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Elucidating Mechanisms of Chronic Traumatic Encephalopathy (CTE); A Systematic Review of the Literature.

Review Article

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ABSTRACT

Background : Chronic traumatic encephalopathy (CTE) is a progressive neurodegeneration that can be widely distributed throughout the brain due to accumulation of neuropathologic lesions following exposure to repetitive head impact (RHI) causing concussions or sub-concussive traumatic brain injury (TBI). Populations at risk include military personnel and contact sports athletes. A neuropathological severity staging system has been developed based on lesion complexity.

Aim : To systematically review the clinicopathologic correlations and neuroimmunologic mechanisms in CTE.

Methods : We conducted a systematic review by literature search through WorldCat.org and ProQuest Central, inclusive of PubMed and EBSCOhost electronic databases, to identify studies on CTE published between 2013 and 2023 in the English language. PubMed was last accessed on 25 January 2024.

Results : A total of 29 articles, 6 experimental and 23 human studies, were included from the US, Canada, Mexico, Germany, Italy, and the UK. Studies accessed brain tissues from the Veterans Affairs–Boston University–Concussion Legacy Foundation (VA–BU–CLF)/ Understanding Neurological Injury and Traumatic Encephalopathy (UNITE) brain bank, the Farmington Heart Study, and the Dublin brain bank. Severity of CTE progression was linked to player position and years played. Neuropathology included brain atrophy in the hippocampus, amygdala, frontal and temporal cortex, phosphorylated-tau (p-tau) neurofibrillary tangles, beta-amyloid plaques, thread and dot-like neurites, demyelination, axonal loss and Lewy bodies. A higher repetitive head injury index correlated with higher axial diffusivity on brain imaging, most severe in the corpus callosum CC1 area. Evidence of neuroinflammation included microglial activation, expression of pro-inflammatory markers, and lymphocyte trafficking of CD4+ helper-T cells followed by CD8+ cytotoxic T cells.

Conclusion : In CTE, neurodegeneration is most likely triggered by immune activation in response to brain tissue damage. Persistent neuroinflammation can perpetuate injury to both neurons and oligodendrocytes, resulting in concurrent neurodegeneration and demyelination. It is urgent that preventive measures be implemented to protect against dementia and neuropsychiatric decline. Recommendations include the use of padded helmets, testing for biomarkers such as Neurofilament Light, monitoring Cumulative Head Impact Index, supportive treatments for associated Post-Traumatic Stress Disorder (PTSD), and education. Further research could identify targetable molecular mechanisms, quantify traumatic load, and test pharmacologic treatment strategies.

KeyWords : Concussion; High-impact head injury; Repetitive traumatic brain injury (TBI); Chronic traumatic encephalopathy (CTE); Tauopathy; Microglial activation; Neuroinflammation; Contact sports; Athletes; Military personnel.

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INTRODUCTION

In 1928, the term "punch drunk" was coined to describe extensive exposure of boxers to neurotrauma, and was later renamed 'dementia pugilistica (DP)' (Carroll, 1936; Millspaugh, 1937). Analysis of postmortem neuropathology in brain tissues from military personnel and high-impact sports athletes has revealed that years beyond the originally sustained concussion-related hemorrhages, many other brain lesions can be seen that are classically found in Alzheimer's dementia, Parkinson's and other neurodegenerative diseases, and that eventually become widely distributed creating a 'geographic tauopathy' correlating with the appearance of early-onset dementia and neuropsychiatric deterioration diagnosed as Chronic Traumatic Encephalopathy (CTE) (Castellani & Perry, 2017, McKee et al. 2023), a devastating consequence of repetitive Traumatic Brain Injury (TBI) (Montenigro et al., 2015; McKee et al., 2013 & 2015). Repetitive TBI occurs in circumstances necessitating constant exposure to repetitive head trauma and concussive events such as from improvised explosive device (IED) roadside blasts, vehicle accidents, physical abuse, and sports requiring head collisions causing high-impact coup and contrecoup injuries. A coup injury occurs when the force from a moving object hits the head, while a countercoup injury results when the momentum of a person hitting a stationary object thrusts the brain in the opposite direction (Hughston, 2021). Populations most susceptible to TBI and CTE include military personnel in combat roles and athletes participating in high impact/contact sports including American football, ice hockey, boxing, lacrosse, soccer, rugby, and skateboarding (Harris, 2023). Mild symptoms of TBI include headaches, nausea or vomiting, fatigue, dizziness, blurred vision, ringing of the ears, sensitivity to light or sound, transient loss of consciousness, confusion or disorientation, memory impairment, mood swings, depression, anxiety, and sleep disturbances (Mayo Foundation, 2021). Moderate to severe symptoms include loss of consciousness for extended periods of time with or without coma, persistent headache, repeated vomiting or nausea, convulsions, pupillary dilation, nasal discharge, motor and sensory deficits, loss of coordination, profound confusion, agitation, combativeness, and slurred speech (Mayo Foundation, 2021). In young children, TBI may result from a bump, blow, or jolt to the head. Pediatric signs of brain injury may be more challenging to recognize as these include changes in eating or nursing habits, irritability, persistent inconsolable crying, distractibility, a loss of interest in favorite toys or activities, seizures, a sad or depressed mood, drowsiness, and dysautonomia (Araki et al., 2017; Parks & Hogg-Johnson, 2023). Furthermore, repetitive sub-concussive injuries, in which impacts to the head do not reach the threshold required for production of concussive symptoms, can also predispose to CTE (Dioso et al., 2022). When they compound over time they disrupt the neuronal membrane causing an efflux of potassium, influx of calcium, and increased glutamate concentrations (Dioso et al., 2022). Subconcussive injuries may be detected by Electroencephalography (EEG) and ImPACT assessments but still pose a challenge for diagnosis (Boshra et al., 2020). A neuropathologic 4-level CTE staging system has been developed based on extent, location, and depth of p-tau threads, dot-like neurites, neurofibrillary tangles, axonal loss, neuronal loss, gliosis, and demyelination (Alosco et al., 2020, McKee et al., 2023).

Interestingly, experimental neuroimmunological studies on models of repetitive head impact (RHI) have revealed evidence of CNS cellular infiltration (Alam et al., 2020) reminiscent of patterns that have been described in other neuroinflammatory, demyelinative and neurodegenerative diseases (Longoria et al., 2022; Uzair et al. 2023, Kashif et al. 2023). Immune responses involving microglia activation are believed to be triggered by brain tissue injury and can result in perpetuation of neurodegenerative cascades described in the pathogenesis of taupathies (Kashif, 2023).

This study reviews the neuropathologic and neuroimmunologic findings in human populations diagnosed with CTE, explores cellular mechanisms implicated in repetitive head impact-related pathology in animal models, and evaluates preventative measures tested in human and animal studies.

MATERIALS AND METHODS

A systematic review of the literature was conducted through the Kean University Nancy Thompson Library and the Saint James School of Medicine Library by literature search using WorldCat.org and ProQuest Central, inclusive of PubMed and EBSCOhost electronic databases. Other records were identified from websites and citation searches. The text words, "concussion", "high-impact head injury", "repetitive traumatic brain injury (TBI)", "Repetitive Head Injury (RHI)", "Chronic traumatic encephalopathy (CTE)", "Sub concussive Impacts" "tauopathy" with the use of the Boolean operator AND "contact sports", "football", "boxer", "high-impact sports", "athletes", "young athlete", "military personnel", "military veterans", "blast neurotrauma", "blast explosive", "roadside bomb", "blast exposure", "suicide", "neuropsychiatry", "p-Tau", "neurodegeneration", "neuroimmunology", "neuroinflammation", and "microglial activation" were used to identify experimental and human studies on TBI and CTE risk groups, neuropsychiatric manifestations, neuropathologic lesions, clinical correlations and disease progression, neurodegenerative, demyelinative and neuroimmunologic mechanisms, and preventative measures.

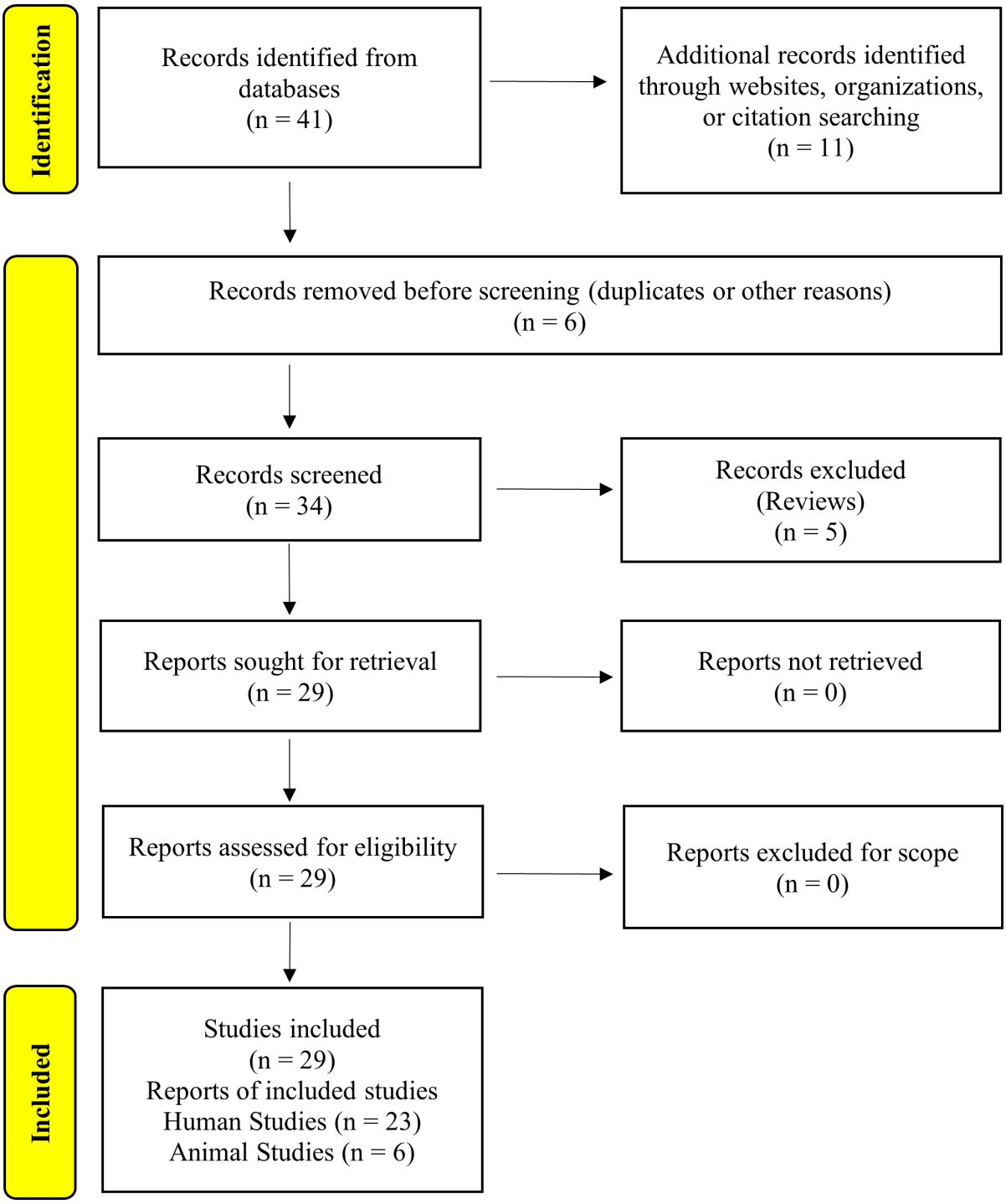
Inclusion criteria were 1) must be a scholarly or peer-reviewed paper, 2) published between 2013 and 2023, and 3) article

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available in the English language. Exclusion criteria were 1) publications potentially used for marketing purposes, 2) articles earlier than 2013, and 3) articles not available in English. The search strategy is recorded in the PRISMA flow diagram (Figure 1).

Data extraction was performed by 3 reviewers and 29 studies were selected for inclusion. Primary outcome measures included detection of neuroradiologic abnormalities or brain histopathologic lesions consistent with CTE. Secondary outcomes included reports of behavioral problems, cognitive impairement, and psychiatric manifestations. Articles were rated according to the following scheme: (1) randomized controlled clinical trial (RCCT), (2) controlled trial without randomization, or prospective comparative cohort studies, (3) case-control studies, or retrospective cohort study, (4) cross-sectional study, and (5) case series, case report, or observational experimental studies.

Figure 1. PRISMA flow diagram for identification of studies



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RESULTS

In total, 29 records were included from the US, Canada, Mexico, Germany, Italy, and the UK with 1 prospective cohort, 9 retrospective cohort, 10 case-control, 2 cross-sectional, 1 case series, and 6 observational experimental studies. Findings from 23 human studies are presented in Table 1, and results from 6 animal studies are presented in Table 2.

CTE and non-CTE human brain tissues analyzed had been obtained from the Veterans Affairs–Boston University–Concussion Legacy Foundation (VA–BU–CLF)/ Boston University CTE Center - Understanding Neurological Injury and Traumatic Encephalopathy (UNITE) brain bank (UNITE 2024), and the Framingham Heart Study Brain Donation Program (Au et al. 2012) in the United States, and the Dublin brain bank in Ireland.

In the RHI experimental rodent models, head injury had been induced by applying either compressed air with a pneumatic impact device, a rubber impactor from a controlled cortical impact device, or fluid pressure that delivered mild lateral fluid percussion.

A cumulative total of 2,496 subjects were included in the human studies, although overlap is presumed since specimen from the same cases may have been used in different studies. Sample sizes were adequate for statistical analysis in the majority of studies.

There was consistent evidence that neuropathologic lesions characteristic of CTE are present in brain tissues of young athletes, old athletes, active military personnel and military veterans, and robust evidence from animal models for the causative role of head impacts. Among the notable findings were the following:

Chronically activated microglia and macrophages have been found in rodent models and humans after TBI. CD45High/ CD11b + macrophages and CD45High/CD11b + cells have been shown to peak within 1 day following controlled cortical impact and remained elevated at 3 days before returning to control levels. Post brain injury repair, infiltrating monocytes disappear from the damaged brain within 1 or 2 months. Most monocytes die in the brain about 5 days after infiltration, whilst some monocytes differentiate into resident brain microglia. The latter pathway provides a source of monocyte-derived microglia to replenish areas in the damaged core that have not been destroyed by resident microglial cells. (Chou et al., 2018).

Incidences of CTE have also been correlated with increased risk of cardiovascular disease. In a 10-year study of TBI patients without previous cardiovascular and neuropsychiatric disease, people as young as 18-40 years old had increased susceptibility of developing hyperlipidemia, hypertension, obesity, and diabetes within 3-5 years following onset of TBI in comparison to individuals in a control group (Yasgur, 2024).

Pathologically CTE produces atrophy of the frontal and temporal lobes, atrophy of the thalamus and hypothalamus, disordered neurites and neurofibrillary tangles composed of hyperphosphorylated tau (McKee et al., 2014). The neuropathologic lesions characteristic of CTE have been seen in brain regions that are involved in problem-solving, judgment, impulse control, emotional regulation and behavior, fear, and anxiety. Like many other neurodegenerative diseases, CTE is diagnosed with certainty only by neuropathological examination of brain tissue.

Recently, there has been concern that repetitive hits to the head, that do not even lead to any symptoms related to concussions (loss of consciousness, headaches, dizziness, vision problems or confusion), may still cause CTE.Studies have shown a ≈2-fold increase in long-term risk of dementia, particularly frontotemporal dementia, among male military veterans with Traumatic Brain Injury (TBI) or Post traumatic Stress Disorder (PTSD) or depression (Mufson et al., 2018; McKee at al., 2013 & 2015). Similarly, a recent study that was examining clinicopathologic data from more than 100,000 older women veterans found that female military veterans with traumatic brain injury (TBI), post-traumatic stress disorder (PTSD) or depression were more likely to develop dementia later in life than peers without those conditions (Barnes et al., 2018;). The Alzheimer's Association is facilitating an ongoing discussion to better understand the pathophysiological mechanisms of traumatic brain injury and post-traumatic stress disorder and how they may be linked to an increased risk of neurodegenerative diseases including Alzheimer's disease in veterans, (Barnes et al., 2018;).

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Table 1. TBI and CTE studies in humans

Study	Demographics	Findings
Labadorf et al. Retrospective Case-control Study 2023	• 76 Post-mortem brain tissue whole transcriptome gene expression by mRNAseq • 64 CTE cases, contact sport athletes (American football, boxing, ice hockey, and professional wrestling) • 10 RHI controls with history of contact sports participation, military service, or domestic violence	• A substantial number of differential expression genes were associated with Anti ptau monoclonal antibody (AT8) for both Low CTE (CTE-L)+RHI and High CTE (CTE-H, severe) (FDR < 0.1) using a log scale • Neuroinflammatory and neuroimmune processes were strongly involved in CTE-H. • 196 and 76 Gene Ontology (GO) terms significantly associated CTE-L+RHI and CTE-H with apolipoprotein E (APOE) risk, respectively (FDR < 0.1) • Significant GO terms related to immune response and inflammation are increased in both CTE-L+RHI and CTE-H
Alosco et al. Retrospective Cohort Study 2021	• 55 deceased symptomatic men with autopsy-confirmed CTE • Age ≥ 60 years	• Among donors with CTE, greater tau severity across 14 regions corresponded to greater atrophy on magnetic resonance imaging ($p < 0.01$). • Donors with CTE had greater atrophy of the orbital frontal (mean diff. = 1.29), dorsolateral frontal (mean diff. = 1.31), superior frontal (mean diff. = 1.05), anterior temporal (mean diff. = 1.57), and medial temporal lobes (mean diff. = 1.60) • Donors with CTE had larger lateral (mean diff. = 1.72) and third (mean diff. = 0.80) ventricles
Kochisek et al. Retrospective Cross-sectional study 2021	• 75 symptomatic former NFL players • Age range 40-69 yrs. • Mean age 55.16 ± 7.98 yrs. • Professional American football ≥ 12 yrs. • NFL activity ≥ 2yrs.	• Cumulative Head Impact Index (CHII): Higher RHI positively correlated with higher axial diffusivity in corpus callosum CC1 on dMRI ($r = 0.32$, $p < 0.05$) • Plasma Total Tau positively correlated with axial diffusivity of corpus callosum CC1 and CC2 areas (CC1: $r = 0.30$; CC2: $r = 0.29$, both $p < 0.05$) • White matter damage in CC1 and CC2 by dMRI parameters also correlated with neuropsychological test scores and measures of neurobehavioral dysregulation ($p < 0.05$)
Mez et al Retrospective Case-control Study 2021	• 244 donors with CTE pathology and 92 without CTE pathology. • Mean age of CTE donors = 63.6 ± 18.6 yrs.	• Cognitive symptoms (odds ratio [OR] = 3.6; 95% confidence interval [CI]: 1.2–5.1), but not mood/behavior or motor symptoms, were significantly associated with CTE pathology
Schwab et al. Retrospective Cohort Study 2021	• 35 male former collision sports athletes with history of mild TBI • Mean age at death = 62.7 ± 17.5 yrs. • Mean age at retirement = 31.1 ± 5.1 yrs. • Primary positions: running back/ quarterback/receiver (football, n = 5), defensive back (football, n = 3), tight end/ linebacker (football, n = 6), offensive/ defensive line (football, n = 10), forward (hockey, n = 7), defense (hockey, n = 4). • Professional (n = 29) • University Varsity/major junior (n = 6) • American football (n = 24) • Hockey (n = 11) players.	• 48.6% show evidence of CTE • Presence of CTE did not correlate with either age at retirement, position played, or penalization histories (Mann-Whitney-Wilcoxon $p > 0.5$)

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Zimmerman et al. Retrospective Cohort Study 2021	• Videos of 32 American football games were analyzed and 166 exemplar events were selected for reconstruction to represent the trauma profile of the 3 distinct groups • American Football Quarterbacks, Wide Receivers and Defensive backs	• Player position had a significant effect on increasing strain ($p < 0.001$) and strain rate ($p < 0.001$) in the sulci, a prominent location of neuropathology in CTE
Alosco et al. Case-control Study 2020	• Post-mortem brain tissue • 366 males with CTE • 304 American Football players • Age range 17-100 yrs (mean age = 61.86 ± 18.90 yrs.) • 58 participants with Stage I CTE, 72 with Stage II CTE, 127 with stage III CTE, 102 with stage IV CTE	• Higher CTE stage was associated with higher scores of p-tau severity (all p's < 0.001) • Older age was associated with increased odds for having a higher CTE stage ($p < 0.001$) • More years of American football play were associated with increased odds for having a higher stage of CTE ($p < 0.001$)
Adams et al. Case-control Study 2020	• Post-mortem brain tissue • 247 males with RHI and neuropathologically diagnosed CTE • (Mean age = 63.1±18.8 yrs.) • 80 (32%) males had probable REM Sleep Behavior Disorder (pRBD)	• pRBD participants experienced the onset of reported RBD symptoms at a significantly younger age (50.3 ± 19.2 yrs, mean ± SD) than the onset of reported cognitive symptoms (56.7 ± 16.0 yrs.) ($p = 0.03$). • CTE participants with pRBD had played contact sports for more years (18.3 ± 11.4) than participants without pRBD (15.1 ± 6.5) ($p = 0.02$) • pRBD participants had played contact sports for significantly more years (18.0 ± 9.9) than non-pRBD participants (15.0 ± 6.1) ($p = 0.02$)
Cherry et al. Retrospective Cohort Study 2020	• Post-mortem brain tissue • 94 American Football players exposed to Repetitive Head Injury (RHI) (74 with CTE, 20 without CTE) • 18 non-RHI controls • 112 diagnosed with Alzheimer's Disease (AD)	• Iba1+/ TMEM119+ activated microglia increased around blood vessels with perivascular pTau as compared to blood vessels without perivascular pTau • Chemokine CCL2 protein levels ratio in dorsolateral frontal cortex / calcarine cortex correlated with density of Iba1+ activated microglia ($p = 0.014$) consistent with a role for CCL2 in microglia recruitment, pTau, and greater years of playing American football ($p = 0.0039$) regardless of age at death ($p = 0.061$) • The CCL2 ratio was observed to correlate with the step-by-step increase across control, RHI without CTE, low CTE, and high CTE ($p < 0.001$), independent of age at death ($p < 0.001$)
Lier et al. Pilot Case-control Study 2020	• 8 individuals who died causatively after suffering from TBI • 5 control cases	• In cases with shorter survival times, morphologically activated microglia expressing IBA1 was present in acute vicinity to the traumatic lesions • IBA1-stainings of microglia in immediate surroundings of the tissue damage showed pronounced dystrophy, while in close vicinity microglial activation, already appeared. • There was not a single accumulation of tau or amyloid in the vicinity to contusion areas in the survival timeframe investigated between minutes and 7 days.

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Butler et al. Case-control Study 2022	• 150 individuals with CTE • Age range 21-80 yrs.	• NFT density was significantly elevated in the cortical sulcus compared to the gyral crest in low-stage CTE ($p < 0.0001$) and high stage CTE ($p < 0.0001$) • There was significantly elevated sulcal astrocytic p-tau density in both low stage ($p < 0.001$) and high stage CTE ($p<0.0001$) • Neuronal p-tau ($p < 0.0001$) and astrocytic p-tau ($p = 0.0014$) were both associated with age • Only neuronal ptau densities were associated with years of exposure to American football play ($p = 0.0005$)
Mez et al. Retrospective Cohort 2020	• 233 deceased American Football Players that met neuropathological diagnostic criteria for CTE • Years of Football experience > 14.5 yrs.	• More years of football played were associated with having CTE ($p = 3.8 \times 10-9$) and with CTE severity (severe vs mild; $p = 3.1 \times 10-4$).
Muraoka et al. Case-control Study 2019	• 15 male former professional football players • Mean age= 56.33 ± 7.31 yrs.	• There was a positive correlation between CSF t-tau, p-tau181 and Extracellular Vesicle t-tau, ptau181 levels in former NFL players (t-tau: $p = 0.0044$; p-tau181: $p = 0.0524$) but not in the CTRL group (t-tau: $p = 0.2150$; p-tau181: $p = 0.1770$)
Querzola at al. Cross-sectional Study 2019	• 69 male American Football players • Age range 17-48 yrs. • (Mean age = 25.2 ± 9.7 yrs.)	• 66.67% of respondents reported aggressiveness • 76.81% of respondents reported attention/concentration difficulties • 78.26% of respondents reported recurrent headache 48.28% of respondents reported having had at least one episode of traumatic transient loss of consciousness in their lifetime
Stern et al. Case-control Study 2019	• 26 male former professional football players • Age range 40-69 yrs. • (mean age = 57.0 ± 8.4 yrs.) • NFL activity ≥ 2 yrs. • Tackle football experience ≥ 12 yrs.	• Mean regional tau standard uptake value ratio measured by Flortaucipir (18F) PET was higher among former players than among controls in the bilateral superior frontal region ($p < 0.001$), bilateral medial temporal region ($p < 0.001$), and left parietal region ($p = 0.002$)
Bari et al. Prospective Cohort Study 2019	• 90 High school athletes, 63 athletes participating in collision sports • 40 male football athletes • Age range 15-18 yrs. • (Mean age 16.21 yrs.)	• Male contact sport athletes exhibited changes in the left dorsolateral prefrontal cortex (DLPFC) associated with Glutamate+Glutamine(Glx) and with total choline containing compounds • Football athletes exhibited changes in the DLPFC with the onset and sustained exposure to collision events, these changes disappeared once exposure to collision events ceased • Neurochemical deviations observed in contact sport athletes during and subsequent to Head Acceleration Events indicate the presence of an altered metabolic state
Lorigan et al. Retrospective Cohort 2019	• 23 Brains from Dublin Brain Bank: 17 neurogenerative disease, 1 CTE case, 5 healthy controls • History of head trauma	• Presence of hyperphosphorylated tau highly specific for CTE (specificity: 0.98) • Validated McKee's findings to demonstrate reproducibility

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Mufson et al. Retrospective Cohort Study 2018	• 17 male athletes who played American Football, ice hockey, and boxing. Two subjects were military veterans	• Age when sport began was correlated with age at symptom onset ($p < 0.008$), greater interval between symptom onset and death ($p < 0.04$), and age at death ($p < 0.0003$) • Downregulation of the nicotinic cholinergic receptor subunit b-2 gene (CHRNB2) ($p = 0.03$), catechol-O-methyltransferase (COMT) and dopa decarboxylase (DDC) ($p = 0.005$), chloride channels CLCN4 and CLCN5 ($p < 0.05$), scaffolding protein caveolin 1 (CAV1) ($p < 0.05$), cortical lissencephaly 1 (LIS1) ($p < 0.05$), and adenylate cyclase 3 (ADCY3) ($p < 0.006$ was observed in pS422-immunreactive nbM neurons in CTE patients
Sanchez et al. Case-control Study 2018	• 133 mTBI patients • (Mean age CT-negative 46 yrs. ± 21) • Mean age CT- positive 61 yrs. ± 26)	• Significantly higher concentrations of Interleukin-10 were found in CT-positive mTBI patients than in CT-negative patients ($p < 0.001$) • Levels of S100B were significantly higher in the blood of CT-positive patients than that of CT-negative patients ($p < 0.001$)
Schultz Retrospective Cohort Study 2018	• 86 male former professional football players • Age range 40-69 yrs. (mean age 54.9 ± 7.9 yrs.) • Organized football ≥ 12 yrs. • NFL activity ≥ 2 yrs.	• Right and left thalamic volume measured by MRI was negatively correlated with total years of play (left, $p = 0.012$; right, $p = 0.03$) • Right thalamic volume was associated with age of first exposure after adjusting for total years of play ($p = 0.014$) • The longer an athlete participated in football and the younger he was when he began playing, the smaller the thalamic volume
Mez et al. Blinded, Case-control Study 2017	• 202 former football players • Interquartile range 47-76 yrs. • (Median age 66 yrs.) • CTE was neuropathologically diagnosed in 177 players (87%)	• In cases with severe CTE pathology, accumulations of amyloid-β, α-synuclein, and TDP-43 were common • 19% of participants with CTE had comorbid Lewy body disease • Behavioral, mood, and cognitive symptoms were common among participants with either mild or severe CTE pathology • In participants with severe CTE pathology, there was marked ptau pathology in brain regions that have been associated with: impulsivity, depressive symptoms, apathy, anxiety, and explosivity (prefrontal cortex, amygdala, locus coeruleus); episodic memory symptoms (hippocampus and entorhinal and perirhinal cortices); and attention and executive function symptoms
Cherry et al. Retrospective Cohort Study 2016	• Post-mortem brain tissue • 66 American Football players with history of RHI (48 with CTE, 18 without CTE) • 18 non-RHI controls	• RHI exposure had a significant direct effect on CD68 cell density ($p < 0.0001$) • The number of years exposed to RHI had a significant effect on AT8 density (anti-Tau phosphorylated at both serine 202 and threonine 205, $p < 0.0001$) and CD68 cell Density ($p < 0.0001$) • CD68 cell density had a significant direct positive effect on AT8 tau pathology ($p < 0.0001$)
McKee et al. Retrospective, Case Series 2013 & McKee et al. Review 2015	• 85 former athletes, military veterans, or civilians with a history of mild traumatic brain injury • Age range 14-98 yrs. • (Mean age = 54.1 ± 23.3 yrs.)	• 68 subjects showed p-tau immunoreactive neurofibrillary tangles and astrocytic tangles in a pattern and neuroanatomical distribution diagnostic of CTE • Amyloid-ß deposition, either as diffuse plaques, neuritic plaques or vascular amyloid, was found in 35.3% of the mild traumatic brain injury samples and 44.1% of the CTE cases • The evidence suggests that CTE begins focally, usually perivascularly, at the depths of the sulci in the cerebral cortex and spreads slowly over decades to involve widespread regions of neocortex, medial temporal lobe, diencephalon, basal ganglia, brainstem and spinal cord

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Table 2. TBI and CTE studies in animals

Study	Model	Findings
Chou et al. Observational Experimental Study 2018	• Rodent TBI models (adult and young males) • Non TBI Controls	• There was an increase in the number of peripherally-derived monocytes at 4 and 7 dpi* in older mice with TBI compared to the younger counterparts ($p < 0.00001$) • There was a higher percentage of BrdU-labeled monocytes in the aged brain at 4 dpi ($p < 0.05$), indicating that age exacerbates monocyte infiltration subchronically • CCL8 ($p < 0.001$) and CCL12 ($p < 0.01$) levels were higher in aged animals at both 4 and 7 dpi compared to young injured at the respective time points • The expression of the anti-inflammatory markers CD206 ($p < 0.0001$), TGF-β ($p < 0.01$), and IL4Ra ($p < 0.001$) was significantly reduced in the aged animals
Moszczynski et al. Observational Experimental Study 2018	• Head trauma induced in 12 adult female Sprague-Dawley rats	• Insoluble tau protein isolated from CTE cases contained all 6 isoforms in both phosphorylated and dephosphorylated isolates. • Both pThr175 and pThr231 tau neuronal immunoreactivity was observed in moderate TBI rat brains • Tau-immunoreactive neurofibrillary tangles (NFTs) and dystrophic neurites throughout the CA1–4 regions and extending into the entorhinal cortex were observed in all cases
Yu et al. Randomized, Observational Study 2018	• Adult male, human Tau mice • rmTBI mouse model was used to deliver a controlled consistent injury to all animals	• The rmTBI resulted in a marked neuroinflammatory response, with persistent and widespread astrogliosis and microglial activation • Repetitive mild traumatic brain injury (rmTBI) results in increased risk-taking and depression-like behaviors • Diets high in phytonutrients were able to attenuate the “CTE-like” pathology provoked by the rmTBI
Bai et al. Observational Experimental Study 2017	• 12 weeks old male Sprague–Dawley rats • 36 rats exposed to Controlled Cortical Impact (CCI) Induced Repetitive Mild Traumatic Brain Injury • 6 rats in Sham group	• Two distinct populations of macrophages and microglia were observed: CD45high/ CD11b+ cells and CD45low/ CD11b+ cells. • In the injured brain, CD3+ T cells showed a bimodal increase during the 42 days post injury (dpi) ($p < 0.01$, $p < 0.05$) • At 7 dpi, the percentage of Iba-1+ microglia was approximately 4 times more than that of 1 dpi ($p < 0.01$). • The percentage of CD4+ T cells continuously declined from 7 to 42 dpi ($p < 0.01$), while the percentage of CD8+ T cells increased from 7 to 42 dpi ($p < 0.01$) • CD3+/CD4+ T cells firstly increased and then decreased ($p < 0.01$, $p < 0.05$), while CD3+ CD8+ T cells had reversed tendency ($p < 0.01$, $p < 0.05$).
Gyoneva et al. Observational Experimental Study 2015	• Mice with one or both copies of Ccr2 (C-C motif chemokine receptor 2) disrupted by red fluorescent protein	• Both injury and genotype had a significant effect on the monocytic reaction ($p = 0.0010$ for Injury and $p < 0.01$ for Genotype) • Ccr2 deletion resulted in a significant decrease in portion of the brain parenchyma containing monocytes ($p < 0.05$) reduced axonal pathology in Ccr2RFP/RFP mice at 3 dpi compared to controls (Fig. 3c; two-way ANOVA and Tukey’s post hoc test, $p < 0.05$).

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Petraglia et al. Observational Experimental Study 2014	• 12 week old mice divided into Control, single, and repetitive mTBI groups	• At 7 dpi, there was a statistically significant increase of GFAP labeling of reactive astrocytes in the cortex ($p < 0.01$) and amygdala ($p < 0.01$) • There was a significant effect of injury on GFAP labeling in the dentate ($p < 0.001$), CA1 ($p < 0.01$), and CA3 ($p < 0.05$, $p < 0.001$) regions of the hippocampus • Astrogliosis was significant in the cortex ($p < 0.05$, $p < 0.01$), ipsilateral amygdala ($p < 0.01$), dentate gyrus($p < 0.05$), CA1 ($p < 0.01$, $p < 0.001$) and CA3 ($p < 0.001$) regions • At 7 dpi, there was a significant effect of injury on microgliosis in the cortex ($p < 0.01$, $p < 0.01$), contralateral amygdala ($p < 0.05$), and CA3 ($p < 0.01$, $p < 0.05$) regions

DISCUSSION

This systematic review of the literature evaluated the evidence for an association between exposure to repetitive head trauma and the development of neurodegenerative disease with induction of neuroinflammation. The experimental results adequately demonstrate that exposure to repetitive head impact results in neuroimmunologic activation and neuropathologic deterioration (**Table 2**). The internal validity was very good in the animal studies because experiments were well designed and well controlled. The external validity of animal studies may be less certain due to (a) differences in anatomy and physiology between rodents and humans, and (b) differences in conditions between controlled head impact experiments and free exposure to head trauma in men and women, which may affect endurance, homeostasis and susceptibility to brain tissue injury. The findings from the human studies offer moderate to strong certainty of evidence that the severity of CTE pathology correlates with the extent of exposure to repetitive head trauma in regards to number of years, position during impacts, and age. The data also strongly supports a role for neuroinflammatory mechanisms in the induction and perpetuation of the neurodegenerative cascade as evidenced by microglial activation, lymphocyte trafficking and proinflammatory cytokine and gene expression profiles (Tables 1 and 2).

Unfortunately, CTE prognosis is poor as prevention options are scarce. Poor prognosis alongside the lack of premortem diagnosis has created an ever-increasing population of people with psychiatric disorders. CTE's wide range of psychiatric manifestations make it a particularly grave public health risk for contact sport athletes, military personnel, and adolescents in America. The current pervasiveness of CTE in these populations emphasizes the need for policy changes alongside safety equipment upgrades. Positively, the United States government and various sports leagues have taken steps to help mitigate TBI and CTE development. Specifically, The National Football League (NFL) has implemented several rule changes to help prevent concussion and brain injuries underlying and CTE. Such changes include penalizing players who use their helmets to initiate forcible contact with their opponents and increasing protection of defenseless players. Additionally, the NFL has launched the Play Smart. Play Safe initiative (https://nflps.org/wp-content/uploads/2018/09/NFL-Fact-Sheet-Health-and-Safety-9.2018-1.pdf) to drive progress in the prevention, diagnosis, and treatment of head injuries, and enhance their medical protocols. Similarly, the Center for Disease Control and Prevention (CDC) launched the HEADS UP campaign (https://www.cdc.gov/heads-up/index.html) to spread awareness of severe brain injury and concussion in children and teens and provide suggestions for injury prevention such as proper helmet maintenance. Furthermore, a newly introduced program, the "Brain fitness program" has been shown to reduce memory loss, post-concussion syndrome, and other cognitive symptoms of various neurological conditions. In an article reviewing this program's impact, it was discovered that 60% to 90% of patients scored higher on cognitive tests after completing the program (Brooks, 2023). Such a program may aid in mitigating the cognitive symptoms of individuals with CTE. Additionally, a recent study highlighted the G8RSkin balaclava, a 5-millimeter-thick hood which can be worn under football helmets and shoulder pads, and its ability to stabilize the head and neck and reduce the risk of concussion by approximately 60% (Ewing, 2023). Such innovations are promising in terms of the future direction of TBI and CTE prevention. Additionally, some studies have accentuated that diet changes and overall lifestyle adjustments may hinder the progression of CTE pathology. Further studies are warranted with the focus on neuroimmunology to explore possible therapeutic strategies that might block neuroinflammatory mechanisms thereby preventing disease progression at the neuropathologic level. Additionally, studies are needed to evaluate neuroprotective treatment strategies, including medical cannabis (Zeine and Teasdale, editors 2023; Lin et al. 2023), for reducing the harmful effects of repetitive concussive trauma in athletes and military personnel. Through minimizing exposure to physical impacts, receiving adequate care for head trauma,

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developing protective strategies, proper equipment, reviewing HR policies, and modifying sports rules, the prevalence of CTE and TBI can be greatly decreased.

Gene expression profiling performed on archival brain tissue from CTE patients, showed dysregulation of key genes in p-tau pretangle marker pS422 positive neurons that had been laser-captured from the nucleus basalis of Meynert (nbM) (Mufson et al., 2018). Specifically, there was downregulation of the nicotinic cholinergic receptor subunit b-2 gene (CHRNB2), monoaminergic enzymes catechol-O-methyltransferase (COMT) and dopa decarboxylase (DDC), chloride channels CLCN4 and CLCN5, scaffolding protein caveolin 1 (CAV1), cortical development/cytoskeleton element lissencephaly 1 (LIS1), and intracellular signaling cascade member adenylate cyclase 3 (ADCY3) (McKee et al., 2014). Additionally, there was upregulation of calpain 2 (CAPN2) and microtubule-associated protein 2 (MAP2) in Stage IV CTE patients (Mufson et al., 2018).

CONCLUSION

For clinical manifestations of chronic traumatic encephalopathy to be present, there must be repeated sublethal trauma. Neuropathologic lesions involve the whole brain with variable spread throughout the parietal, temporal, occipital, and frontal cortex. Recommendations for prevention of CTE include the use of padded helmets. Tests for examining the neuropsychiatric and behavioral symptoms of CTE include the Cumulative Head Impact Index, Trail Making Test, Controlled Oral Word Association Test, Stroop Interference Test, Behavioral Regulation Index, and Behavior Rating Inventory of Executive Function. Potential biomarkers for CTE include Neurofilament Light, Ubiquitin carboxyl-terminal hydrolase L1, GFAP and TNF-a. Provision of supportive treatments for PTSD, depression, aggression, and other neurologic deficits is crucial. Neuroimmunological mechanisms are implicated in triggering neurodegenerative pathology in CTE and need to be further elucidated using experimental models. Future research is needed to quantify the traumatic load in contact sport athletes and military personnel exposed to TBI, differentiate the risk of long-term neurological consequences for contact sport players who perform individually or in different field positions in team sports, develop monitoring practices for populations at risk, correlate clinical and neuropsychological progression with radiological findings obtained from functional neuroimaging, and research novel stem cell therapy and other treatment strategies for neurodegeneration.

Core Tip: Chronic traumatic encephalopathy (CTE) is emerging as an urgent health concern for military personnel and athletes participating in a contact sport due to repetitive traumatic brain injuries (TBI). Concussions accumulate neurodegenerative lesions causing early dementia, and neuropsychiatric decline. This paper reviews the neuropathology and clinicopathologic findings in CTE with a focus on recent neuroimmunology associations with disease pathogenesis. It also explores the efficacy of preventive protocols introduced to alleviate CTE and TBI symptoms and occurrences. This review also meticulously evaluates the alignment and discrepancies within existing clinical guidelines for CTE, with particular emphasis on diagnostic methodologies and post-diagnostic interventions.

Author contributions

Awadalla A, Bhigroog A, Williams B†, Alicius L, Kanu F, and Zeine R designed the research; Aryee J, Awadalla A, Bhigroog A, Williams B†, Alicius L, Kanu F, and Zeine R performed the research; Aryee J, Awadalla, A and Zeine R analyzed the data; Aryee J, Awadalla A, Bhigroog A, Williams B†, Alicius L, and Kanu F wrote the draft of the paper; Zeine R reviewed and edited the paper.

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