Long-term exposure to repeated head impacts can lead to persistent cognitive and neuropsychiatric symptoms and progressive, neurodegenerative disease known as chronic traumatic encephalopathy (CTE). In this study, the authors from the United States investigated whether CTE could be found in the brain histopathological samples of young athletes who played contact sports and were younger than 30 years at the time of death.

CTE is a histopathological diagnosis that can only be diagnosed *postmortem.* It is based on neuronal perivascular accumulation of hyperphosphorylated tau (p-tau) aggregates in the depths of the cortical sulci, comprising pathognomonic lesions of p-tau immunoreactive neurofibrillary tangles and dotlike neurites, oriented around small vessels.

The clinical presentation of suspected CTE is described by a clinical syndrome known as traumatic encephalopathy syndrome (TES) based on cognitive, behavioral, and other features. The diagnostic criteria for TES include repetitive head trauma, clinical manifestations of cognitive impairments (especially in episodic memory and executive functions), neurobehavioral and emotional dysregulation, a progressive course of disease, and clinical manifestations that another condition cannot fully explain. Athletes from a variety of sports have been found to have CTE. Young athletes who play contact sports are also at risk of developing chronic brain disorders, including CTE.

About the study

The authors examined brain samples from brain donors younger than 30 years of age at the time of death, which were identified in the Understanding Neurologic Injury and Traumatic Encephalopathy (UNITE) Brain Bank. The brains were donated over 14 years, from 2008 to 2022. The authors explained that they selected a limit of less than 30 years to minimize any age-related effect on the results.

Most of these young athletes played contact sports only at the amateur level, as members of teams affiliated with educational institutions.

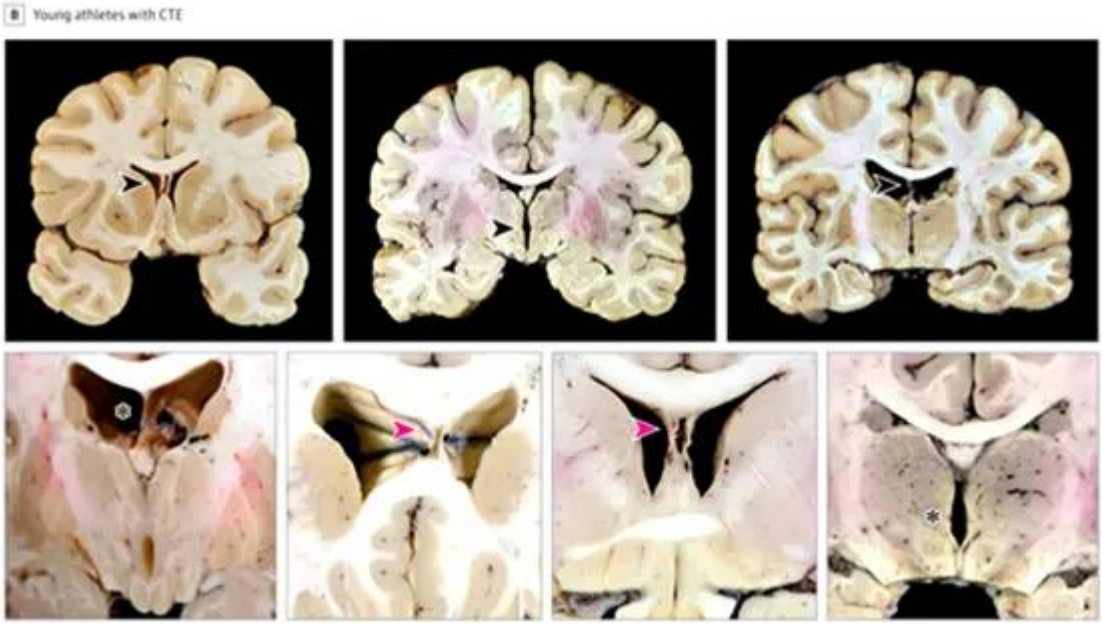
The pathohistological diagnoses were based on the NINDS National Institute of Biomedical Imaging and Bioengineering criteria for CTE and other neurodegenerative diseases. Brain samples were also examined for other pathologies, such as vascular abnormalities, white matter rarefaction, and the presence of perivascular pigment–laden macrophages within the deep cerebral white matter. Four neuropathologists reviewed the pathohistological diagnoses.

In addition, the authors used online questionnaires, modified for retrospective use, and/or structured and semistructured telephone interviews to conduct retrospective clinical evaluations of potential cognitive, mood, and neurobehavioral disorders in 143 deceased brain donors. They used several instruments, including the BRIEF–A Metacognition Index, BRIEF–A Behavioral Regulation Index, Cognitive Difficulties Scale, Functional Activities Questionnaire, and Barratt Impulsiveness Scale.

Results

The authors examined brain samples from 152 brain donors, younger than 30 years of age at the time of death. The mean age of death was 23, ranging from 13 to 29 years. The majority (92.8%, 141 individuals) were men, and 7.2% were women. The most common cause of death was suicide, followed by accidental overdose.

Histopathological diagnosis of CTE was found in 41.4% of brain samples of deceased young athletes. One of them was a woman (1.6%). Of 63 young athletes with histopathologically confirmed CTE, 71% were men who played amateur sports, such as American football, ice hockey, soccer, rugby, and amateur and professional wrestling, at the high school or college level. Several of them were military veterans.



Examples of macroscopic brain abnormalities in CTE. Original illustration from the study of McKee A.C et al, 2023

Histopathological diagnosis of CTE is based on neuronal p-tau aggregates, including pathognomonic lesions of p-tau immunoreactive neurofibrillary tangles and dotlike neurites, oriented around small vessels. Compared to brain samples without CTE, the brains diagnosed with CTE had significantly more p-tau neurofibrillary tangles in all brain regions, such as the superior frontal, dorsolateral frontal, and superior temporal cortices, except in the mammillary bodies and the calcarine cortex.

Interestingly, there were no p-tau astrocytes in the parenchyma or subpial region. The authors noted that the absence of p-tau astrocytes was unexpected, as subpial p-tau thorn-shaped astrocytes are common findings in older individuals with CTE. They concluded that this result suggests that p-tau astrocytes are not an early or essential feature of CTE.

The histopathological examination revealed other pathological abnormalities such as enlargement of the frontal horns of the lateral ventricles and notching of the medial thalamus. The number of perivascular pigment–laden macrophages in the frontal subcortical white matter was significantly greater in brains diagnosed with CTE. Since these findings were associated with exposure to repeated head impacts, the authors suggested that blood-brain barrier disruption is critical for the pathogenesis of CTE.

Mild CTE was diagnosed in nearly all (95%) young brain donors, 62% in stage I, 33% in stage II, and 4.8% in stage III. There were no brain donors diagnosed with stage IV CTE.

Brain donors with CTE had a higher educational level, and a college degree or higher. They were more likely to play American football and for a longer time than those without CTE. According to these findings, the development of CTE is affected by the age and duration of exposure to repeated head impacts, even in young athletes.

There was no statistically significant difference between brain donors with or without CTE for any clinical symptom.

Conclusion

CTE was found in 41% of brain samples from young athletes who played contact sports and died before 30 years of age. The researchers emphasized a need for better clinical characterization and prospective objective evaluation of athletes exposed to repeated head impacts.

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Journal Reference

McKee A. C et al. Neuropathologic and clinical findings in young contact sport athletes exposed to repeated head impacts. JAMA Neurol. 2023;80(10):1037-105
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