Repetitive Head Impacts and Chronic Traumatic Encephalopathy

Ann C. McKee, MD[a,b,c,d,*], Michael L. Alosco, PhD[b,c], Bertrand R. Huber, MD, PhD[a,b]

KEYWORDS

• Chronic traumatic encephalopathy • Repetitive head impacts • Traumatic brain injury • Neurodegenerative disease • Tau protein • Subconcussion • Concussion

KEY POINTS

- A panel of expert neuropathologists recently defined chronic traumatic encephalopathy (CTE) as a unique neurodegenerative tauopathy characterized by a pathognomonic lesion. The pathognomonic lesion consists of a perivascular accumulation of abnormally hyperphosphorylated tau in neurons and astrocytes distributed in an irregular fashion with a propensity for sulcal depths of the cerebral cortex.
- The development of research criteria for the clinical diagnosis of CTE, known as traumatic encephalopathy syndrome, will facilitate clinical research in CTE.
- The number of years of exposure to contact sports, not the number of concussions, is significantly associated with more severe tau pathology in CTE, suggesting that repetitive head trauma, including subconcussive injury, is the primary stimulus for disease.
- Recent studies in neurodegenerative disease brain bank cohorts suggest that among amateur athletes, changes of CTE are more common than previously recognized.
- The development of in vivo biomarkers for CTE to facilitate the diagnosis of CTE during life and therapeutic strategies to help individuals with suspected CTE are critically needed.

INTRODUCTION

There are growing concerns that cumulative repetitive head impact exposure through routine participation in contact and collision sports is associated with increased risk of chronic neurologic and neuropsychiatric problems.[1,2] Among the issues associated with cumulative repetitive mild traumatic brain injury are persistent postconcussive symptoms and long-term problems in memory and cognition, including the development of chronic traumatic encephalopathy (CTE).[1–6]

CTE is a unique neurodegenerative disorder that occurs as a latent consequence of cumulative repetitive head impacts (RHIs), including concussion and subconcussion. CTE was first associated with the sport of boxing in 1928, when Harrison Stanford Martland described the clinical features of a neuropsychiatric syndrome that affected pugilists, a condition then known as "punch drunk" or "dementia pugilistica."[7] Over the following decades, it was gradually recognized that the condition affected men and women with a broad

Disclosures/Funding: See last page of article.
All authors report no financial conflicts.
[a] Department of Pathology and Laboratory Medicine, VA Boston Healthcare System, 150 South Huntington Avenue, Boston, MA 02130, USA; [b] Department of Neurology, Boston University School of Medicine, 72 East Concord Street, Boston, MA 02118, USA; [c] CTE Program, Alzheimer's Disease Center, Boston University School of Medicine, 72 East Concord Street, Boston, MA 02118, USA; [d] Department of Pathology, Boston University School of Medicine, 72 East Concord Street, Boston, MA 02118, USA
* Corresponding author. 72 East Concord Street, Robinson 7800, Boston, MA 02118.
E-mail address: amckee@bu.edu

Neurosurg Clin N Am 27 (2016) 529–535
http://dx.doi.org/10.1016/j.nec.2016.05.009
1042-3680/16/$ – see front matter Published by Elsevier Inc.

range of exposure to repetitive brain trauma, including physical abuse,[8] head banging,[9,10] poorly controlled epilepsy, dwarf-throwing,[11] and rugby.[10] The term "chronic traumatic encephalopathy" or "CTE" was introduced by Critchley in his 1949 monograph "Punch drunk syndromes: the chronic traumatic encephalopathy of boxers,"[12] and has subsequently become the preferred designation. Recently, CTE has been described in athletes playing popular modern contact sports including American football, soccer, baseball, wrestling, ice hockey, as well as in military personnel exposed to RHI during military service, including explosive blast.[1,2,5,13–15] Currently, one of the great concerns to public heath is the identification of CTE in teens and amateur athletes at the high school and collegiate levels.[2,5,16] Although this past decade has seen a dramatic increase in public awareness of CTE and an equally dramatic rise in scientific research focused on the long-term effects of RHI, the science to identify the precise risks of RHI exposure and the development of CTE in amateur and professional athletes and military veterans lags behind. Like many neurodegenerative diseases, currently CTE can only be diagnosed after death by neuropathologic examination, and the precise incidence and prevalence of CTE remain unknown. Large-scale, longitudinal prospective studies are needed to directly address these public concerns and close the existing gaps in the basic and clinical science related to the natural history, evaluation and management, and long-term effects of RHI exposure.

NEUROPATHOLOGY OF CHRONIC TRAUMATIC ENCEPHALOPATHY

Microscopic Pathology

The neuropathology of CTE is increasingly well defined. In 2013, in the largest case series study to date, McKee and colleagues[2] reported the spectrum of p-tau pathology in 68 male subjects with a history of exposure to RHI with neuropathological evidence of CTE, ranging in age from 17 to 98 years (mean 59.5 years). In young subjects with the mildest forms of CTE, focal perivascular epicenters of hyperphosphorylated tau (p-tau) immunoreactive neurofibrillary tangles (NFTs) and astrocytic inclusions were found clustered at the depths of the cortical sulci; in subjects with severe disease, a profound tauopathy involved widespread brain regions. Other abnormalities encountered in advanced disease included abnormal deposits of phosphorylated TAR DNA-binding protein of 43 kDa (TDP-43) protein, neuroinflammation, varying amounts of beta amyloid plaques, neuronal loss, and white matter degeneration. Based on these findings, preliminary criteria for the neuropathological diagnosis of CTE and a 4-tiered staging system for grading pathologic severity were proposed (Fig. 1).

In 2015, as the first part of a series of consensus panels funded by the National institute of neurological disorders and stroke/National institute of biomedical imaging and bioengineering (NINDS/NIBIB) to define the neuropathological criteria for CTE, these preliminary neuropathological criteria were used by 7 expert neuropathologists to blindly evaluate 25 cases of various tauopathies, including CTE, Alzheimer disease, progressive supranuclear palsy, argyrophilic grain disease, corticobasal degeneration, primary age-related tauopathy, and parkinsonism dementia complex of Guam without

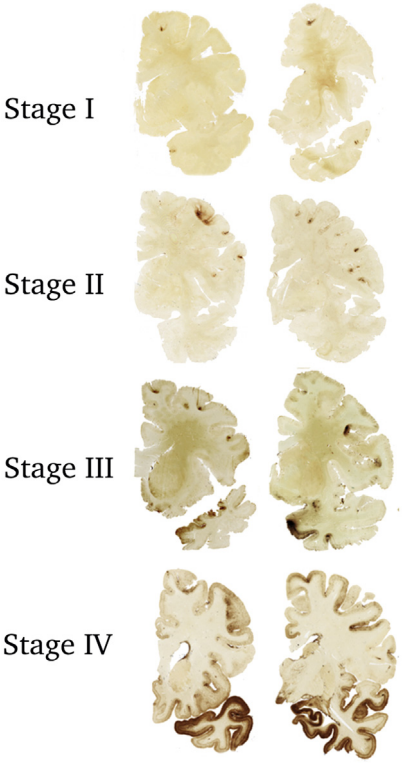

Fig. 1. Stages of hyperphosphorylated tau pathology in CTE. In stage I CTE, p-tau pathology is restricted to isolated foci in the cerebral cortex; the focal lesions consist of perivascular accumulation of p-tau as neuronal and astrocytic inclusions, with NFTs and dot-like structures. In stage II CTE, there are multiple p-tau lesions typically found at the depths of the cerebral sulci. In stage III CTE, p-tau pathology is widespread in the cortex, and the amygdala, hippocampus and entorhinal cortex show neurofibrillary pathology. In stage IV CTE, there is widespread severe p-tau pathology affecting most regions of the cerebral cortex and the medial temporal lobe, with sparing of the calcarine crtex. All images, CP-13 immunostained 50 μm tissue sections.