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REVIEW

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Tau Pathology in Chronic Traumatic Encephalopathy: Mechanisms and Diagnostic Advances

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Chronic Traumatic Encephalopathy (CTE) is a progressive neurodegenerative tauopathy associated with repetitive head impacts (RHI), yet it remains diagnosable only at post-mortem. Tau, a microtubule-associated protein, normally stabilizes neuronal microtubules and regulates cytoskeletal dynamics. Mechanical strain from RHI is thought to disrupt calcium homeostasis and kinase-phosphatase balance, driving hyperphosphorylation and phosphorylated-tau (p-tau) formation. This results in detachment from microtubules and subsequent p-tau aggregation. These mechanically-induced biochemical changes produce CTE's characteristic lesion: perivascular p-tau deposition in the depths of cortical sulci, reflecting the non-uniform mechanical loading experienced by brain tissue following head impacts. Advances in molecular neuropathology have revealed that CTE tau filaments adopt a unique conformational fold, and that early tau species may contribute to neurotoxicity. Despite this growing understanding, antemortem diagnosis remains challenging. Structural MRI demonstrates frontotemporal atrophy and white-matter abnormalities in impact-exposed individuals, but these findings lack disease specificity. Tau-PET tracers developed for Alzheimer's disease (AD) show limited affinity for the distinct CTE tau fold, while fluid biomarkers variably reflect cumulative exposure but cannot yet discriminate CTE from other tauopathies. Future progress will depend on mechanistically informed diagnostic tools, including conformation-specific biomarkers and PET radiotracers tailored to CTE-specific tau. Multimodal approaches integrating neuroimaging, molecular profiling, exposure metrics, and computational modelling will be essential for early detection, disease monitoring, and informed public health policy around repetitive head impacts.

INTRODUCTION

Tau is a neuronal microtubule-associated protein (MAP) that stabilizes microtubules and regulates dynamic "growth" and "shrinkage" [1,2]. Tau is tightly regulated, predominantly through phosphorylation; increased phosphorylation (p-tau) decreases tau's affinity for microtubules. When dysregulated, tau becomes hyperphosphorylated, detaches and aggregates into pathological species. P-tau accumulation is a hallmark feature

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Abbreviations: CTE, chronic traumatic encephalopathy; TBI, traumatic brain injury; RHI, repetitive head impacts; p-tau, phosphorylated-tau; AD, Alzheimer's disease; BBB, blood-brain barrier; TES, traumatic encephalopathy syndrome; PET, positron emission tomography; FTP, flortaucipir; CSF, cerebrospinal fluid.

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of Chronic Traumatic Encephalopathy (CTE), a neurodegenerative disease associated with repetitive head impacts (RHI) presenting with behavioral and cognitive disturbances [3].

Unlike other tauopathies, CTE is associated with repeated biomechanical insult, rather than one primarily mediated by metabolism or genetics. Repetitive sub-concussive and concussive traumatic brain injuries (TBI) impose shearing forces on neurons, disrupting calcium homeostasis and kinase-phosphatase balance, potentially promoting pathological tau phosphorylation. This trauma-dependent cascade frames CTE as a disorder of mechanical biochemistry and may underlie its defining feature: perivascular p-tau deposition within sulcal depths, reflecting non-uniform loading of brain tissue during head impacts.

Despite growing public and scientific concern—driven largely by CTE's association with contact sports and military activity—CTE remains diagnosable only after death, limiting early intervention and accurate epidemiology. Reliance on limited brain bank samples introduces selection bias, as brain donors were often disproportionately symptomatic or high-exposure cases. Advances in molecular neuropathology, including identification of a CTE-specific tau filament fold [4], are refining understanding of injury-driven tau misfolding and its diagnostic implications. Early oligomeric and cis-tau species have been implicated as potential initiators of neurodegeneration [5,6]. Together, these observations propose CTE as a structurally distinct tauopathy, supporting the need for biomarker discovery.

CURRENT UNDERSTANDING OF CTE TAU PATHOLOGY

CTE is defined by the accumulation of hyperphosphorylated tau in perivascular foci at the depths of cortical sulci, typically arranged in a patchy distribution. This pattern underpins the McKee staging framework (I-IV) and the more recent binary "high vs low CTE" classification [3,7,8]. Although this unique p-tau topology is pathognomonic of CTE, p-tau deposition occurs in other tauopathies such as Alzheimer's disease (AD), necessitating biomarkers that capture CTE-specific molecular or topographical features.

Understanding Tau – Physiology Becomes Unique Pathology Upon RHI

Tau exists as six isoforms, comprising three or four microtubule-binding repeats (3R/4R) [9]. Many tauopathies show predominance for 3R or 4R, however, CTE exhibits a balanced 3R/4R profile, similar to AD. In healthy brains, tau is unfolded and exhibits no tendency to aggregate. Following RHI, a neuroinflammatory cascade is triggered, promoting tau phosphorylation and aggregation. The injury also likely causes direct axonal injury, demyelination, and disruption of the blood-brain barrier (BBB) [10,11].

Following injury, tau aggregates into neurofibrillary tangles (NFTs) within neurons and astrocytic inclusions in astrocytes. These aggregates may act as damage-associated molecular patterns (DAMPs), activating microglia and perpetuating inflammatory signaling with repeated trauma. Computational models suggest that rotational acceleration and shear strain may converge disproportionately in the sulcal depths, providing a putative mechanistic explanation for the distinct focal pattern of tau accumulation [12,13]. The perivascular predilection likely reflects the BBB disruption following RHI or the physical presence of blood vessels, both of which alter the local distribution of strain forces and may facilitate cofactor exposure [14].

The Process of Tau Hyperphosphorylation

Much of the evidence on CTE's pathophysiology derives from general tauopathy research and experimental TBI models rather than confirmed human CTE. Accordingly, findings should be interpreted as suggestive of possible mechanisms rather than definitive proof of causation.

At the molecular level, tau hyperphosphorylation in CTE appears to arise from dysregulated kinase-phosphatase signaling triggered by mechanical injury. Although the upstream mechanisms of this imbalance are not fully defined, calcium influx into neurons after brain injury can activate kinases, initiating tau-phosphorylation, and providing a plausible link between strain and hyperphosphorylation [15-17]. Hyperphosphorylation in CTE does not arise from a single kinase or phosphorylation event but reflects a multi-site pattern of modification. Experimental work has demonstrated that phosphorylation at key sites—such as Thr212, Thr231, and Ser262—can destabilize microtubule binding and promote cytoskeletal disassembly, nominating these residues as important contributors to tau dysfunction [18]. Although these findings derive from pseudo-phosphorylation models rather than trauma-induced kinase activity, they highlight how combined phosphorylation can synergistically impair tau function. In the context of RHI, trauma-induced activation of kinases such as GSK-3ß and CDK5, alongside reduced phosphatase activity, provides a plausible means through which these patterns may emerge *in vivo.*

Although no single enzymatic pathway has been definitively implicated in CTE, multiple lines of evidence suggest the involvement of a convergent kinase-driven axis—particularly GSK-3ß and CDK5. Immunohisto-

chemical analyses of neuropathologically-confirmed CTE tissue show evidence of Thr175 and Thr231 phosphorylation, co-localization of Thr175 with activated GSK-3ß, and a trauma-associated re-localization of GSK-3ß from a predominantly nuclear distribution in control tissues to a cytosolic pattern in CTE tissues, placing the active kinase closer to tau. A TBI rat model produced similar findings in Thr175/Thr231 and GSK-3ß months after injury, lending indirect support to this injury-kinase-phosphorylation sequence *in vivo* [19]. Pharmacological inhibition of GSK-3ß in human-tau transgenic mice correlates with reduced phosphorylation, aggregation, and axonal degeneration when administered early in tangle development [20]. This supports a functional role for this kinase in tauopathy progression. Complementary genetic models suggest that CDK5 overactivation may amplify tau hyperphosphorylation, aggregation, and NFT formation in human-tau transgenic mice, and both CDK5 and GSK-3ß frequently co-localize with aggregated tau in affected neurons [21]. Alongside kinase upregulation, transcriptomic analyses reveal reduced expression of several tau-directed phosphatases in CTE brain tissue [22]. Although data remain limited, phosphatase down-regulation is plausible given that TBI induces calcium dysregulation and calpain activation—processes known to disrupt regulatory subunits such as PP2B [16]. Evidence from human studies remains limited and model systems vary in their fidelity, but these findings collectively support a framework whereby repetitive strain may drive enzymatic dysregulation, promoting multi-site tau hyperphosphorylation and aggregation.

EMERGING MECHANISTIC HYPOTHESES AND STRUCTURAL INSIGHTS

Understanding of tau pathology in CTE has advanced considerably over the past decade, driven by progress in structural biology, biochemical modelling, and biobank development. These advances increasingly support the view that CTE represents a mechanochemically distinct tauopathy.

Distinct Tau Filament Fold and Cofactor Hypothesis

A landmark advance in recent years was made with use of cryo-electron microscopy. Tau filaments from individuals with neuropathologically-confirmed CTE adopt a unique conformational "fold," seen in over 97% of filaments, distinct from those observed in classical tauopathies like AD and Pick's disease [4]. Notably, the fold includes a hydrophobic cavity, creating a potential binding pocket for a small, non-tau cofactor. While speculative, this raises the possibility that tau aggregation in CTE may depend on factors delivered or concentrated within selective microenvironments, such as the perivascular regions subject to BBB disruption after RHI [23].

Oligomeric and Cis-Conform Tau as Early Toxic Species

After detaching from microtubules, tau aggregates into a "pre-tangle" oligomeric form, and then into filaments. Biochemical analyses of human CTE tissue demonstrate a reduction in physiological and monomeric p-tau across CTE stages, and a concomitant rise in oligomeric p-tau, indicating that oligomerization precedes filament formation [5]. Emerging evidence suggests that earlier tau species exert disproportionate neurotoxicity. Oligomeric p-tau has previously been shown to propagate its pathological state by sequestering normal tau, thus creating a "snowball" effect [24]. The polymerization of p-tau into NFTs is suggested to have an inhibitory effect on this sequestering ability, proposing the notion that higher-order filament accumulation reflects a protective mechanism in response to harmful p-tau oligomers [25]. Alternative theories propose the role of a cis-p-tau isomer conformation generated by TBI which induces a trans-to-cis conformational change, known as "cistauosis." Cis-p-tau has been reported to arise rapidly after TBI, propagate misfolding, impair axonal function, and may drive neurodegeneration, though these findings largely stem from experimental models that do not fully replicate CTE conditions. Targeted monoclonal antibodies block this switch, mitigating injury-induced deficits in animal models [6]. Together, these findings implicate early tau species and cis-p-tau as candidate drivers of CTE pathogenesis.

Mechanistic Integration and Implications for Biomarker Development

Collectively, these findings support a unifying model in which biomechanical strain not only triggers kinase-phosphatase imbalance but also creates trauma-specific microenvironmental conditions that may contribute to tau misfolding. Mechanical forces, BBB disruption, and exposure to extracellular cofactors may converge to favor distinct folding pathways, potentially generating CTE-specific tau strains. The existence of a CTE-specific tau fold raises the prospect of designing fold-selective PET tracers or conformation-sensitive proteomic assays capable of distinguishing CTE "cistauosis" from AD during life.

Tau conformational and phosphorylation changes may provide a window for early detection, before extensive fibrillar deposition. Oligomeric and cis-p-tau species may be detectable in cerebrospinal fluid (CSF) or plasma-derived exosomes before radiographic abnormalities, providing a possible avenue for identifying individuals at risk during an early disease stage. Integration of conformational tau assays with multimodal imaging strategies

may enable early diagnosis and intervention [26].

EMERGING DIAGNOSTIC APPROACHES FOR ANTEMORTEM IDENTIFICATION OF CTE

Efforts to detect CTE during life focus on neuroimaging and fluid biomarkers, yet no modality offers sufficient sensitivity and specificity for diagnosis. Clinical identification relies on the construct of Traumatic Encephalopathy Syndrome (TES), developed to group CTE-like presentations based on the following: exposure to RHI; clinical features; a lack of symptoms accounted for by other disorders; and the level of functional dependence. Although TES is highly sensitive (97%), its specificity is 21% [27], complicating biomarker validation in cohorts without neuropathological confirmation.

Structural MRI

Structural MRI reliably demonstrates patterns that correlate with neuropathological CTE stage. Autopsy-confirmed cases of CTE show frontotemporal atrophy, particularly in orbital, dorsolateral, and superior frontal regions, along with ventricular enlargement, but these findings are not specific to CTE [28]. White matter hyperintensities (WMH) on FLAIR MRI are also over-represented in CTE and correlate with more advanced neuropathological stage in brain donors, reflecting cumulative neurovascular stress. However, similar structural patterns emerge in ageing and when other vascular risk factors are present [29,30], so MRI abnormalities alone cannot reliably distinguish CTE from other forms of chronic brain degeneration.

Tau-PET Imaging

Tau-PET has been the most intensively investigated imaging technique for antemortem CTE detection, but existing tracers show fundamental limitations. First-generation tau-PET tracers such as flortaucipir (FTP) demonstrate elevated uptake in some symptomatic former athletes; however, post-mortem validation reveals minimal binding of FTP to CTE tau compared to its traditional use in AD [31]. Earlier work with FDDNP yielded similar patterns and lacked specificity and has not translated into reliable diagnostics [32,33]. Second-generation tracers such as MK-6240 show early promise in isolated case reports, but these studies are limited by sample size and lack the supportive neuropathological diagnosis [34]. These findings suggest that tau-PET will likely require radiotracers tailored to the CTE-specific tau conformation [4], rather than re-purposed from other tauopathies like AD.

CSF and Blood Biomarkers

CSF biomarkers provide important insights into tau pathology but currently lack the specificity required for antemortem diagnosis. Although total tau and conventional p-tau epitopes rise after RHI, these changes overlap extensively with AD and acute TBI. More recently, CSF p-tau231 has demonstrated the ability to discriminate between different severities of autopsy-confirmed CTE, AD, and controls in cross-sectional studies [35]. These findings suggest potential for exposure-sensitive CSF markers. Blood-based biomarkers, such as plasma total tau, show modest associations with head-impact burden but lack the ability to distinguish between symptomatic former athletes and controls; however, certain t-tau thresholds appear highly specific to individuals with extensive exposure histories [36]. Despite the appeal of scalability, current fluid biomarkers do not capture the topographical specificity that defines CTE pathology, underscoring the likely need to combine imaging and fluid biomarker strategies in future diagnostic approaches.

Collectively, imaging and fluid biomarkers capture components of the CTE neuropathological cascade, yet neither generates a pathognomonic signature. Failures of existing tau-PET tracers reflect the structural divergence of CTE tau filaments from Alzheimer-type tau, while early toxic conformers (oligomeric or cis-tau) remain poorly investigated using current assays. Antemortem diagnosis will therefore require a multimodal framework, integrating advanced neuroimaging and conformation-sensitive molecular markers, rather than reliance on any single marker.

CONCLUSION AND FUTURE DIRECTIONS

Despite major advances, understanding of CTE remains constrained by reliance on post-mortem diagnosis, leaving a substantial gap between clinical presentation and confirmed pathology. Current knowledge is limited by several factors: a lack of longitudinal, neuropathologically-confirmed cohorts; the low specificity of TES criteria; the overlap of imaging and fluid biomarkers with other neurodegenerative diseases; and the absence of conformation-specific tools.

Future research must therefore address these limitations from multiple angles. Mechanistically, improved experimental models are needed to capture the biomechanical triggers that begin the CTE pathology cascade. Current rodent and cellular systems inadequately reproduce the complex forces experienced within human cortical sulci, limiting their ability to resolve how mechanical trauma triggers tau misfolding and hyperphosphorylation. Therefore, future efforts should prioritize injury models that more closely reflect the magnitude, direction, and repetition of forces observed in head trauma. More phys-

iologically-relevant systems—such as 3D human-derived neuronal cultures or brain organoids—will be essential for outlining the transition from repetitive injury to tau dysregulation, and for informing *in vivo* rodent and large-animal models that better approximate the human brain anatomy and biomechanics.

Importantly, alongside the type of model used, critical exposure variables must be accounted for, including the magnitude of impact, the interval between injuries, cumulative injury burden, age at exposure, and sex [37]. Controlling for these variables will allow for systematic identification of the significance of each one to determine their influence on tau dysregulation and identify which research directions warrant further prioritization. Furthermore, model outcomes should incorporate multiple endpoints as discussed above—fluid biomarkers, advanced neuroimaging, and histopathology—aligned with established human neuropathological criteria. Such an approach will improve translational fidelity and reduce overinterpretation of findings from simplified replications of this complex disease.

Similarly, the consistent perivascular topology of CTE lesions highlights the need to investigate the neurovascular interface including BBB permeability and glymphatic drainage changes, which may subject local neurons to higher concentrations of CTE-specific cofactors. The importance of cofactors is amplified with the discovery of the CTE-specific tau filament fold, and its hydrophobic cavity. The fold also presents an opportunity to shift development from repurposing AD biomarkers, towards CTE conformation-specific diagnostics, including mass-spectrometry fingerprints, antibody development, and PET radiotracers.

Equally important is the need for large, longitudinal cohorts which are crucial for testing whether molecular signatures of RHI—such as phosphorylation patterns or conformational tau species—develop a form of "biomechanical memory," encoding cumulative exposure which cannot be captured through cross-sectional interrogation. It is possible that computational models trained on multimodal data may allow for risk stratification, early detection and monitoring of disease progression.

In summary, CTE sits at the intersection of neuroscience, sports and military medicine, and public policy. Developing reliable diagnostic tools is not only essential for patient care and pharmaceutical development, but also for informing evidence-based guidelines for contact sports and occupational safety. Despite recent progress, major gaps remain. Addressing these will require mechanistically informed, longitudinal, and multidisciplinary research, combining neurology, neuropathology, biomechanics, data science and engineering. Only through such collaborative efforts can we hope to achieve accurate antemortem diagnosis, meaningful disease-modifying treatments, and adequate prevention strategies for this complex disease of mechanical biochemistry.

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