perivascularly at the depths of the cerebral sulci, spread to the superficial layers of the adjacent cortex, and eventually become widespread throughout the medial temporal lobes, diencephalon, and brainstem. Abnormalities in 43 kDa TAR DNA-binding protein are also found in most cases of CTE. To date, CTE can only be diagnosed by postmortem neuropathological examination, although there are many ongoing research studies examining imaging techniques and biomarkers that might prove to have diagnostic utility. Currently, the incidence and prevalence of CTE are unknown, although great strides are being made to better understand the clinical symptoms and signs of CTE. Further research is critically needed to better identify the genetic and environmental risk factors for CTE as well as potential rehabilitation and therapeutic strategies [10].

Neuropathology

Chronic traumatic encephalopathy neuropathology

Clinical features

Its clinical presentation is insidious; patients show mild cognitive and emotional symptoms before progressing to parkinsonian motor signs and finally dementia.

The clinical features of CTE are often progressive, leading to dramatic changes in mood, behavior, and cognition, frequently resulting in debilitating dementia [11].

Parkinsonian symptoms may occur in chronic traumatic encephalopathy, see dementia pugilistica

Diagnosis

Several recent reviews have focused on the various neuropathological findings and the clinical criteria used for the diagnosis of CTE and have drawn attention to the confusion and inconsistency of the diagnosis of CTE [12] [13].

Results from new experimental diagnostic tools are promising, but these tools are not yet available.

Omalu et al. present a modality that may be instrumental to the definitive diagnosis of CTE in living patients based on brain autopsy confirmation of [F-18]FDDNP PET findings in an American football player with CTE. [F-18]FDDNP-PET imaging was performed 52 mo before the subject's death. Relative distribution volume parametric images and binding values were determined for cortical and subcortical regions of interest. Upon death, the brain was examined to identify the topographic distribution of neurodegenerative changes. Correlation between neuropathology and [F-18]FDDNP-PET binding patterns was performed using Spearman rank-order correlation. Mood, behavioral, motor, and cognitive changes were consistent with chronic traumatic myeloencephalopathy with a 22-yr lifetime risk exposure to American football. There were tau, amyloid, and TDP-43 neuropathological

substrates in the brain with a differential topographically selective distribution. [F-18]FDDNP-PET binding levels correlated with brain tau deposition (rs = 0.59, P = .02), with highest relative distribution volumes in the parasagittal and paraventricular regions of the brain and the brain stem. No correlation with amyloid or TDP-43 deposition was observed. [F-18]FDDNP-PET signals may be consistent with neuropathological patterns of tau deposition in CTE, involving areas that receive the maximal shearing, angular-rotational acceleration-deceleration forces in American football players, consistent with distinctive and differential topographic vulnerability and selectivity of CTE beyond brain cortices, also involving midbrain and limbic areas. Future studies are warranted to determine whether differential and selective [F-18]FDDNP-PET may be useful in establishing a diagnosis of CTE in at-risk patients [14)].

Differential diagnosis

Chronic postconcussion syndrome, and chronic neurocognitive impairment [15)].

Management

The mainstay of managing this disease is prevention and early detection of its first symptoms.

see endocannabinoid.

Retrospective cohort studies

A retrospective examination of consecutive, deceased, male brain donors with repetitive head impact exposure from the Understanding Neurologic Injury and Traumatic Encephalopathy Study at Boston University from 2014 to 2021. Neuropathologists diagnosed CTE using established National Institute of Neurological Disorders and Stroke criteria. Informants were administered the Brown-Goodwin Assessment for Lifetime History of Aggression (BGLHA) and were queried regarding 1°FHMI. Exploratory factor analysis evaluated BGLHA factor structure. Stratified by CTE status, linear regression analyses examined relationships between 1°FHMI and standardized adult BGLHA scores and factor scores. Models were adjusted for race, age at death, education, years of contact sports play, military history, substance use treatment history, psychologically traumatic event history, and BGLHA childhood score.

Results: Among 845 brain donors, the mean age at death was 60.3 (SD = 19.6) years. 589 donors (69.7%) had CTE, and 383 donors (45.3%) had a 1°FHMI. 1°FHMI was significantly associated with standardized adult BGLHA scores in those with CTE, but not in those without CTE (CTE present: β = 0.16, 95% CI 0.02-0.29; CTE absent: β = 0.10, 95% CI -0.12 to 0.32). The largest effects were observed among those with CTE, aged 40-59 years (CTE present: β = 0.64, 95% CI 0.32-0.96; CTE absent: β = 0.05, 95% CI -0.44 to 0.54), particularly for BGLHA factors of emotional dysregulation/impulsiveness (CTE present: β = 1.68, 95% CI 0.78-2.58; CTE absent: β = 0.09, 95% CI -1.20 to 1.37) and antisocial behavior (CTE present: β = 1.56, 95% CI 0.64-2.47; CTE absent: β = 0.10, 95% CI -1.19 to 1.40).

Discussion: Among brain donors exposed to repetitive head impacts, CTE pathology moderated the effect of 1°FHMI on BGLHA scores, with the largest effects in midlife. Predisposition to mental illness

and CTE pathology may increase the risk of aggression beyond each risk factor's additive effects. Prospective studies are needed to confirm these results [16)]

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