Review

The Neurobiology and Impact of Chronic Traumatic Encephalopathy in Athletes: A Focused Review

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Posted Date: 25 February 2025

doi: 10.20944/preprints202502.1912.v2

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 doi:10.20944/preprints202502.1912.v2

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The Neurobiology and Impact of Chronic Traumatic Encephalopathy in Athletes: A Focused Review

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Abstract: Recent reports have highlighted a troubling pattern of athletes exhibiting pronounced and unexplained behavioral changes. This phenomenon is often linked to Chronic Traumatic Encephalopathy (CTE), a progressive neurodegenerative disorder associated with repeated head injuries in contact sports. The term CTE was coined by Dr. Bennet Omalu to describe the condition distinguished by the accumulation of abnormal tau protein in the brain. This paper provides a focused review of the neurological and neurobehavioral mechanisms, prevention and treatments, and the role of animal models in advancing our understanding of CTE. Key findings have identified the accumulation of tau proteins and neuroinflammation as major contributing factors in the development of CTE. However, gaps in the literature remain, including the need for standardized injury models and biomarkers for diagnosing CTE in living individuals, pointing to future directions in refining diagnostic tools and developing targeted therapeutic interventions.

Keywords: C-reactive protein; Cerebrospinal Fluid; Chronic Traumatic Encephalopathy; Controlled Cortical Impact; Fluid Percussion

Background

CTE is a progressive neurodegenerative disorder associated with repeated head injuries (RHI), mostly seen in athletes participating in contact sports [1]. Today, CTE is recognized not only in professional athletes but also in teens and amateur athletes, raising pronounced public health concerns [1–3].

CTE was first described in 1928 by Dr. Harrison Martland as "punch drunk syndrome" in a group of boxers. CTE has since been reported to have similar symptoms in other cases [1,4,5]. However, it was not until Dr. Bennet Omalu, physician and forensic pathologist, published evidence in 2002 of CTE in former NFL player Mike Webster—who had passed away at age 50 after experiencing cognitive impairment, mood changes, and Parkinsonian symptoms—that this condition gained attention and was named [6]. CTE is associated with, but not limited to, sports such as American football, ice hockey, rugby, and wrestling, where athletes are exposed to frequent and repeated head impacts [1,2,7]. Originally, it was described as a clinical syndrome that primarily affected boxers [4]. This disorder is associated with cognitive decline, mood disturbances, and behavioral changes that may lead to more severe neurological conditions over time [1,2,7,8]. These symptoms commonly emerge eight to ten years following repeated mild traumatic brain injuries (mTBI) [9]. An epidemiology study has shown that more than 40% of deceased individuals with a history of contact sports have CTE [10]. Currently, CTE can only be diagnosed by examining brain tissue once deceased [10,11]. Despite significant advancements, there are currently no effective therapeutic options available to combat this progressive disorder, highlighting the urgent need for continued research into effective treatments and preventive measures [12]. Research efforts are focused on understanding the types of head impacts that carry the highest risk of developing the

 doi:10.20944/preprints202502.1912.v2

disorder, improving diagnostic methods, and further characterizing neurobiological mechanisms underlying CTE [13]. Additionally, addressing CTE involves preventative strategies, including modifications in sports practices and regulations aimed at reducing head injuries and protecting athletes [14,15].

This paper reviews the literature on the symptoms and diagnosis, as well as the neurobehavioral and neurobiological mechanisms, prevention and treatment strategies, and the use of mouse models to study the disease.

Clinical Presentation in Athletes

Examining the clinical presentation of CTE in athletes can help us better understand the signs, severity, and outcomes that this debilitating disease has. While this disease cannot be diagnosed while alive [16], there are common symptoms associated with CTE such as memory impairment, confusion, mood disturbances, dementia, and motor dysfunction [8,17]. Furthermore, the occurrence and prognosis of CTE is unique to the sport that caused it [6,18,19].

The clinical presentation of CTE is severe in NFL athletes [10]. This is due to the high frequency and severity of head impacts they face as well as the duration of exposure starting as early as adolescence [20]. This, in turn, has produced severe symptoms such as advanced dementia and more intense behavioral changes compared to their soccer and boxing counterparts [4,21]. However, the severity and progression of CTE is due to differences in impact mechanisms. Studies indicate that NFL players experience greater linear acceleration forces from helmet-to-helmet and helmet-to-ground collisions, whereas boxers sustain higher rotational forces from punches [22,23]. These differences contribute to distinct patterns in the types of symptoms observed in each sport [24]. Moreover, football positions influence the incidence rates of mTBI. Running backs and wide receivers, who experience more frequent head impacts, suffer from a higher rate of mTBI than linemen [25]. Linemen, who generally have stronger necks and larger girths, experience a reduction in the linear accelerations of their heads compared to running backs, which lower their risk of getting a concussion [24]. These positional differences can partially explain the varying severity of CTE in football athletes. Furthermore, it is essential to consider that linemen often experience more sub-concussive helmet-to-helmet impacts, while wide receivers are exposed to more intense impacts from tackles, which may explain the differences in clinical presentations of CTE [24].

While the clinical presentation in CTE in NFL athletes can vary in severity depending on factors such as position and impact type, it is generally severe in athletes who experience high-frequency and high-intensity head impacts. In contrast, the clinical presentation in soccer athletes is often more evasive (26). For high school sports, the frequency of concussions in soccer was seen at a rate much lower than American football [26]. American football constituted 47.1% of all concussions and girls' soccer constituted over eight percent of all concussions [26]. Head contact in soccer is also limited to headers, which at the professional level is done on average twelve times a game [27], and at the youth level is done on average once a game [28]. However, if the soccer ball has a pressure too high and/or becomes water-logged, the chances of head trauma dramatically increases [27]. Due to this, presentation of CTE in soccer athletes still exists at a mild level. For example, a team of Norwegian Football players displayed mild to severe deficits in attention, concentration, memory and judgment reflecting the presentation that soccer athletes exhibit when dealing with CTE [21]. An investigation done on a Dutch Soccer Club took this further identifying the effect of soccer positions for CTE. After comparing the Dutch Club to a control group of 27 elite noncontact sport athletes, they determined a general presentation consisting of impaired memory, planning, and visuoperceptual processing [29]. They also concluded that forward and defensive positions exhibited more impairment due to their higher likelihood of heading the ball [29]. Implementing better rules and protocols, such as reducing ball pressure, will cause CTE cases in soccer players to decrease [27]. CTE does not have to be a prevalent issue for soccer players soon.

As noted above, research on CTE initially began with boxing, where it was originally referred to as "Punch Drunk Syndrome". A report in 1928 outlined this syndrome, recognizing boxers who were

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summarized by fans to be "cuckoo" and "goofy". Boxers exhibiting these 'cuckoo' behaviors were known to have sustained significant head trauma [4,30]. A study was conducted on twenty-three of these punch drunk boxers who shared presentations of minute changes in gait or staggered walks back to their corners between rounds [31]. This study also noted that the syndrome had severe cases where presentation also included parkinsonian gait, tremulousness, vertigo, and cognitive symptoms such as 'mental deterioration' [31]. The presentation of CTE in boxers depends on their style. Boxers who displayed a grit and grind style showed their symptoms on stage whereas boxers who utilize footwork and speed may avoid symptoms altogether [4]. The autopsies of 309 traumatic cerebral hemorrhage patients give us a glimpse into the late-life prognosis of these boxers ridiculed with CTE. Out of these 309 autopsies, nine cases were not associated with any signs of overt cortical injuries or skull fractures. These nine cases came from boxers who had sustained excessive head trauma and were labeled as "punch drunk" [4,31]. This study shows us that the effects of CTE follow boxers into their late lives. While a stylistic change may reduce your chances of developing the brain disorder, CTE will always be a worry for boxers.

While the presentation of CTE in football, soccer, and boxers all share a commonality in 'mental deterioration', they are all also unique in their own ways. The severity behind CTE in NFL athletes is unmatched due to the repeated head trauma they endure on every play. Soccer athletes show a mild presentation of CTE because of their infrequent use of using their head in their sport. Boxers can show symptoms of CTE even while on stage fighting. Further examination of these symptoms will better allow us to better understand CTE and the signs, severity, and outcomes that this debilitating disease has.

Neurobehavioral & Neurological Mechanisms

Understanding the neurobiological and neurological mechanisms causing CTE is important for developing effective treatments and preventive strategies. Repeated brain injuries lead to the accumulation of the tau protein (p-tau), a hallmark of CTE. The protein forms neurofibrillary tangles, astrocytic tangles, and tau-positive neurites, often clustered around small blood vessels in the cortical sulci [16,32]. Additionally, in the early or mild stages of CTE, observable brain changes are often minimal, but may include the cavum septum pellucidum, slight enlargement of the frontal and temporal horns of the lateral ventricles, and prominent perivascular spaces, particularly in the temporal lobe's white matter [32].

CTE is a distinctive tauopathy characterized by neurodegeneration that progresses through four stages [32]. In Stage 1, the brain appears normal, with p-tau accumulation limited to certain areas, such as the lateral and frontal cortices, and proximal to small blood vessels in the depth of sulci [33–35]. By Stage 2, localized macroscopic abnormalities become apparent [33,34]. In Stage 3, there is a global reduction in brain weight, with mild frontal and temporal lobe atrophy and ventricular dilation [33,34]. Stage 4, the most severe stage, is marked by profound brain atrophy, particularly in the frontal and medial temporal lobes, with brain weights as low as 1,000 grams reported [33,34].

Along with tau protein accumulation, individuals with CTE may also show the buildup of phosphorylated Transactive Response DNA-binding protein 43 (p-TDP43) in both the white matter and cortical regions [8,35,36]. This protein appears as neuritic accumulations and inclusions within neurons and glial cells [8,37–39]. The National Institute of Neurological Disorders and Stroke and the National Institute of Biomedical Imaging and Bioengineering (NINDS-NIBIB) panel identified TDP43 pathology as a feature of CTE and recognized its role as a criteria for diagnosis post-mortem [40].

Pathological investigations have shown that repeated brain injuries can trigger chronic neuroinflammation, which may contribute to neuronal damage and the progression of CTE [41–44] Neuroinflammation is also linked to more extensive p-Tau pathology in CTE [37]. The significant role of neuroinflammation in the development and progression of CTE, suggests that inflammatory markers could be valuable for future diagnosis and possible treatment [41,45].

Additionally, targeting these inflammatory pathways may offer new opportunities for managing CTE. Research from the DIAGNOSE CTE Project [41] found that cerebrospinal fluid (CSF)

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analysis in former football players with neurobehavioral dysregulation showed a 21.8% increase in IL-6 levels compared to controls (1.73 pg/mL vs 1.42 pg/mL, $p = 0.032$), along with elevated C-reactive protein (CRP) [41]. IL-6 levels were significantly associated with greater emotional dyscontrol, affect lability, and impulsivity, reinforcing its role in neurobehavioral symptoms. However, IL-6 levels in unexposed individuals were not significantly different ($p = 0.071$) suggesting overlap that may limit its clinical utility [41]. Additionally, plasma neurofilament light (NfL), a marker of neurodegeneration, was linked to executive dysfunction and processing speed deficits in older former players highlighting the interplay between inflammation and neurodegeneration in CTE pathology [41].These findings highlight the role of chronic inflammation, along with tau pathology, in the processes associated with CTE.

Diagnosis of CTE

Despite advancements in understanding CTE's mechanisms, diagnosing CTE remains challenging. Currently, there is no definitive method for diagnosing CTE in living individuals [16].

Current efforts to isolate CTE biomarkers in cerebrospinal fluid (CSF) rely on the known mechanisms of cerebral ventricular injury associated with mTBI [2,46]. These mechanisms alter the composition of CSF, but the exact reasons for elevated CSF biomarkers in CTE are not fully understood [24,46]. Elevated CSF biomarkers, such as tau, neurofilament protein, glial (fibrillar astrocytic) protein (GFAP), and S100β, may persist for extended periods after repetitive mTBI. While some biomarkers, like phosphorylated tau, return to baseline within two weeks, others, such as neurofilament light polypeptide, remain elevated for longer durations, though the exact timeframe is still under investigation [24].

Imaging techniques such as CT and MRI are commonly used to evaluate mTBI but often fail to definitively reveal brain injury associated with CTE [46]. Positron Emission Tomography (PET) imaging may help differentiate CTE from other neurodegenerative diseases by detecting beta-amyloid, but it remains an experimental tool rather than a definitive diagnostic method [24,47].

Currently, the most accurate diagnosis of CTE is made through postmortem neuropathological analysis, where the brain is examined microscopically after death [16,33]. While clinical assessments can help determine a likely diagnosis based on symptoms and history of head trauma, most current exams and imaging techniques primarily serve to rule out other conditions rather than confirm CTE [16]. Moreover, most available diagnostic data is based on male subjects, with limited research on how CTE presents in women [35]. Since CTE diagnosis relies on postmortem analysis, the overwhelming focus on male athletes in these studies means there is little understanding of whether the disease manifests differently in women [35]. Without targeted research on female populations, it remains unclear whether gender-based differences exist in biomarker expression, symptom progression, or imaging findings, potentially leading to misdiagnosis or underdiagnosis in women. Addressing this gap is crucial for developing more accurate and inclusive diagnostic criteria.

Treatment of CTE

Due to gaps in understanding the pathogenesis of CTE and the limitations of pre-mortem brain analysis, treatment focuses on symptom management rather than reversing the disease [16]. Supportive treatments such as cognitive rehabilitation, motor therapy, mood and behavior therapy, aerobic exercise, a healthy diet, and mindfulness practices can help mitigate symptoms and improve patients' quality of life [33,48]. Cognitive rehabilitation is a particularly beneficial intervention, as it helps individuals improve memory, decision-making, and overall cognitive functioning following traumatic brain injury [49]. To do so, memory is reviewed continuously to help build cognitive functioning. It guides the brain back to certain thoughts and decisions, helps recall past knowledge, positively impacts emotional barriers and reactions. It also allows individuals to determine their weaknesses and strengths after suffering from a brain injury [49]. These interventions help improve attention as well, a fundamental cognitive ability that supports processing and understanding

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various other cognitive skills [49]. Improving attention can aid motor recovery, which is crucial for learning and adapting to motor recovery [49].

Preventative Measures

Preventive measures are crucial for managing the risk of CTE, due to repetitive concussions and blows in sports being known to contribute to its development as well [50,51]. Prevention strategies include but are not limited to rule changes, stricter regulations, and the use of safer head equipment [50,52]. Although these helmets have effectively reduced injuries, they may not provide sufficient protection against lower-force impacts, which are thought to contribute significantly to concussions, particularly in athletes [50]. The authors performed a thorough review of existing literature to examine the origins and evolution of helmet design, along with the establishment of regulatory standards for helmet usage, construction, and tackling guidelines. With the introduction of National Operating Committee on Standards for Athletic Equipment (NOCSAE) regulations, fatalities dropped by 74%, and serious head injuries declined from 4.25 per 100,000 to 0.68 per 100,000. Both the materials and the protective design of helmets play a crucial role in preventing head injuries [53]. Competition among top helmet manufacturers has further advanced safety innovations. Therefore, continuous advancements in helmet design are necessary for better protection against all types of head impacts [54–56].

CTE in Rodents

Rodent models have been widely developed to study the mechanical forces underlying concussions and their long-term effects, particularly in the context of CTE [57]. Various models, including controlled cortical impact (CCI), fluid percussion (FP), and weight drop, have been used to simulate repeated mild traumatic brain injury (rmTBI) and its potential role in CTE pathogenesis [56–63].

The CCI model is one of the most commonly utilized paradigms for studying brain injury in animals [56,64]. It provides precise control over biomechanical parameters such as impact force, velocity, and tissue deformation, allowing researchers to replicate aspects of TBI [64]. Typically, CCI involves a craniotomy to induce a focal conducive injury in an animal restrained within a stereotaxic device. However, to more accurately simulate concussive injuries, modifications have been made to eliminate the need for craniotomy. These adaptations include using rubber or silicone tips to impact the skull directly or employing a form-fitting steel cap to prevent focal necrotic lesions [57]. Research has shown that avoiding craniotomy produces a more clinically relevant injury, as direct impact on the dura rather than the skull leads to significant cortical tissue loss and hematoma formation [56–66].

Studies using the modified CCI model have demonstrated that varying impact parameters can influence injury severity and outcomes. Larger impactor tip sizes (six to ten mm) reduce focal structural damage but may not effectively replicate concussive injuries. Conversely, reducing the strike depth to one mm prevents extensive hemorrhaging, but limitations arise due to the model's inability to replicate the rotational and linear acceleration forces that induce concussions in humans [57]. The impact parameters used in studies modeling repeated concussions range from over three to six m/s for acceleration and from 31.5 to 500 ms for dwell time [57]. However, many studies lack objective measures of injury severity, such as the presence of an apneic period or the loss of the righting reflex, making it difficult to compare results across different models [56–58].

Despite these limitations, rodent models have successfully replicated several features of CTE, including long-term behavioral and neuropathological changes. Some models examine injury effects over extended periods, up to a year post-injury, providing insights into the progressive nature of CTE pathology [67,68]. However, challenges remain in translating these findings to humans, as rodent lifespans differ significantly from human lifespans, potentially affecting the disease time course.

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Nonetheless, these models are crucial for investigating the long-term consequences of repeated head trauma and understanding the underlying mechanisms of neurodegeneration.

The fluid percussion (FP) model, another widely used approach, has been modified to produce less severe injuries by reducing the force of the fluid pulse [56,69]. Unlike CCI, FP delivered injury through intact dura, generating brain displacement and deformation via a craniotomy and fluid pressure pulse [56–72]. However, this model does not fully replicate the rotational and linear forces implicated in concussive injuries. Studies using repeated FP injuries have demonstrated cognitive deficits in both the short and long term, similar to findings from modified CCI models [69,70]. However, FP-induced injuries often result in more severe motor impairments, likely due to increased cortical damage [56].

Repetitive brain trauma has been linked to neuropathological changes consistent with CTE, including axonal degeneration and neuroinflammation [67,68]. In athletes, repeated concussions can initiate long-term neurodegenerative processes such as dementia pugilistica and CTE [67,68,72]. Closed-head injury models, which apply force directly to the intact skull, better mimic real-world concussive injuries by allowing unrestricted head movement, including lateral and rotational forces [73]. These models produce diffuse brain injuries without the cortical contusions or hemorrhages seen in CCI and FP models [56,73]. Research using the weight-drop model has demonstrated cognitive deficits persisting up to a year post-injury, along with delayed motor impairment and depressive behaviors following repeated impacts over six weeks (56–60). These findings suggest that early behavioral symptoms may serve as indicators of chronic neuropathology associated with repeated head trauma [56,68,73].

Comparisons across studies remain challenging due to variations in experimental parameters. However, there is a well-established correlation between repeated head injuries and an increased risk of developing CTE. When examining CTE in retired athletes, confounding factors such as alcohol and drug use must be considered, as studies suggest that retired athletes have higher rates of alcohol misuse, which may influence brain volume and pathology [74]. While post-mortem human studies remain essential for understanding CTE pathology, rodent models offer a controlled environment to study the direct effects of repeated mild TBI, free from lifestyle-related confounds [74]. These models continue to provide valuable insights into the mechanisms linking repeated head injuries to neurodegeneration and the development of CTE [56].

Conclusion

To advance the diagnosis, treatment, and prevention of CTE, it is crucial to address existing research gaps—particularly the underrepresentation of women in studies [75]. Most CTE research has focused on male athletes, limiting our understanding of how the condition may present differently in women. To date, there are only two documented cases of CTE in women [35]: one involving a domestic abuse victim [76] and the other an autistic individual with self-injury [77]. This lack of data restricts the ability to analyze gender-specific outcomes and develop targeted interventions. Future research should prioritize the inclusion of female participants to ensure a more comprehensive understanding of CTE across all populations.

Additionally, differences in diagnostic study methodologies, including inconsistencies in imaging techniques and analysis, complicate the interpretation and comparison of results across studies. Only two studies have compared histologic and imaging analyses, a step needed for validating imaging for diagnostic criteria [78,79]. To address this, future research should focus on creating and following consistent imaging techniques and procedures. By doing so, it can make it easier to compare results across different studies and ensure that the findings are more reliable.

Therefore, more work is needed to expand research efforts to include diverse populations and conducting longitudinal studies to track the progression of CTE, both of which are important areas for future research. Addressing these gaps and continuing efforts to better understand CTE and its mechanisms will advance the development of more effective diagnosis, treatment, and prevention strategies for this condition.

 doi:10.20944/preprints202502.1912.v2

Acknowledgements: We would like to express our gratitude to Jasmine Alvarado (jalvarado1@geisinger.edu) and Sagar Patel (spatel038@som.geisinger.edu) for their assistance and support in this focused review article.

Conflicts of Interest: Authors have no conflict of interest and no other disclosures.

Abbreviations

C-reactive protein = CRP
Cerebrospinal Fluid = CSF
Chronic Traumatic Encephalopathy = CTE
Controlled Cortical Impact = CCI
Fluid Percussion = FP
Glial (fibrillar astrocytic) protein = GFAP
IL-6 = interleukin-6
Mild Traumatic Brain Injury = mTBI
National Institute of Biomedical Imaging and Bioengineering = NIBIB
National Institute of Neurological Disorders and Stroke = NINDS
Neurofilament light = NfL
Phosphorylated Transactive Response DNA-binding protein 43 = p-TDP43
Positron Emission Tomography = PET
Repeated Head Injuries = RHI
rmTBI = repetitive mild traumatic brain injury
Tau = p-tau

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