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From Repetitive Head Trauma to Neurodegeneration: A Comprehensive Review of CTE

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Abstract
Chronic Traumatic Encephalopathy (CTE) is a progressive neurodegenerative disorder that arises due to repetitive head trauma. Initially identified in boxers as “dementia pugilistica,” it is now recognized as a nosological entity affecting various occupational and social groups, including contact sports athletes, military personnel, and victims of domestic violence. The ante-mortem diagnosis of CTE remains a significant clinical challenge, as current definitive diagnosis relies exclusively on post-mortem neuropathological examination, characterized by deposits of hyperphosphorylated tau protein, their specific distribution, and associated neuroinflammatory and degenerative alterations. Extensive research is underway to identify fluid biomarkers (e.g., NfL, p-tau, GFAP, UCH-L1, S100B) and neuroimaging modalities (e.g., PET, MRI, DTI) that may enable in vivo detection of CTE and differential diagnosis from other tauopathies. The clinical phenotype of CTE is highly heterogeneous, encompassing cognitive, behavioral, affective, and motor disturbances. Emerging evidence suggests the existence of neuropathological subtypes of CTE, which holds relevance for biomarker development and therapeutic strategies. This review synthesizes current knowledge on the molecular pathogenesis, established neuropathological criteria, epidemiology, clinical manifestations, biomarkers, and neuroimaging modalities of CTE, as well as contemporary therapeutic and preventive approaches. The manuscript highlights the diagnostic and therapeutic challenges and underscores the need for further research to develop effective ante-mortem diagnostic tools and treatment strategies for CTE.

Aim of study
The aim of this study is to provide a comprehensive review of the current state of knowledge regarding chronic traumatic encephalopathy (CTE). The paper aims to summarize the molecular mechanisms underlying the disease, describe the neuropathological diagnostic criteria, outline the epidemiology and risk factors, and present the clinical symptomatology of CTE.

Additionally, the study seeks to discuss the proposed pathological subtypes of CTE and to distinguish it from other tauopathies. A special focus is placed on in vivo diagnostic challenges, including the utility of fluid and imaging biomarkers, as well as neuroimaging techniques.
The study also aims to address current therapeutic and preventive strategies and to highlight controversies and knowledge gaps, providing directions for future research to improve early diagnosis and management of CTE.
Materials and Methods
In this review, a comprehensive analysis of the literature on chronic traumatic encephalopathy (CTE) was conducted. The search was performed in PubMed, Scopus, and Google Scholar databases using the following keywords: "chronic traumatic encephalopathy," "CTE," "tauopathy," "biomarkers," "diagnosis," "neuroimaging," "PET," "MRI," "fluid biomarkers," "traumatic brain injury," and "sports concussion." Publications from 2010 to 2025 were considered, with a particular focus on recent findings (last five years) to ensure an up-to-date and thorough overview of the current state of knowledge regarding the pathogenesis, neuropathology, diagnosis, and treatment of CTE. Original research articles and review papers published in English and Polish were included. The literature review was narrative in nature and did not include a meta-analysis or an assessment of methodological quality of the selected studies.

Key words: chronic traumatic encephalopathy (CTE); tauopathy; neuropathology; fluid biomarkers; imaging biomarkers; neuroimaging; PET; MRI; differential diagnosis; clinical manifestations; head injuries; risk groups; contact sports athletes; military personnel; domestic violence.

Introduction

Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease that develops as a consequence of repeated head injuries. Initially described primarily in boxers and known as "dementia pugilistica," contemporary studies have demonstrated that CTE also affects other occupational and social groups, such as contact sports athletes, military personnel, and victims of domestic violence. The growing interest in this disease entity is related to its potential impact on public health, the safety of athletes and military personnel, as well as the diagnostic and therapeutic challenges that remain current. The diagnosis of CTE poses a significant clinical challenge, as confirmation of the disease is currently only possible post-mortem based on neuropathological analysis. A key element is the presence of hyperphosphorylated tau (p-tau) deposits that accumulate in characteristic locations in the brain, including perivascular regions, particularly in the depths of cortical sulci. These deposits are accompanied by neuroinflammatory and degenerative changes that influence the clinical presentation of the disease. Previous studies have shown that CTE is characterized by a wide diversity of clinical symptoms, including cognitive, behavioral, affective, and motor disturbances. These symptoms often appear at a young age and may progress with the development of brain pathology. An additional challenge is the differentiation of CTE from other tauopathies, such as Alzheimer's disease, progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), which may exhibit similar clinical and neuropathological features. Reports in the literature increasingly highlight the existence of neuropathological subtypes of CTE, which may be important in the context of biomarker identification and the development of therapeutic strategies. At the same time, there remains a lack of definitive data on the natural course of the disease, genetic and environmental factors, and the risk of diagnostic errors, such as overdiagnosis or missed cases. This paper provides a review of the current state of knowledge regarding CTE. It discusses the molecular mechanisms underlying the disease, the established neuropathological diagnostic criteria, epidemiology and risk factors, clinical manifestations, proposed subtypes of the disease, and its differentiation from other tauopathies. Special attention is given to in vivo diagnostic challenges, including the use

of biomarkers and neuroimaging techniques, as well as current therapeutic and preventive options. The review concludes with an analysis of controversies and future research directions that are essential for developing effective early detection and treatment methods for CTE.

2. Research materials and methods

2.1 Materials and Methods

In this review, a comprehensive analysis of the literature on chronic traumatic encephalopathy (CTE) was conducted. The search was performed in PubMed, Scopus, and Google Scholar databases using the following keywords: "chronic traumatic encephalopathy," "CTE," "tauopathy," "biomarkers," "diagnosis," "neuroimaging," "PET," "MRI," "fluid biomarkers," "traumatic brain injury," and "sports concussion."

Publications from 2010 to 2025 were considered, with a particular focus on recent findings (last five years) to ensure an up-to-date and thorough overview of the current state of knowledge regarding the pathogenesis, neuropathology, diagnosis, and treatment of CTE. Original research articles and review papers published in English and Polish were included. The literature review was narrative in nature and did not include a meta-analysis or an assessment of methodological quality of the selected studies.

2.2 AI

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

3. Pathogenesis of Chronic Traumatic Encephalopathy (CTE)

The pathogenesis of chronic traumatic encephalopathy (CTE) involves a multifaceted molecular cascade precipitated by repetitive traumatic brain injuries (TBIs) or, less frequently, by a single episode of severe TBI. Traumatic brain injury is defined as a disruption of normal brain function caused by an external mechanical force that induces transient or permanent neurological, structural, or metabolic dysfunction. Such injury may result from direct impact, acceleration-deceleration forces, skull penetration, or rotational forces, which provoke both diffuse and focal damage to neural tissue [1]. Based on the severity of trauma, TBI is classified as mild, moderate, or severe; however, even seemingly innocuous microinjuries can culminate in long-term neurological sequelae [2]. A critical component of CTE pathogenesis is the aggregation of hyperphosphorylated tau protein. This process commences with tau dissociation from microtubules secondary to calcium influx and kinase activation, leading to pathological aggregation and neurotoxicity [3]. Aggregation of tau protein is further exacerbated by chronic neuroinflammation, disruption of the blood–brain barrier, microglial activation, and extensive neuronal and synaptic injury. Another pivotal element in the pathogenesis of CTE is the chronic activation of microglia. Cherry et al. demonstrated that the

duration of exposure to repetitive head trauma correlates with an increase in the density of activated microglial cells (CD68+), which is directly associated with the severity of tau pathology [4]. Post-mortem examinations have revealed elevated counts of CD68+ cells in the frontal cortex, which correlate with tau pathology severity. The authors suggest that microglia may not only react to injury but also perpetuate neurodegeneration, rendering them a potential therapeutic target.

Furthermore, impairment of the glymphatic clearance system plays a substantial role. Iliff et al. demonstrated that TBI can compromise glymphatic function by altering the polarization of aquaporin-4 (AQP4) in astrocytes, thereby impeding the removal of neurotoxic proteins and fostering the accumulation of pathological tau [5]. Concurrently, the cis p-tau isoform exhibits cytotoxic effects and has been identified as a key initiator of synaptic degeneration and neuronal death [6]. Co-pathologies involving other proteins are also critically relevant. TDP-43, a protein known from other neurodegenerative disorders, has been detected in over 80% of individuals with CTE. According to observations by Nicks et al., the presence of TDP-43 pathology was significantly more frequent in individuals with CTE and was accompanied by hippocampal sclerosis [7]. Emerging evidence suggests that CTE is also associated with demyelination abnormalities. Alosco et al. reported decreased expression of myelin proteins—specifically, myelin basic protein (MBP) and proteolipid protein 1 (PLP1)—in the brains of athletes diagnosed with CTE, which may underlie the functional and cognitive deficits observed in these patients [8]. In summary, CTE is a multifactorial disorder encompassing complex interactions between mechanical injury, inflammation, impaired protein clearance, demyelination, and concomitant proteinopathies.

As noted by Bergauer et al.: “CTE should be conceptualized as a disease of cumulative pathology involving tauopathy, inflammation, axonal injury, and disrupted clearance mechanisms” [9]. Elucidation of these mechanisms forms the foundation for the discovery of biomarkers and the development of targeted therapies. The distribution of these morphological alterations and their association with head trauma will be discussed in detail in the subsequent section on neuropathology.

4. Neuropathological Diagnostic Criteria for CTE

In distinction from other neurodegenerative disorders, there are currently no established diagnostic criteria for chronic traumatic encephalopathy (CTE) that can be applied during the lifetime of the patient, thereby rendering post-mortem neuropathological evaluation the sole standard for diagnosis. The definitive diagnosis of CTE requires the identification of strictly defined neuropathological features that differentiate it from other tauopathies. A key diagnostic hallmark is the presence of hyperphosphorylated tau (p-tau) deposits located perivascularly within neurons, often in the depths of cortical sulci, with an irregular distribution, sometimes accompanied by tau pathology in glial cells, which constitutes the pathognomonic lesion [12]. According to the Second NINDS/NIBIB Consensus Criteria, a neuropathological diagnosis of CTE can be rendered in the presence of at least one such lesion in a single region of the neocortex [10]. The co-occurrence of p-tau aggregates in astrocytes (e.g., thorn-shaped astrocytes) may support the diagnosis, but is not required in the absence of neuronal pathology. Establishing a neuropathological diagnosis of CTE necessitates meeting the following criteria: the presence of hyperphosphorylated tau (p-tau) aggregates in neurons (an obligatory feature); the localization of p-tau deposits immediately adjacent to blood vessels (i.e., perivascular distribution); the distribution of pathology in the depths of cortical sulci (with exclusion of pathology limited solely to subpial regions); and the potential presence of p-tau in astrocytes, which may be observed but is not mandatory for

diagnosis. Lesions restricted exclusively to astrocytic p-tau without neuronal involvement, lesions confined only to subpial regions, or a regular, non-specific pattern of p-tau distribution do not meet the neuropathological criteria for CTE. Such findings may be consistent with age-related tau astrogliopathy (ARTAG) and do not constitute a basis for the diagnosis of CTE [10]. The dorsolateral frontal cortex (DLF) is frequently among the earliest affected regions by CTE-related pathology [11], suggesting that this region may serve as a sensitive indicator of early disease. Additional regions commonly involved include the parietal and temporal cortices, the amygdala, and the hippocampus [12]. As noted by Armstrong et al., a distinguishing feature of CTE relative to other tauopathies is the characteristic distribution of tau deposits, which are primarily located in the depths of cortical sulci [13].

4.1 Staging of CTE

Four pathological stages of CTE have been delineated, ranging from Stage I (mild) to Stage IV (severe). The early stages of the disease (Stages I and II) correspond to milder forms of CTE and are characterized by the presence of dispersed perivascular p-tau deposits within the cerebral cortex, most frequently in the frontal cortex. In the more advanced stages (Stages III and IV), there is a progressive accumulation of tau pathology within the neocortex, with the extension of lesions to the medial temporal lobe, basal ganglia, and brainstem. In Stage III, macroscopic findings often include cortical atrophy, ventricular enlargement, and degenerative changes within the hippocampus, while in Stage IV, there is pronounced neuronal loss, marked gliosis, demyelination, and axonal injury in the most severe cases [10,11].

The standard neuropathological protocol recommends the sampling of at least five regions of the neocortex—including the superior frontal gyrus, inferior parietal lobule, superior temporal gyrus, and medial temporal lobe (e.g., entorhinal cortex). Immunohistochemical staining for p-tau (AT8) and meticulous evaluation of perivascular pathology in the depths of cortical sulci are essential [10,12]. Byard et al. emphasize that the characteristic lesions of CTE may remain undetected without targeted sampling and immunohistochemical staining for p-tau [14], underscoring the importance of standardized assessment protocols. According to consensus guidelines, neuropathological diagnosis of CTE in older individuals requires particular caution due to the frequent coexistence of age-related tauopathies (ARTAG, PART, AGD, Alzheimer's disease). Diagnosis should not rely solely on isolated astrocytic pathology or changes confined to the medial temporal lobe. Small biopsy specimens may fail to reflect the full extent of the disease, and although hemispheric sections are preferred, the established protocol permits evaluation in limited samples. Routine examination of the brainstem, hippocampus, thalamus, and entorhinal cortex is recommended in equivocal cases [10].

Table 4.2 presents the simplified neuropathological classification of CTE developed during the Second NINDS/NIBIB Consensus Meeting (Bieniek et al., 2021). This classification is based on the extent and distribution of pathognomonic lesions within the brain and enables a practical assessment of the neuropathological stage of CTE in postmortem tissue samples.

Table 1. Proposal of a Simplified Neuropathological Classification of CTE According to the NINDS/NIBIB Consensus (2021) [9]

Classification	Clinical-Anatomical Criteria

Classification	Clinical-Anatomical Criteria
Low-grade CTE	Focal pathognomonic lesions limited to the neocortex. Corresponds to stages I–II according to McKee.
High-grade CTE	Widespread pathognomonic lesions with the presence of neurofibrillary tangles (NFTs)[1] in multiple brain regions, including the hippocampus, amygdala, entorhinal cortex, thalamus, mammillary bodies, and dentate nucleus of the cerebellum. Corresponds to stages II–IV according to McKee.

[1]NFT (neurofibrillary tangles) – filamentous aggregates of hyperphosphorylated tau protein in neurons.

In summary, at present, the only definitive method for confirming a diagnosis of CTE is through post-mortem neuropathological identification of characteristic pathognomonic changes in the patient's brain. In the absence of approved in vivo diagnostic criteria, this remains of critical importance not only for research but also for forensic practice. In this context, understanding the prevalence of CTE in at-risk populations and identifying risk factors that may contribute to the development of this encephalopathy are of particular relevance—topics that will be discussed in the next section.

5. Epidemiology and Risk Factors

Repetitive head impacts (RHI) are the most significant risk factor for the development of chronic traumatic encephalopathy (CTE). A critical aspect of research on CTE remains the dose–response relationship between exposure and disease risk. Mez et al. (2020) demonstrated that the number of years of playing American football was significantly associated with the severity of CTE in a dose-dependent manner, providing evidence for the cumulative nature of the risk of developing this encephalopathy [15]. This finding indicates that the longer the duration of exposure to RHI, the greater the likelihood of developing advanced neuropathological changes. The authors also emphasize that not only the number of concussions but also the overall length of the sports career plays a key role in the pathogenesis of the disease. Consequently, the researchers propose that cumulative RHI exposure should be considered one of the primary determinants of risk for this condition. Populations particularly at risk for CTE include athletes involved in contact sports, such as soccer [16-18], wrestling [19], rugby [18,20], and baseball [16], as well as military personnel, victims of domestic violence, and individuals with poorly controlled epilepsy [21]. In autopsy analyses of the brains of professional American football players, characteristic CTE lesions were identified in over 90% of cases [11]. Similar findings have been observed in boxers, hockey players, war veterans, and individuals exposed to domestic violence [22,23]. In recent years, an increasing body of evidence suggests that CTE may also develop in women subjected to chronic physical abuse. As early as 1990, Roberts et al. described a case of a 76-year-old woman with a long-standing history of domestic violence who exhibited dementia and neuropathological findings consistent with the so-called punch-drunk syndrome, typically observed in boxers. This was one of the first cases to suggest that CTE could occur in women exposed to repetitive head trauma outside of a sports context [24]. Danielsen et al. (2021) reported a case of a 29-year-old woman who, following her death, was found to have pathognomonic tau pathology consistent with CTE and had a documented history of chronic domestic abuse [22]. Furthermore, Tiemensma et al. (2024) described two additional cases of women with long-term histories of abuse and multiple head injuries who exhibited

neuropathological changes characteristic of CTE [25]. However, it is important to note that not all cases of domestic violence result in neuropathological changes characteristic of CTE. In a study by Dams-O'Connor et al. (2023), the brains of 84 women with histories of chronic physical abuse were examined. The authors reported evidence of microvascular damage, diffuse axonal injury, and microglial activation but did not observe deposits of phosphorylated tau in locations typically associated with CTE. These findings suggest that the mechanisms of neurodegeneration in victims of abuse may differ from those observed in contact sport athletes and warrant further investigation to fully understand their implications [26].

An important predictive factor in the development of CTE appears to be the age at which exposure to RHI begins. Studies indicate that initiating American football play before the age of 12 is associated with a higher risk of cognitive impairment and greater tau pathology in later life [27]. Therefore, the age of exposure may influence the vulnerability of the developing brain to injury. Additionally, the overall length of a sports career remains a strong predictor of risk—Mez et al. (2020) reported that individuals with the longest exposure had the highest probability of developing advanced-stage CTE. There is also evidence that genetic factors contribute to the risk of developing CTE. The APOE ε4 allele, known for its role in Alzheimer's disease, has also been linked to more severe tau pathology and worsened cognitive function in CTE patients. A study conducted by Atherton et al. (2022) found that among individuals over the age of 65, carriers of the APOE ε4 allele were significantly more likely to develop advanced-stage CTE.Additionally, these individuals exhibited a substantially higher accumulation of pathological tau protein in the dorsolateral prefrontal cortex, suggesting that the presence of this genetic variant may influence both the severity of the disease and the extent of neuropathological changes in the brain [28].

Moreover, allelic variants of the TMEM106B gene, which is involved in lysosomal metabolism, may modulate neuroinflammatory responses and the accumulation of p-tau in the brains of individuals with CTE [29]. The minor allele of the TMEM106B gene has been associated with less severe neuropathological changes, potentially indicating a neuroprotective effect [29].

Collectively, these data suggest that genotype may play a significant role in determining both susceptibility to CTE and its clinical manifestations. In summary, the pathogenesis of CTE is influenced not only by the intensity and duration of head trauma exposure but also by the timing of its onset and individual biological factors. As emphasized by numerous authors, understanding the full spectrum of risk factors is crucial not only for prevention but also for the early identification of at-risk individuals and the implementation of potential interventions.

6. Clinical Manifestations of Chronic Traumatic Encephalopathy (CTE)

The clinical presentation of CTE is heterogeneous and stage-dependent; however, four primary symptomatic domains can be distinguished: cognitive impairment, behavioral changes, mood disturbances, and motor symptoms. Cognitive deficits are among the most frequently observed symptoms, particularly in the later stages of the disease. These include memory impairment, executive dysfunction, difficulties with concentration, and planning deficits. Neuropathological studies have demonstrated that memory loss, executive dysfunction, and attentional deficits are among the most prominent clinical features in patients with confirmed neuropathological CTE [11].

In a clinical study of former athletes, it was observed that in the later stages of the disease, the most prominent and dominant clinical feature is progressive cognitive decline [30]. Behavioral changes represent an early manifestation of CTE, often appearing prior to cognitive deficits. In a clinical assessment of symptom profiles in individuals with CTE,

authors highlighted that episodes of explosiveness, aggression, impulsivity, and difficulties in emotional regulation were among the most commonly reported behavioral disturbances [31]. These symptoms can lead to significant social, occupational, and familial difficulties.Mood disturbances constitute the third pillar of the clinical presentation of CTE. Patients often experience depressive symptoms, anhedonia, apathy, irritability, emotional lability, and suicidal ideation. A systematic review revealed that mood disturbances, including depression and suicidal tendencies, frequently occur in individuals with CTE [32]. Mez et al. further emphasized that depressed mood and a sense of hopelessness are commonly present at the onset of the symptomatic phase of the disease [30]. These data suggest that affective disturbances may be not only a consequence of progressive neurodegeneration but also an early warning sign. Motor symptoms, although less frequent than cognitive and behavioral symptoms, represent an important component of the clinical presentation of CTE in advanced stages. The most commonly reported motor symptoms include parkinsonism, resting tremor, dysarthria, ataxia, and muscle rigidity. According to Ling et al. [33], parkinsonian features and gait difficulties may be part of the clinical picture of the disease, whereas McKee et al. [12] emphasized the presence of speech and coordination disturbances, especially in more advanced cases. A study by Alosco et al. (2024) provides important insights into the relationship between the distribution of p-tau deposits in the brain and the specific clinical symptoms of chronic traumatic encephalopathy. The clinical and neuropathological data of 364 individuals meeting the neuropathological criteria for CTE were analyzed. The authors demonstrated that severe p-tau pathology in the dorsolateral prefrontal cortex was associated with a higher likelihood of cognitive deficits, particularly in executive function and memory, as well as with difficulties in daily functioning [34].

Additionally, severe p-tau pathology in the amygdala and inferior parietal cortex was associated with a greater severity of neuropsychiatric symptoms, such as impulsivity and apathy [34]. These findings suggest that the distribution of p-tau deposits in specific brain regions may explain the diverse clinical presentation of CTE.

Accumulation of tau in the frontal and parietal cortices—areas responsible for executive control and information integration—was closely associated with the severity of dementia symptoms and behavioral disorganization. Conversely, changes in limbic structures, such as the amygdala, were associated with the occurrence of depressive symptoms and mood disturbances. The aforementioned data clearly indicate that CTE is characterized by a multidimensional and dynamically evolving clinical presentation, which may significantly complicate differential diagnosis, particularly in the early stages of the disease. In vivo diagnosis of CTE remains a challenge, underscoring the need for further development of biomarkers and diagnostic tools.

7. Subtypes of Chronic Traumatic Encephalopathy (CTE)

An expanding body of research suggests that chronic traumatic encephalopathy (CTE) is not a homogeneous pathological entity but rather encompasses different neuropathological variants that differ in the topography of tau protein deposits and their associated clinical manifestations. Identification and classification of these subtypes may be important for differential diagnosis and for the development of specific biomarkers. An example of such a variant is the cortical-sparing chronic traumatic encephalopathy (CSCTE) described by Alexander et al. (2024), in which relatively minor involvement of p-tau pathology was observed in the neocortex, despite a significant burden of pathology in subcortical structures, particularly the medial temporal lobe and brainstem nuclei. This distinguishes it from the classical form of CTE, where lesions predominantly affect the frontal and temporal cortices

(35). This different anatomical distribution translates into a modified clinical profile. Researchers emphasize that CSCTE may present with less pronounced cognitive and neuropsychiatric disturbances in the early stages of the disease, due to relatively preserved frontal and temporal cortical structures (35). This means that patients may experience milder problems with memory, mood, or autonomic functions, which often delays the correct diagnosis.

Nicks et al. (2023) also proposed the identification of a subtype of CTE characterized by predominant TDP-43 pathology with coexisting hippocampal sclerosis (HS). These lesions resemble the neuropathological features characteristic of frontotemporal lobar degeneration (FTLD) disorders and may influence a different clinical trajectory. The authors suggest that HS and TDP-43 may help define CTE subtypes with distinct clinical courses (7). These differences are highly relevant for the selection of imaging biomarkers. Currently used PET ligands for imaging p-tau may fail to detect subcortical changes characteristic of CSCTE. Alexander et al. (35) emphasize that the recognition of this subtype highlights the need to develop new imaging techniques and fluid biomarkers that would enable the detection of subcortical tauopathy, which current PET techniques may miss. In summary, consideration of CTE subtypes, such as CSCTE or forms with predominant TDP-43 pathology, underscores the need to update diagnostic criteria and to develop more complex diagnostic tools. Their identification could improve diagnostic accuracy and better predict the clinical course.

8. Comparison of CTE with Other Tauopathies

Chronic traumatic encephalopathy (CTE) is classified among the tauopathies, a group of neurodegenerative disorders characterized by abnormal accumulation of hyperphosphorylated tau protein in the brain. Although CTE shares certain pathological features with other tauopathies, such as Alzheimer's disease (AD), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), it is distinguished by its unique pattern of tau deposition, as well as by its clinical course and etiopathogenesis. Unlike CTE, in Alzheimer's disease, p-tau predominantly accumulates in the medial temporal lobe, particularly in the hippocampus, parahippocampal gyrus, and entorhinal cortex, and exhibits a characteristic progression toward the associative cortex.

Additionally, AD invariably presents with amyloid plaques, which differentiates it from CTE, where amyloid pathology is not a typical finding [13]. In contrast, progressive supranuclear palsy (PSP) is characterized by symmetrical deposition of p-tau within glial cells, particularly in "tufted astrocytes" in the basal ganglia and midbrain. Studies by Koga et al. have demonstrated that tau expression in PSP astrocytes may be associated with increased expression of the MAPT gene, suggesting an active role of astrocytes in the pathogenesis of the disease [36]. Unlike CTE, PSP does not exhibit a selective distribution of tau pathology in the cortical sulci nor a typical perivascular pattern. Corticobasal degeneration (CBD) is characterized by the presence of "astrocytic plaques," as well as tau-positive inclusions in neurons and oligodendrocytes, mainly within the cerebral cortex and caudate nucleus. The pathology exhibits a marked asymmetry and does not preferentially involve sulcal depths or perivascular regions [37]. Additionally, the literature describes cases of mixed neuropathological presentations that include features of both PSP and CBD. Examples are reported by Koga et al. (2023), suggesting the existence of a spectrum of tauopathies with overlapping features, although they remain distinguishable based on the distribution and cellular type of tau pathology [37].In summary, while CTE shares features with other tauopathies, its unique topographical pattern—namely, the presence of p-tau deposits in the depths of cortical sulci, perivascular distribution, primary neuronal involvement, and strong

association with repetitive head trauma—allows it to be considered a distinct subtype of tauopathy. For this reason, precise analysis of tau deposit distribution and the types of cells involved in its pathogenesis is crucial.

9. Fluid and Imaging Biomarkers in the Diagnosis of Chronic Traumatic Encephalopathy (CTE)

The diagnosis of chronic traumatic encephalopathy (CTE) during life remains a clinical challenge, as definitive confirmation is currently possible only post-mortem based on characteristic neuropathological findings. Therefore, intensive research is underway to identify biomarkers that could enable in vivo diagnosis of CTE.

9.1 Fluid Biomarkers

Neurofilament light chain (NfL) is considered one of the most promising fluid biomarkers in the diagnosis of CTE. Its concentration in plasma and cerebrospinal fluid is associated with axonal injury and neurodegenerative processes. Currently, its diagnostic utility is being evaluated within the DIAGNOSE CTE cohort, which includes former contact sports athletes and a control group, with the goal of identifying biomarkers enabling the diagnosis of CTE during life (Alosco et al., 2021) [38]. Hyperphosphorylated tau protein (p-tau) is a key pathological hallmark of CTE, but in fluid diagnostics, its specificity is limited, as its concentration may also be elevated in other tauopathies, including Alzheimer's disease [38]. Inflammatory and glial markers, such as GFAP, UCH-L1, and S100B, have also attracted significant interest, particularly in the context of acute brain injuries. Elevated concentrations of these markers have also been observed in individuals exposed to repetitive head trauma; however, their specificity in diagnosing CTE remains limited. Bergauer et al. emphasize that in chronic neurodegenerative disorders such as CTE, the diagnostic value of these markers still requires further investigation [9]. The literature also highlights the potential of using analyses of proteins and other molecules in cerebrospinal fluid and plasma to search for new biomarkers of chronic traumatic brain injury.

This approach may help in identifying individuals at increased risk of developing CTE, although currently none of the fluid or imaging biomarkers studied exhibit sufficient diagnostic power to differentiate CTE from other tauopathies, underscoring the need for continued research and validation of these indicators (Bergauer et al., 2022) [9].

Similar conclusions were presented by Trofimov et al. (2023), indicating a lack of biomarkers with adequate specificity to distinguish CTE from other neurodegenerative diseases, further highlighting the need for ongoing research on their diagnostic value [27].

9.2 Imaging Biomarkers

Positron emission tomography (PET) utilizing tau-binding ligands, such as [^18F]AV-1451, allows for the visualization of p-tau deposits in the living brain. However, as noted by the authors, these ligands (e.g., flortaucipir) bind to areas consistent with CTE pathology but lack sufficient specificity to distinguish it from Alzheimer's disease [39]. Magnetic resonance imaging (MRI), especially techniques such as diffusion tensor imaging (DTI), may play a significant role in detecting neurodegenerative changes in individuals exposed to repetitive head trauma. Reduction in white matter integrity and cortical volume loss, detected using DTI, suggest permanent structural damage that may underlie the clinical symptoms observed in CTE. As noted by Bergauer et al. (2022), these changes are present in individuals with a history of multiple head injuries, supporting the potential utility of DTI as a tool for detecting neurodegeneration characteristic of CTE. However, the lack of specificity of these changes to

CTE requires their interpretation within a broader clinical and biochemical context. The DIAGNOSE CTE project emphasizes the necessity of integrating various diagnostic methods, including neuropsychological assessments, analyses of fluid and imaging biomarkers, and structured clinical tools, to improve the diagnostic accuracy of traumatic encephalopathy syndrome (TES). The authors highlight that the use of a multimodal approach, incorporating clinical, fluid, imaging, and genetic data, is essential to establish robust diagnostic criteria for this syndrome [38].

10. Treatment and Prevention

Currently, no disease-modifying therapy for chronic traumatic encephalopathy (CTE) exists, and clinical interventions focus solely on mitigating psychiatric, behavioral, and cognitive symptoms. As emphasized by Pierre et al. (2021), "there is currently no disease-modifying therapy for CTE; current management strategies focus on symptom reduction and patient support" [40]. In clinical practice, antidepressants, antipsychotics, and cognitive enhancers are employed; however, their efficacy in the context of CTE has not been formally confirmed in controlled studies.In the realm of preclinical studies, increasing interest has been directed towards neuroprotective interventions, including cyclin-dependent kinase (CDK) inhibitors, which have the potential to inhibit tau protein phosphorylation. As reported by Cherry et al. (2021), "animal models of CTE have demonstrated that CDK inhibitors can reduce pathological tau accumulation and neuroinflammation" [4]. Studies in rodent models have also suggested potential benefits from the use of GSK-3β kinase inhibitors and anti-inflammatory agents, although their translation to clinical settings requires further investigation. Given the lack of effective treatments, primary prevention represents the most critical strategy for reducing the risk of developing CTE. This is particularly pertinent for populations exposed to repetitive head impacts, such as athletes, military personnel, and victims of domestic violence. Mez et al. (2020) demonstrated that "a longer duration of football play was significantly associated with increased risk and severity of CTE pathology" [40], indicating a clear dose–response relationship and underscoring the need to limit exposure.Proposed measures include reducing the frequency of contact training sessions, extending recovery periods following injuries, and employing modern helmets designed to mitigate impact forces.

In conclusion, although no disease-modifying therapy for CTE is currently available, research into molecularly targeted treatments is ongoing.

Based on the available data, however, the most effective means of reducing disease incidence remains prevention—achieved through limiting exposure to repetitive head impacts and implementing protective measures at both individual and systemic levels.

12. Conclusions and Future Directions

Advancements in research on chronic traumatic encephalopathy (CTE) have significantly expanded the understanding of its pathogenesis, biomarkers, and potential risk factors. Concurrently, there is increasing recognition that the development of reliable diagnostic tools necessitates the integration of clinical, neuropathological, neuroimaging, and molecular data. Researchers emphasize the need for long-term studies combining neuroimaging, behavioral assessments, and fluid biomarkers to establish robust diagnostic criteria: "more longitudinal studies combining imaging, neurobehavioral, and biochemical approaches are warranted to establish robust biomarkers for CTE" [42]. Despite considerable progress, knowledge regarding the natural history of CTE remains limited. The authors of the DIAGNOSE CTE project highlight the necessity of conducting long-term, prospective cohort studies to enable

the identification of symptom sequences and to evaluate the utility of biomarkers in predicting disease progression. The objective of this project is to develop and validate in vivo biomarkers for CTE, to characterize its clinical course, to identify potential risk factors, and to provide data resources and biological samples to the scientific community [38]. Furthermore, as emphasized by Fortington et al., studies on CTE should avoid simplistic assumptions of causality based solely on associations with repetitive head impacts (RHI). "Overconfidence in assigning causality to repetitive head impacts can obscure the complexity of symptom presentation," the authors caution, underscoring the need for critical data analysis and epidemiological rigor [41]. Future research should also consider genetic factors that may influence susceptibility to CTE and the disease course. Mez et al. (2017) demonstrated that "TMEM106B variants were significantly associated with risk and severity of CTE, independent of age and exposure duration," indicating the role of genetic polymorphisms as potential risk biomarkers. In summary, further research on CTE must be based on a multidisciplinary approach that encompasses biological, clinical, and environmental contexts. Only in this way will it be possible to develop precise tools for diagnosing, monitoring, and potentially treating CTE, while avoiding diagnostic overreach and oversimplified causal inferences.

13. Conclusions

Chronic traumatic encephalopathy (CTE) remains a clinically challenging entity to diagnose in vivo, primarily due to the lack of validated, disease-specific biomarkers and the overlap of its symptoms with other tauopathies and neuropsychiatric disorders. Despite considerable progress in understanding the molecular and neuropathological mechanisms of the disease, the diagnosis of CTE still relies exclusively on post-mortem confirmation of hyperphosphorylated tau protein deposits in characteristic brain locations. To date, studies investigating fluid and imaging biomarkers—including neurofilament light chain (NfL), p-tau, GFAP, UCH-L1, S100B, PET, and DTI—have not demonstrated sufficient specificity or sensitivity to support the diagnosis of CTE in vivo. Therefore, further prospective and validation studies are required to enable the development of reliable diagnostic and prognostic tools. Additionally, cohort studies including individuals from high-risk groups (contact sport athletes, military personnel, and victims of domestic violence) are essential, with consideration given to genetic factors such as APOE ε4 and TMEM106B alleles.

The increasing number of described neuropathological variants of CTE (e.g., CSCTE, TDP-43+) highlights the need to account for morphological heterogeneity in both diagnosis and biomarker interpretation.

From a clinical perspective, primary prevention is currently the most effective strategy for limiting the incidence of CTE, especially by reducing head impact exposure and implementing protective measures. Currently, symptomatic treatment focuses solely on alleviating psychiatric, behavioral, and cognitive symptoms, while disease-modifying therapies are still under preclinical investigation.

14. Author's contribution

Conceptualization: Marta Piotraszewska; methodology: Marta Piotraszewska and Magda Skudzińska; software: Dominika Błonka and Maria Grys; Check: Filip Kochański and Karolina Wołk; Formal analysis: Magdalena Bartold and Janina Pohrybieniuk; Investigation: Magdalena Bartold and Janina Pohrybieniuk; Resources: Magda Skudzińska and Marta Piotraszewska; Data curation: Aleksandra Jaskulska and Jan Pietrzak; Writing – rough preparation: Marta Piotraszewska; writing - review and editing: Marta Piotraszewska and

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The authors declare no conflict of interest.

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