European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 04, 2022

Original Research Article

To study and investigate chronic traumatic encephalopathy disease severity

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Abstract

Chronic traumatic encephalopathy is a form of tauopathy that develops after minor trauma to the brain occurs repeatedly. We found indications of chronic traumatic encephalopathy in 68 out of 85 persons whose postmortem brains we examined, all of whom had histories of recurrent mild TBI. There were a total of 64 athletes, 21 veterans (86% of whom were also athletes), and one individual with a history of self-harming head banging; their ages ranged from 17 to 98 (mean 59.5). Eighteen participants of similar ages and sexes who had never experienced moderate traumatic brain injury were utilised as controls. Hyper phosphorylated tau pathology in chronic traumatic encephalopathy progressed from mild to severe, from localised perivascular epicentres of neurofibrillary tangles in the frontal neocortex to widespread tauopathy impacting several brain regions, including the medial temporal lobe. At all stages of chronic traumatic encephalopathy, multifocal axonal varicosities and axonal loss were discovered in deep cortex and subcortical white matter. DNA-binding protein TAR In 85% of the cases, there were also 43 immunoreactive inclusions and neurites, ranging from focal disease in stages I through III to extensive inclusions and neurites in stage IV. Stage I chronic traumatic encephalopathy was characterised by symptoms such as headache and inability to focus. Additional symptoms in stage II were hopelessness, impulsivity, and memory loss. Both executive dysfunction and cognitive decline characterised stage III, while dementia, difficulty communicating, and irritability characterised stage IV. Sports-related exposure data was available for 34 American football players; the stage of chronic traumatic encephalopathy was associated with greater football playing time, greater post-football survival, and greater age at death.43 individuals (63%) had a single diagnostic of chronic traumatic encephalopathy; eight had a second diagnosis of motor neuron disease (12%), seven had Alzheimer's disease (11%), 11 had Lewy body disease (16%), and four had frontotemporal lobar degeneration (6%).

Keywords: Brain trauma, lobar degeneration, neurodegenerative diseases, axonal injury, and traumatic brain injury

ISSN 2515-8260 Volume 09, Issue 04, 2022

Introduction

The contemporary diagnosis of chronic traumatic encephalopathy (CTE) has a lengthy history. Around a century ago, reports on the long-term effects of repeated head injury (RHI) started to appear in the scientific literature. Boxing fans had long observed that fighters who frequently took punches to the head were more likely to become "punch-drunk," as the condition is known colloquially. Martland provided the first comprehensive medical description of punch drunk in 1928, describing a range of neurological and psychosocial deterioration [1, 2]. With widespread axonal damage and loss, hyperphosphorylated tau abnormalities move in an organised and predictable manner through the nervous system in chronic traumatic encephalopathy. TAR DNA-binding protein 43, amyloid beta protein, and alpha-synuclein are three other abnormally aggregated proteins that may accumulate as a result of repetitive brain trauma and hyperphosphorylated tau protein deposition, according to the frequent associations between chronic traumatic encephalopathy and other neurodegenerative diseases [3-6].

Short-term memory loss, sadness, impulsivity, aggression, irritability, and increased suicidality are all clinically linked to CTE and often appear 8-10 years after recurrent mild traumatic brain damage. More severe neurological changes, including as dementia, problems in speech and movement, and Parkinsonism, appear as the disease progresses [7-9]. Clinically, frontotemporal dementia or Alzheimer's disease may be mistaken for CTE in its later stages. Motor neuron illness is linked to a subset of CTE cases (MND). Alzheimer's disease and other tauopathies can be clearly separated from the neuropathological alterations of CTE. Generalized atrophy of the cerebral cortex, medial temporal lobe, diencephalon, and mammillary bodies, as well as enlarged ventricles, cavum septum pellucidum, frequently with fenestrations, extensive p-tau-immunoreactive neurofibrillary tangles, and astrocytic tangles in the frontal and temporal cortices, particularly around small cerebral vessels and at the depth [10-16].

Materials and Methods

Fifty brains from ex-athletes, military personnel, and citizens with a history of mild traumatic brain injury were studied in Department of Neurosurgery Osmania Medical College (2019-2021). Brain Bank, we collected the brains of 18 additional individuals who were cognitively normal and had no history of mild traumatic brain damage. The participant's next of kin gave their written approval to take part and donate brain tissue. The Osmania Medical College and Hospital was able to get approval from their institution's ethics committee to accept a brain donation. Osmania Medical College and hospital committee gained consent from the institutional review board to do a postmortem review of clinical records, conduct interviews with family members, and conduct a neuropathological examination.

Clinical assessment

A neuropsychologist who was not aware of the findings of the neuropathological examination at the time of the interview conducted post-mortem interviews with the next of kin in order to ascertain the patient's history of concussion and mild traumatic brain injury, history of cognitive and behavioural changes, and clinical status prior to death. Before learning the findings of the neuropathological examination, informants were questioned. The telephone interview was semi-structured and took place. Demographic information, athletic and military history, concussion and brain trauma history, medical history (including neurological, psychiatric, and substance use history), family history, social/occupational history, and reported/observed changes in mood, behaviour, motor skills, cognition, and daily living activities were all questioned. Modifications of common tests or interviews were given to the informant to gauge their perception of the subject in the months or years leading up to death

in order to semi-quantify cognitive, emotional, and functional changes [17-19].

Neuropathological Examination

The Osmania Medical College and Hospital's standard protocols were followed for the neuropathological processing. The previously reported techniques were used to stain paraffin-embedded sections with Luxol fast blue, haematoxylin and eosin, Bielschowsky's silver, AT8, alpha-synuclein, amyloid-ß, TDP-43, phosphorylated TDP-43 (pTDP-43), SMI-31, and SMI-34. Additionally, many substantial coronal slabs of the cerebral hemispheres were cut at 50 mm on a sledge microtome and stained with AT8, amyloid-ß, TDP-43, pTDP-43, CP13, and PHF-1 as free-floating sections. Without having access to the subjects' clinical histories, one neuropathologist made a diagnosis that was later validated by two additional neuropathologists [20-22].

Neuropathological Diagnoses

The existence of the following criteria (Table 1) was used to make the diagnosis of CTE based on our previous research and review of the literature on CTE: These include I clusters of subpial and periventricular astrocytic tangles in the cerebral cortex, diencephalon, basal ganglia, and brainstem; (ii) irregular cortical distribution of p-tau immunoreactive neurofibrillary tangles and astrocytic tangles with a predilection for the depth of cerebral sulci; and (iv) neurofibrill Clinical confirmation of amyotrophic lateral sclerosis according to the updated El Escorial criteria for the diagnosis of amyotrophic lateral sclerosis and the pathological diagnosis of CTE, as outlined above, were prerequisites for a CTE-MND diagnosis. TDP-43 or pTDP-43 positive neuronal, glial, neuritic, or intranuclear inclusions in anterior horn cells and white matter tracts of the spinal cord. I degeneration of lateral and ventral corticospinal tracts of the spinal cord. (ii) Marked loss of anterior horn cells from cervical, thoracic, and lumbar spinal cord with gliosis [23-26].

Statistical Analysis

CTE stage was considered as an imprecise ordinal variable, and the statistical dependence between CTE stage and all relevant linear variables was assessed using Spearman's rank order correlation (e.g. age, years of education, total number of reported concussions, total number of years of American football played and number of years between retirement and death). For non-linear independent variables, the Kruskall-Wallis test was used for variables with more than two groupings, while the Wilcoxon-Mann-Whitney two-sample rank-sum test was used for independent variables with only two groups (such as the presence of at least one ApoE e4 allele and lifetime history of steroid use) (e.g. position played). Additionally, a Chi-square goodness of fit test was run on all 65 CTE patients to compare them to the expected percentage in the US population to see if the proportion of people with at least one ApoE e4 allele was higher in people who had been diagnosed with CTE.

Table 1: Variations in the pathophysiology of hyper phosphorylated tau between Alzheimer's disease and CTE

Sr. No.	Pathological Parameters	CTE	Alzheimer's disorder
1.	**Tau protein**		
	Six isoforms	All six isoforms present	All six isoforms present
	3or4repeattau	3repeatand4repeattaupresent	3repeatand4repeattaupresent
2.	**Cell origin**		
	Neuronal	NFT sand pre-tangles	NFTs and pre-tangles
	Astrocytic	Prominent astrocytic tangles	Not present
3.	**Neuronal domain**		
	Cellbuddy	Prominent	Prominent

	Dendrite	Prominent	Prominent
	Axon	Prominent	Sparse
4.	**Distribution**		
	Mild pathology	CTE stagesI–II:	Braak stagesI–III:
5.	Advanced pathology	CTE stagesIII–IV	Braak stages IV–VI
		High density of NFTs in widespread cortical areas and medial temporal lobe, uniform distribution	High density of NFT sin widespread cortical areas and medial temporal lobe, patchyir regular distribution

Results

Forty-two athletes, three military veterans with no history of contact sports, one civilian who had undergone several falls, and one individual who engaged in self-injurious repetitive head-banging behaviour made up the 50 brain donors with a history of mild traumatic brain injury (84 males, one female, age range 14-98 years, mean 54.1 23.3 years). We also examined the brains of 18 people who were otherwise healthy and had no history of repetitive mild traumatic brain injury (17 men and 1 woman, aged 18 to 88 years with a mean of 62.0 17.4 years). Of these, 7 were veterans of the armed forces, and 3 were athletes who had participated in activities such as skiing, sailing, golf, and trap shooting.

Pathological findings

Eleven of the control brains showed Alzheimer's-type neurofibrillary pathology limited to the hippocampus and entorhinal cortex consistent with Braak neurofibrillary stages I and II (mean age: 48.1119.8 years), while seven of the control brains were completely negative for p-tau neurofibrillary tangles. Amyloid-ß was found in low concentrations in the blood vessels and the nervous systems of three healthy controls. Neurofibrillary tangles, astrocytic tangles, neurofibrillary tangles located to the depths of the cerebral sulci, and neurofibrillary tangles largely localised to the superficial cortical laminae were not present in any of the control cases. CTE was not seen in the brains of 17 of the 50 people who had a history of repetitive mild traumatic brain injury. Multiple system atrophy was found in a high school football player. Neurofibrillary tangles and astrocytic tangles, both immunoreactive for p-tau, were found in the brains of 38 of the 47 individuals, with a pattern and neuroanatomical distribution characteristic of CTE.

Neuropathology of chronic traumatic encephalopathy

There were 13 diffuse plaques (25.5%), 10 neuritic plaques (19.6%), 7 vascular amyloid (13.7%), and 13 neuritic plaques in those with CTE or CTE-MND. These 41 brains displayed a consistent spectrum of different p-tau pathology that could be separated into four discrete illness stages. Stage I/IV, n = 7, age range 17-56 years, mean 28.3 years 13.5, mild (stage II/IV, n = 14, age range 21-87 years, mean 44.3 years 16.7), moderate (stage III/IV, n = 15, age range 38-82 years, mean 56.0 years 14.2), and severe (stage IV/IV, n = 15, age range 51-98 years, mean 77.4 years 11.7) were the four stages of CTE disease severity. Astrocytic tangles were predominately immunoreactive for 4 R tau, while p-tau neurofibrillary tangles were immunoreactive for both 3 R and 4 R tau at all stages.

Stage I chronic traumatic encephalopathy

Three of the five intact brain specimens showed mild lateral ventricular enlargement, while seven brains displayed stage I CTE. Otherwise unremarkable were the gross

ISSN 2515-8260 Volume 09, Issue 04, 2022

neuropathological characteristics and brain weights. Microscopically, stage I was characterised by focal epicentres of perivascular p-tau neurofibrillary and astrocytic tangles, which were frequently seen in the superior and dorsolateral frontal cortices and were particularly noticeable in the sulcal depths. With the exception of a few uncommon isolated neurofibrillary tangles in superficial laminae, the cortex around the epicentres was normal. Two instances had locus coeruleus lesions with low concentrations of neurofibrillary tangles. In one example, the hippocampus, entorhinal cortex, and substantia nigra had sparse neurofibrillary tangles; in another, the medulla displayed p-tau neurofibrillary tangles and altered axonal profiles [27-29].

Stage II chronic traumatic encephalopathy

In 14 brains, stage II pathology was present. Grossly, the average brain weight of 1463.3 100.1 g showed no signs of cerebral atrophy. Six of the 11 whole specimens had a somewhat enlarged third ventricle or frontal horn of the lateral ventricles, and four had a tiny cavum septum (0.2-0.7 cm). The third ventricle was enlarged and sharply concave in three of the specimens. The substantia nigra and locus coeruleus were paler in three cases. In one case, one mammillary body atrophy and significant gliosis were present. The superior, dorsolateral, lateral, inferior, and subcallosal frontal, anterior, inferior, and lateral temporal, inferior parietal, insular, and septal cortices were the most frequently affected regions of the brain by P-tau disease. The cortex's outermost layers also contained neurofibrillary tangles. Even in the younger people, moderate levels of neurofibrillary tangles were discovered in the amygdala, nucleus basalis of Meynert, and locus coeruleus [30-32].

Stage III chronic traumatic encephalopathy

Stage III pathology was present in 15 brains. The majority of brains had minor cerebral atrophy and lateral and third ventricles that were dilated; the mean brain weight was 1394 106.7 g. 5 of the 12 intact brain specimens (or 42%) had septal anomalies, ranging from cavum septum, septal perforations, or complete lack of the septum. Six brains displayed mild depigmentation of the substantia nigra (42%), while seven displayed significant depigmentation of the locus coeruleus (58%). Atrophy of the mammillary bodies and thalamus, a medial thalamus with a markedly convex contour, thinning of the hypothalamic floor, and thinning of the corpus callosum were other prevalent gross clinical characteristics. The superior frontal, dorsolateral frontal, inferior orbital, septal, insular, temporal pole, superior middle, inferior temporal, and inferior parietal cortices all showed extensive neurofibrillary tangles under a microscope. The hippocampus, entorhinal cortex, amygdala, nucleus basalis of Meynert, and locus coeruleus all had significant neurofibrillary tangles as well [33-35].

Stage IV chronic traumatic encephalopathy

Stage IV CTE was deemed to be present in fifteen people. The cerebral cortex and white matter shrank, and the medial temporal lobe, thalamus, hypothalamus, and mammillary body all underwent significant atrophy. Compared to lower stage CTE, the mean brain weight was substantially lower. The majority of the brains displayed septal perforations or septal absence, ventricular enlargement, a third ventricle with a strongly concave contour, and cavum septum pellucidum ranging in size from 0.5 to 1.0 cm. In all cases where it could be evaluated, pallor of the locus coeruleus and substantia nigra was observed. Microscopically, there was pronounced astrocytic p-tau pathology, hippocampal sclerosis affecting CA1 and subiculum, and neuronal loss in the cortex [35, 36].

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Cause of death and suicide

Five of the 50 individuals with CTE and CTE-MND died by suicide; four others had suicidal thoughts at some point in their lives (13% attempted or completed suicide, 9% completed suicide). Six people died as a result of drug or alcohol overdoses. Respiratory failure, cardiac disease, suicide, overdose, failure to thrive brought on by end-stage dementia, and cancer were the most frequent reasons of death.

Discussion

Repetitive mild traumatic brain damage leads to CTE, a degenerative tauopathy with unique clinical and pathological characteristics. Although chronic traumatic encephalopathy (CTE) has typically been linked to boxing, it may also be a result of playing American football, hockey, wrestling, rugby, and being exposed to blast or concussion injury while serving in the military. Evidence of CTE was identified in the brains of 60 percent of the 50 people we studied who had a history of repetitive mild traumatic brain injury. These individuals were all male and ranged in age from 17 to 98 years old; 42 were athletes, and one had engaged in self-injurious head-banging behaviour. Repetitive mild traumatic brain injury alone is sufficient to initiate CTE in certain people, as shown by the development of CTE in one subject in this series and two others in the literature in whom self-injurious head pounding was the only environmental exposure. The frontal lobes, specifically the superior, dorsolateral, and lateral regions, are particularly vulnerable to CTE's degenerative effects. Clinical signs of disinhibition, lack of insight, and impaired executive function have been observed in people with CTE at very early stages, suggesting that pathology in these regions may underlie these symptoms. Frontal symptoms, as well as the irritability, impulsivity, explosivity, and outbursts of violence so typically observed in early signs of CTE, may be attributable to pathological involvement of the inferior temporal lobe and amygdala. Cognitive problems may be related to pathology in the septal nuclei or the nucleus basalis of Meynert. Common signs of depression and mood instability may also be linked to dysfunction in the subcallosal and inferior orbital frontal cortex and brainstem, namely the locus coeruleus and median raphe. Brain damage in the mammillary body, anterior thalamus, and hippocampus probably all contribute to memory problems, cognitive decline, and dementia.

Conclusion and future prospective

To address the limitations, more prospective longitudinal studies will be conducted in the future. For instance, differences between people with and without clinical and neuropathological evidence of Parkinson's disease can be examined by prospectively studying a large number of retired National Football League players and performing neuropathological analyses at death on a control group matched on age, education, athletic history, medical comorbidities, and cause of death. Similar studies will shed light on the overlap between traumatic brain injury, CTE, and post-traumatic stress disorder as well as the role of combat-associated injury in causing CTE. These studies are focused on a large cohort of Iraq and Afghanistan veterans with histories of blast and concussive traumatic brain injuries as well as post-traumatic stress disorder. It is necessary to establish and test the clinical parameters for the diagnosis of CTE. In this autopsy series, ApoE does not appear to be a risk factor for the onset of CTE or the degree of CTE pathology; however, in order to answer this question definitively, large prospective population-based studies must be conducted. The recent findings demonstrate that a particular pattern of neuropathological changes, which had previously been primarily described in boxers, may also be observed in other athletes and

Veterans and they serve as a strong foundation for future research. CTE is a rare form of neurodegeneration linked to repeated mild traumatic brain injury. This study unequivocally demonstrates that for some athletes and combatants, repetitive brain trauma that has historically been regarded as only mild may have severe and devastating long-term effects. Although there are many issues that still need to be thoroughly investigated, such as how much, what kind and how frequently head trauma is causal, the age when players are most susceptible and whether some people are genetically more prone than others, these issues must be thoroughly investigated.

Conflict of Interest: None

Funding Support: Nil

References

1. Lövestam S, Koh FA, van Knippenberg B, Kotecha A, Murzin AG, Goedert M, *et al*. Assembly of recombinant tau into filaments identical to those of Alzheimer's disease and chronic traumatic encephalopathy. Elife. 2022;11:e76494.
2. Bergauer A, van Osch R, van Elferen S, Gyllvik S, Venkatesh H, Schreiber R. The diagnostic potential of fluid and imaging biomarkers in chronic traumatic encephalopathy (CTE). Biomedicine & Pharmacotherapy. 2022;146:112602.
3. Soyombo NKDS, Rocha EL, Xavier LB, Oliveira RA, Torres R. Biomarkers for Differential Diagnosis between Chronic Traumatic Encephalopathy and Alzheimer Disease: A Systematic Review. Neurology. 2022;98(1 Supplement 1):S15-S16.
4. Priemer DS, Iacono D, Rhodes CH, Olsen CH, Perl DP. Chronic Traumatic Encephalopathy in the Brains of Military Personnel. New England Journal of Medicine. 2022;386(23):2169-2177.
5. Turk KW, Geada A, Alvarez VE, Xia W, Cherry JD, Nicks R, *et al*. A comparison between tau and amyloid-β cerebrospinal fluid biomarkers in chronic traumatic encephalopathy and Alzheimer disease. Alzheimer's research & therapy. 2022;14(1):1-12.
6. Omalu B, Hammers J. In reply: recommendation to create new neuropathologic guidelines for the postmortem diagnosis of chronic traumatic encephalopathy. Neurosurgery. 2022;90(1):e21-e23.
7. Butler ML, Dixon E, Stein TD, Alvarez VE, Huber B, Buckland ME, *et al*. Tau Pathology in Chronic Traumatic Encephalopathy is Primarily Neuronal. Journal of Neuropathology & Experimental Neurology, 2022.
8. Suter CM, Affleck AJ, Lee M, Davies D, Burns AL, Sy J, *et al*. Chronic Traumatic Encephalopathy in a Routine Neuropathology Service in Australia. Journal of Neuropathology & Experimental Neurology, 2022.
9. De Los Reyes FV. Differential Gene Expression of Nystagmus-Associated Genes in Chronic Traumatic Encephalopathy, Parkinson's Disease, and Alzheimer's Disease. Science Open Preprints, 2022.
10. Abad LHS, Lessa RT, de Mesquita FBM, Silva VL, Cesar MR, Ferreira TB, *et al*. Chronic Traumatic Encephalopathy in Sports Practice: A Literature Review. Arquivos Brasileiros de Neurocirurgia: Brazilian Neurosurgery, 2022.
11. Buckland ME, Affleck AJ, Pearce AJ, Suter CM. Chronic traumatic encephalopathy as a preventable environmental disease. Frontiers in Neurology, 2022, 1107.
12. Varlow C, Knight AC, McQuade P, Vasdev N. Characterization of neuroinflammatory positron emission tomography biomarkers in chronic traumatic encephalopathy. Brain Communications. 2022;4(1):fcac019.
13. Hurley D. New Questions about Military Service and Chronic Traumatic

Encephalopathy. Neurology Today. 2022;22(14):1-21.
14. Labadorf AT, Agus F, Aytan N, Cherry J, Mez J, McKee A, *et al*. Inflammation and neuronal gene expression changes differ in early vs late chronic traumatic encephalopathy brain. Bio Rxiv, 2022.
15. Aranha MR, Coutinho AM, Costa Leite CD, Buchpiguel CA. Traumatic Brain Injury and Chronic Traumatic Encephalopathy. In Hybrid PET/MR Neuroimaging. Springer, Cham, 2022, 479-492.
16. Vink R, Corrigan F. Chronic traumatic encephalopathy: genes load the gun and repeated concussion pulls the trigger. Neural Regeneration Research. 2022;17(9):1963.
17. Patel A, Abou-Al-Shaar H, Mathkour M, Maroon JC. Chronic Traumatic Encephalopathy: Past, Present, and Future. In Neurosurgical Care of Athletes. Springer, Cham, 2022, 253-261.
18. Atherton K, Han X, Chung J, Cherry JD, Baucom Z, Saltiel N, *et al*. Association of APOE Genotypes and Chronic Traumatic Encephalopathy. JAMA neurology.
19. Narayan M, Ghanim D, Spencer E, Bovet C. Do repetitive concussions lead to chronic traumatic encephalopathy? Evidence-Based Practice. 2022;25(3):15-16.
20. Suter CM, Affleck AJ, Lee M, Pearce AJ, Iles LE, Buckland ME. Chronic traumatic encephalopathy in Australia: the first three years of the Australian Sports Brain Bank. Suicide, 2022, 6, 1.
21. Kerwin J, Yuecesoy A, Vidhate S, Davila-Montero BM, Van Orman JL, Pence TJ, *et al*. Sulcal cavitation in linear head acceleration: possible correlation with chronic traumatic encephalopathy. Frontiers in Neurology, 2022, 13.
22. Terry DP, Zuckerman SL, Yengo-Kahn AM, Kuhn AW, Brett BL, Davis GA. In Reply: Recommendation to Create New Neuropathologic Guidelines for the Postmortem Diagnosis of Chronic Traumatic Encephalopathy. Neurosurgery. 2022;90(6):e206-e207.
23. Andrikopoulos J. A false chronic traumatic encephalopathy dichotomy, 2022.
24. Ilut S, Vadan I, Muresanu D. The impact of cognitive reserve in the recovery of chronic encephalopathy associated with traumatic brain injury. Journal of Medicine and Life. 2022;15(6):723.
25. Batty GD, Kujala UM, Sarna S, Valencia-Hernandez C, Kaprio J. Alzheimer disease in retired elite collision sports athletes: cohort study. Med Rxiv, 2022.
26. Imms P, Chui HC, Irimia A. Alzheimer's disease after mild traumatic brain injury. Aging (Albany NY). 2022;14(13):5292.
27. Ladak AA, Madhani SI, Gauhar F, Aftab K, Mubarak F, Enam SA. Traumatic brain injury and molecular biology: A new narrative. In Cellular, Molecular, Physiological, and Behavioral Aspects of Traumatic Brain Injury. Academic Press, 2022, 41-54.
28. Rahman MM, Rahman S, Dominic RE, Mittal M, Cincu R, Moscote-Salazar LR, *et al*. Traumatic Brain Injury and Plant-based Immunotherapy. Indian Journal of Clinical Practice, 41-54, 32(8).
29. Irimia A, Rostowsky KA, Law EM, Chui HC. Cerebral hemorrhages in traumatic brain injury. In Diagnosis and Treatment of Traumatic Brain Injury. Academic Press, 2022, 87-99.
30. Smith C. Traumatic brain injury. In Neurobiology of Brain Disorders. Academic Press, 2023, 443-455.
31. Randolph C. Is chronic traumatic encephalopathy a real disease?. Current sports medicine reports. 2014;13(1):33-37.
32. Mez J, Stern RA, McKee AC. Chronic traumatic encephalopathy: where are we and where are we going?. Current neurology and neuroscience reports. 2013;13(12):1-12.
33. Randolph C. Chronic traumatic encephalopathy is not a real disease. Archives of clinical neuropsychology. 2018;33(5):644-648.
34. Ling H, Holton JL, Shaw K, Davey K, Lashley T, Revesz T. Histological evidence of

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chronic traumatic encephalopathy in a large series of neurodegenerative diseases. *Acta neuropathologica*. 2015;130(6):891-893.
35. Montenigro PH, Corp DT, Stein TD, Cantu RC, Stern RA. Chronic traumatic encephalopathy: historical origins and current perspective. Annual review of clinical psychology. 2015;11:309-330.
36. Katsumoto A, Takeuchi H, Tanaka F. Tau pathology in chronic traumatic encephalopathy and Alzheimer's disease: similarities and differences. Frontiers in Neurology. 2019;10:980.