Review strengthens evidence that repetitive head impacts can cause CTE

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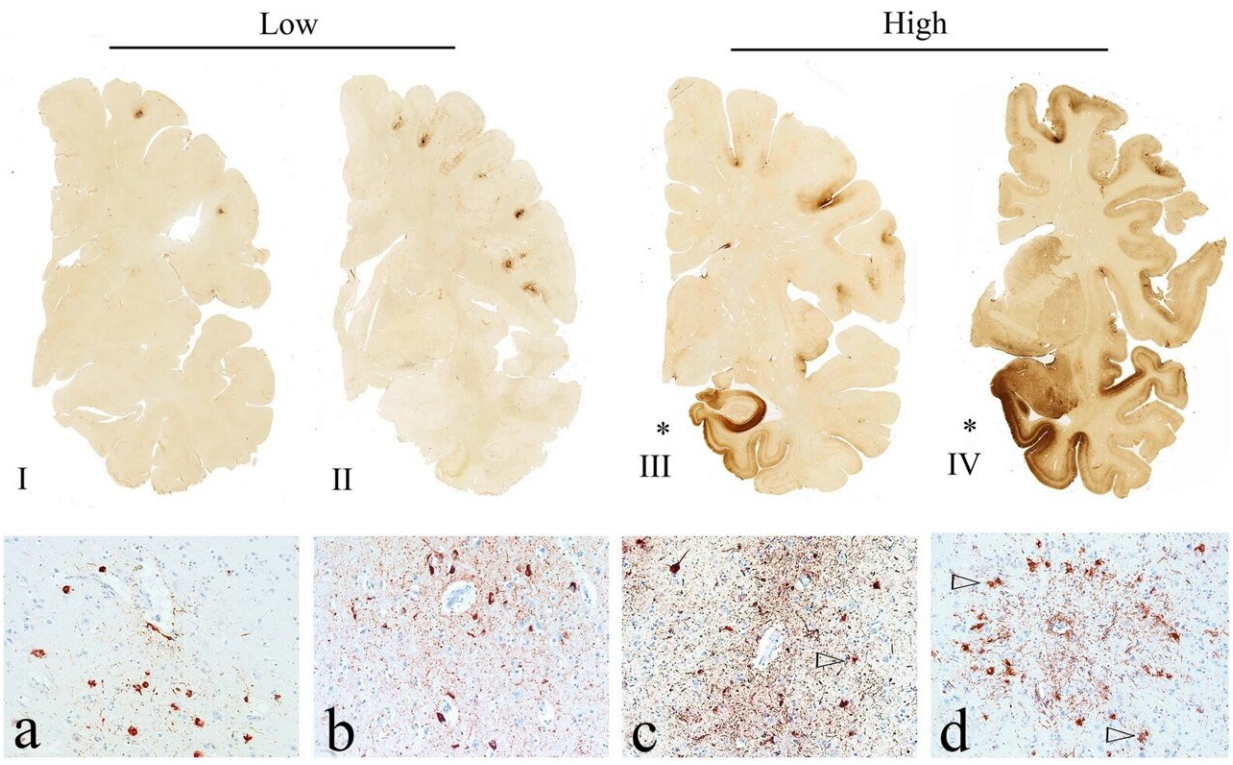

The pathognomonic lesion of CTE and the staging schemes of pathological severity (adapted with permission from [83]). Representative images of p-tau pathology at Low and High chronic traumatic encephalopathy (CTE) pathological stage using the abbreviated staging scheme recommended by the second NINDS/NIBIB consensus panel (low–high) [11] and the McKee staging scheme (I–IV) [4, 79]. Low CTE is characterized by p-tau pathology restricted to focal cortical lesions. High CTE shows widespread p-tau pathology in the medial temporal lobe structures and diencephalon in addition to focal cortical lesions. McKee Stage I CTE is characterized by one or two isolated CTE lesions at the

depths of the cortical sulci. In stage II, three or more cortical CTE lesions are found. In stage III CTE, there are multiple CTE lesions and diffuse NFTs in the medial temporal lobe. In stage IV CTE, CTE lesions and NFTs are widely distributed throughout the cerebral cortex, diencephalon, and brainstem. Top row: hemispheric 50-µm tissue sections immunostained with CP-13, directed against phosphoserine 202 of tau (courtesy of Peter Davies, Ph.D., Feinstein Institute for Medical Research; 1:200); positive p-tau immunostaining appears dark brown. Bottom row: 10-µm paraffin-embedded tissue sections immunostained for phosphorylated tau (AT8) (Pierce Endogen). Positive p-tau immunostaining appears dark red, hematoxylin counterstain. **I** A 26-year-old former college football player with stage I CTE (Low). Two perivascular p-tau CTE lesions are evident at the sulcal depths of the frontal cortex; there is no neurofibrillary degeneration in the medial temporal lobe. **II** A 49-year-old former NFL player with stage II CTE (Low). There are multiple perivascular p-tau CTE lesions at depths of sulci of the frontal cortex; there is no neurofibrillary degeneration in the amygdala or entorhinal cortex. **III** A 53-year-old former NFL player with stage III CTE (High). There are multiple CTE lesions in the frontal cortex and insula; there is diffuse neurofibrillary degeneration of hippocampus and entorhinal cortex (asterisk). **IV** A 62-year-old former NFL player with stage IV CTE (High). There are multiple CTE lesions in the cerebral cortex with widespread neurofibrillary degeneration. There is also extensive neurofibrillary degeneration of the amygdala and entorhinal cortex (asterisk). **a** Pathognomonic CTE lesion in stage I CTE. AT8 immunopositive neurofibrillary tangles, dot-like and threadlike neurites encircle a small blood vessel. **b** Pathognomonic CTE lesion in stage II CTE. A cluster of AT8 immunopositive neurofibrillary tangles and dense dot-like neurites surround several small blood vessels, **c** pathognomonic CTE lesion in stage III CTE. A large collection of AT8 immunopositive neurofibrillary tangles and dense dot-like neurites enclose several small blood vessels. With increasing age, AT8 immunoreactive astrocytes are increasingly evident within the pathognomonic lesion (open triangle). **d** Pathognomonic CTE lesion in stage IV CTE. A large accumulation of AT8 immunopositive neurofibrillary tangles, most of them ghost tangles, encompass several small blood vessels. With increasing age, AT8 immunoreactive astrocytes are increasingly prominent (open triangles) and there may be evidence of neuronal loss. **a–d** All magnification × 200. *P-tau* phosphorylated tau, *CTE* chronic traumatic encephalopathy, *NFL* National Football League. Credit: *Acta Neuropathologica* (2023). DOI: 10.1007/s00401-023-02540-w

During the past 17 years, there has been a remarkable increase in scientific research concerning chronic traumatic encephalopathy (CTE) with researchers at the BU CTE Center at the forefront. While some sports organizations like the National Hockey League and World Rugby still claim their sports do not cause CTE, a new review of the evidence by the world's leading CTE expert strengthens the case that repetitive head impact (RHI) exposure is the chief risk factor for the condition.

CTE became national news in the United States in 2007, but it wasn't until 2016 that the National Institute of Neurological Disorders and Stroke/National Institute of Biomedical Imaging and Bioengineering (NINDS-NIBIB) criteria for the neuropathological diagnosis of CTE were published, and they were refined in 2021. Rare, isolated case studies reporting aberrant findings or using non-accepted diagnostic criteria have been disproportionately emphasized to cast doubt on the connection between RHI and CTE.

In a review article in the journal *Acta Neuropathologica*, Ann McKee, MD, chief of neuropathology at VA Boston Healthcare System and director of the BU CTE Center, stresses that now over 600 CTE cases have been published in the literature from multiple international research groups. And of those over 600 cases, 97 percent have confirmed exposure to RHI, primarily through contact and collision sports.

CTE has been diagnosed in amateur and professional athletes, including athletes from American, Canadian, and Australian football, rugby union, rugby league, soccer, ice hockey, bull-riding, wrestling, mixed-martial arts, and boxing.

What's more, 82 percent (14 of the 17) of the purported CTE cases that occurred in the absence of RHI, where up-to-date criteria were used, the

study authors disclosed that families were never asked what sports the decedent played.

According to the researchers, despite global efforts to find CTE in the absence of contact sport participation or RHI exposure, it appears to be extraordinarily rare, if it exists at all.

"In studies of community brain banks, CTE has been seen in 0 to 3 percent of cases, and where the information is available, positive cases were exposed to brain injuries or RHI. In contrast, CTE is the most common neurodegenerative disease diagnosis in contact and collision sport athletes in brain banks around the world. A strong dose response relationship is perhaps the strongest evidence that RHI is causing CTE in athletes," she added.

"The review presents the timeline for the development of neuropathological criteria for the diagnosis of CTE which was begun nearly 100 years ago by pathologist Harrison Martland who introduced the term 'punch-drunk' to describe a neurological condition in prizefighters," explained McKee, corresponding author of the study. The review chronologically describes the multiple studies conducted by independent, international groups investigating different populations that found CTE pathology in individuals with a history of RHI from various sources.

CTE is characterized by a distinctive molecular structural configuration of p-tau fibrils that is unlike the changes observed with aging, Alzheimer's disease, or any other diseases caused by tau protein.

More information: Ann C. McKee et al, Chronic traumatic encephalopathy (CTE): criteria for neuropathological diagnosis and relationship to repetitive head impacts, *Acta Neuropathologica* (2023). DOI: 10.1007/s00401-023-02540-w

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