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Chronic Traumatic Encephalopathy and Neuropathological Comorbidities

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Abstract

With age, the presence of multiple neuropathologies in a single individual becomes increasingly common. Given that traumatic brain injury and the repetitive head impacts (RHIs) that occur in contact sports have been associated with the development of many neurodegenerative diseases, including chronic traumatic encephalopathy (CTE), Alzheimer's disease, Lewy body disease, and amyotrophic lateral sclerosis, it is becoming critical to understand the relationship and interactions between these pathologies. In fact, comorbid pathology is common in CTE and likely influenced by both age and the severity and type of exposure to RHI as well as underlying genetic predisposition. Here, we review the major comorbid pathologies seen with CTE and in former contact sports athletes and discuss what is known about the associations between RHI, age, and the development of neuropathologies. In addition, we examine the distinction between CTE and age-related pathology including primary age-related tauopathy and age-related tau astrogliopathy.

Keywords

chronic traumatic encephalopathy; traumatic brain injury; neurodegenerative disease; Alzheimer's disease; comorbidity

The cooccurrence of multiple neuropathologies is the most common driver of cognitive decline and dementia with increasing age.[1,2] Occam's razor, the "law of parsimony," in

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essence states that the simplest solutions are more likely correct then complex ones. In diagnostic neuropathology, this approach compels us to seek a single diagnosis, rather than conclude multiple complex processes are occurring simultaneously. While this, in principle, seems reasonable, in practice, it is not. In the aging brain, comorbid or mixed pathologies with similar features are increasingly recognized as the rule, rather than the exception.[1] In fact, in almost 80% of autopsies included in a recent study, 2 or more of the 9 most common neuropathologies were identified, and there were > 230 different neuropathological combinations.[1] Recent advances in our understanding of the cellular, genetic, and molecular bases of neurodegenerative diseases have allowed us to greatly improve our ability to recognize distinct pathological processes and thus diagnose comorbidities. Overall, dementia is often caused by mixed pathologies, and age is one of the most significant driving factors.

In addition to age, head impacts, either in the form of traumatic brain injury (TBI) or repetitive head impacts (RHIs) such as in contact sports, may be a risk factor for the development of multiple neuropathologies. Although nascent, recent studies suggest that TBI and RHI can have similar, yet distinct heterogeneous pathologies.[3-8] Remote moderate to severe TBI has long been viewed as a risk factor for Alzheimer's disease (AD), yet recent large cohort studies indicate that TBI of all severities (mild, moderate, severe) is a risk factor for dementia, the neuropathology of which is largely unknown.[3-10] Following acute TBI, amyloid precursor protein (APP) and β-amyloid (Aβ) increase in brain tissue and cerebrospinal fluid (CSF), and there can be rapid formation of diffuse cortical Aβ plaques.[11] Both APP and Aβ increase within damaged axons, and the release of Aβ into the surrounding tissue may be the basis for plaque formation.[12] RHIs are associated with chronic traumatic encephalopathy (CTE), a neurodegenerative disease. In addition, recent studies suggest that RHI may lead to, or alter, multiple neuropathologies including cerebral amyloid angiopathy (CAA), Lewy body disease (LBD), amyotrophic lateral sclerosis (ALS), and others.

Approaching CTE in the context of comorbidities is challenging given its complex clinical presentation, with symptoms that are variable and overlap with other brain diseases. Variable degrees of coexistent cognitive, motor, movement, and psychiatric dimensions are all common and blur diagnostic certainty. In contrast to the clinical criteria for CTE, which are still in development, the neuropathological criteria that are applied on the tissue level are highly specific and sensitive especially at later disease stages.[13] Advanced neuroimaging and biomarkers in blood and CSF are in development and hold promise for improving diagnosis ante-mortem[14,15]; until that time, a postmortem examination is paramount, as it allows for evaluation of the molecular and cellular changes occurring in degenerating neurons and glia and localization to specific brain regions. Sorting out these changes is the foundation to making these challenging diagnoses.

The main molecular feature used to evaluate neurodegenerative diseases is intracellular aggregates of abnormal protein inclusions such as tau, α-synuclein, and TDP-43. Extracellular aggregates can also occur, the most common being the Aβ plaque in AD. Identification of these aggregates in postmortem brain is critical, but not sufficient, for making the diagnosis, as they must also be localized to specific brain regions and cells types. In this way, the overlap and blurred distinctions seen in the clinical context are mirrored on

the tissue level where advancements in understanding disease-specific cellular vulnerability have greatly increased our ability to resolve differences. Here, we summarize the multiple neuropathologies seen in association with RHI and CTE and describe the similarities and differences in their pathological presentations. In addition, we discuss the current models linking RHI to multiple neuropathologies and discuss the role of aging and age-related pathologies in CTE.

Beta-Amyloid in CTE

Unlike AD, which requires the presence of both tau pathology and Aβ deposition for diagnosis, CTE is defined by the unique spatial distribution of tau pathology only. However, though Aβ is not a defining feature of CTE, it is the most frequent comorbid pathology and may play a role in disease progression. Deposition of Aβ has been reported in approximately 30% of cases of acute trauma and APP abnormalities occur following axonal injury.[11,12,16-19] Early reports using Aβ immunohistochemistry demonstrated that the majority of boxers with CTE had widespread diffuse Aβ deposits.[20,21] However, as more cases were described, it was found that many cases of CTE exhibit no Aβ pathology; this was particularly true in young individuals[22-26] and early stages of CTE.[27] Postmortem analysis of 114 contact sport athletes and military veterans with CTE who had a mean age of death of 60 years demonstrated that Aβ deposition was present in just over half (52%) and varied by both age and stage.[28] Various types of Aβ plaque can be distinguished by their morphology. Two major types typically used for AD classification include neuritic plaques with argyrophilic dystrophic neurites, with or without dense amyloid cores and diffuse plaques with noncompact amyloid and no apparent dystrophic neurites.[29] The type of Aβ plaque was significantly different in CTE: in contrast to AD where neuritic plaques are necessary for the diagnosis, participants with CTE were far more likely to have diffuse Aβ plaques, while only about one-third of participants had neuritic plaques (►Table 1). Furthermore, the deposition of Aβ occurred at an earlier age and at an accelerated rate in CTE compared with a normal aging population.[30] Similar to these findings, a recent report of 11 cases of soccer and rugby players found that AD pathology was a common comorbidity with CTE in older athletes.[31]

The biochemical type and pattern of Aβ deposition was subtly different in CTE. Quantitative enzyme-linked immuno-sorbent assays showed that levels of Aβ1–40, but not Aβ1–42 were greater in the sulci than the gyri in CTE-AD subjects. This correlates with the location of peak mechanical force following RHI and with ptau pathology in CTE and is distinct from the even distribution of Aβ in gyri and sulci in AD.[28] Biochemical analysis of an early tau phosphorylation site present in AD (ptau231) showed that the presence of neuritic plaques was associated with increased ptau231 levels in CTE, but that levels were still greatest in AD or in subjects with both CTE and AD. Thus, ptau231 appears to be a phosphorylation site that is largely driven by Aβ pathology in CTE.

The presence of Aβ plaques in CTE was associated with other more severe pathologies. Linear regression analysis adjusting for age showed that CTE subjects with Aβ had worse tau pathology and were more likely to have clinical symptoms, dementia, and

parkinsonism.[28] These findings suggest that RHI may accelerate Aβ deposition and that Aβ, in turn, accelerates ptau pathology and worsens clinical outcomes in CTE.

Cerebral Amyloid Angiopathy in CTE and Contact Sports

CAA consists of Aβ deposition within the basement membrane of meningeal and superficial cortical arteries and arterioles that leads to the replacement of smooth muscle cells.[32] CAA is a frequent comorbidity with AD, but may also occur independently. Moderate to severe CAA is also associated with cerebral hemorrhages, cortical microinfarcts, and dementia independent of AD pathology.[33,34] CAA is more common in the posterior cerebral cortex (parietal and occipital lobes) than the frontal lobes in AD and the general aging population.[35-39] Aβ deposition in the blood vessel wall can cause progressive weakening and dysfunction of the vessel wall and lead to rupture and subsequent intracerebral hemorrhage.[38,40,41] Independent of other pathologies, CAA is associated with age as well as impaired cognitive function and dementia likely due to a combination of hemorrhage, ischemia, and synaptic damage.[42,43]

Previous studies have documented the presence of CAA in postmortem subjects with a moderate to severe TBI history.[44] However, a retrospective study of three large autopsy cohorts did not find an association between TBI and the presence of moderate to severe CAA,[5] although alterations in the distribution of CAA were not examined. RHIs may be distinct from TBI and may lead to small vessel pathology such as CAA. For instance, amateur football players were found to have blood–brain barrier dysfunction by dynamic contrast-enhanced magnetic resonance imaging analysis after a single season of play compared with noncontact sport athletes.[45] In addition, both TBI and RHI may lead to an altered distribution of CAA.

A recent postmortem study of contact sport participants found that CAA was most severe in the frontal leptomeningeal vessels in 251 participants with CTE.[46] This distribution was significantly different from AD where CAA was more likely to involve the intracortical vessels and the parietal and occipital lobes. The frontal predilection of CAA also aligns with where tau pathology first occurs and where injury is likely greatest. Indeed, head collisions predominantly involve the anterior aspect of the skull in American football, and mathematical models of a helmet-to-helmet collision in football predicted that the greatest strain occurs in the frontal convexities and at the depths of sulci.[47-49] Examination of three different brain bank groups demonstrated that in subjects with CAA, RHI was associated with increased CAA severity in the frontal leptomeningeal vessels, adjusting for AD, *apolipoprotein E* (*APOE*) *ε4*, and age. Overall, RHI and CTE were associated with increased leptomeningeal CAA, and CAA was independently associated with worse pathological and clinical outcomes, suggesting that altered CAA is another mechanism by which RHI may lead to cognitive decline.[46]

Lewy Body Disease in CTE and Contact Sports

While the hypothesis that TBI might play a role in the pathogenesis of Parkinson’s disease (PD) dates back to the original description,[50] several recent studies have begun to elucidate

this link.[6,51-54] Analysis of a large veteran cohort showed that a history of TBI, including mild TBI, was associated with increased risk of PD.[6] Furthermore, TBI with loss of consciousness greater than 1 hour occurring early in life was associated with increased risk of cortical Lewy bodies in pooled brain banks from three community aging cohorts. This study also found a clinical association between TBI with loss of consciousness and incident PD in one cohort and progression of parkinsonian signs in two others.[5]

Parkinsonism appears to be relatively common in patients thought to have CTE.[55,56] On the other hand, one study did not find significant deficits in motor function in Canadian football players compared with a small group of controls.[57] However, few studies have examined associations between RHI, PD symptoms, and pathology. A recent study by our group examined the clinical and pathological relationships between RHI exposure, CTE, and LBD within a group of deceased athletes with RHI exposure, a community-based aging cohort, and a cohort enriched for AD. The number of years of exposure to RHI through contact sports was associated with the development of neocortical LBD in the community-based aging cohort, the contact sport athlete cohort, and in a pooled analysis controlling for age, sex, and *APOE ε4* allele status. The distribution of LBD in CTE was distinct from that in AD such that in CTE, LBD was most often limbic, neocortical, or brainstem, while in AD, the distribution of Lewy bodies was more likely to be amygdala-predominant. Clinically, across three autopsy groups, dementia was significantly associated with neocortical LBD, CTE stage, AD, and age at death. Parkinsonism was significantly associated with LBD and age at death, but not CTE stage.[58] Therefore, the increased frequency of LBD following RHI exposure may partially explain the extrapyramidal motor symptoms sometimes observed in CTE. However, it remains to be determined whether tau or other pathology in the substantia nigra in CTE might also partially contribute to Parkinsonism in those cases without LBD.

Given that even a single TBI might be associated with LBD and Parkinsonism, the threshold for the number of years of contact sport participation might be low. Analysis of the community-based aging cohort and the contact sport athlete group showed that a threshold of 8 years of contact sport play was the greatest predictor for neocortical LBD, suggesting this may be an important threshold.[58] However, this analysis is limited by retrospective and autopsy-based selection biases as well as the fact that the athlete cohort was selected for a high level of contact sport play. Future prospective studies will be needed to determine how the risk of LBD is influenced by the type and amount of contact sport play as well as the development of CTE.

Amyotrophic Lateral Sclerosis and CTE

Motor neuron disease or ALS is a progressive, fatal neurodegenerative disorder involving degeneration of both motor cortex and spinal motor neurons. ALS is more common in males, military veterans, and former American football players.[59-62] It is a relatively common comorbid pathology with CTE, occurring in approximately 6% of American football players with CTE in an autopsy group (►Table 1).[63] The role of TBI in the development of ALS is unclear. One study found ALS was more likely in those that reported multiple head injuries within the past 10 years prior to diagnosis,[64] although other studies have not found a modifying effect of head injury on ALS.[65] In a veteran cohort, those with

head injuries, especially within 15 years prior to diagnosis, were found to be significantly more likely to develop ALS.[66] We found CTE in approximately 6% of a veteran ALS cohort (n = 155).[67] Participants with ALS + CTE were more likely to have a TBI history, have served during the first Persian Gulf War, and have more severe ptau pathology in the frontal cortex and spinal cord. One-half of ALS participants with a history of TBI had comorbid CTE. In those with ALS + CTE, the most common RHI exposures were from contact sport exposure (e.g., tackle football) (44%), military service (frequent aircraft carrier landings) (11%), or both (bull riding and grenade blast exposure) (11%). Most of these exposures have been previously related to the development of CTE, including bull riding.[68] CTE is sometimes associated with TDP-43 inclusions even in the absence of ALS.[27] It may be that trauma potentiates TDP-43 pathology and that this is one mechanism by which RHI and CTE are associated with ALS. In fact, in the veteran cohort there was a significantly increased TDP-43 stage[69] in participants with ALS + CTE.[67] Clinically, participants with ALS + CTE were more likely to have bulbar onset ALS, behavioral changes, and/or mood changes, which may represent a combination or synergy of the two diseases. Overall, compared with ALS alone, comorbid ALS + CTE is associated with RHI and TBI and has an altered clinical and pathological presentation.

Vascular Disease and White Matter Damage in CTE

Cerebrovascular disease is often comorbid with neurodegenerative disease and contributes to cognitive decline.[70-75] Arteriolosclerosis, infarcts, microinfarcts, and white matter (WM) degeneration are common with aging and cardiovascular disease. Cardiovascular disease is frequent in former American football players,[76,77] and WM degeneration and cerebrovascular disease are common comorbidities in CTE.[27,78-80] Therefore, RHI may be associated with cerebrovascular disease and contribute to cognitive decline in CTE.

A recent study found that moderate to severe WM rarefaction (46.6%) and arteriolosclerosis (47.2%) are common in 180 deceased football players with autopsy-confirmed CTE (Table 1).[81] Simultaneous equations regression model controlling for age and race showed more years of play corresponded to more severe WM rarefaction and greater tau pathology accumulation. Arteriolosclerosis and years of play were not related, but arteriolosclerosis was independently associated with dementia. The odds of dementia were further increased with more severe WM rarefaction and arteriolosclerosis independent of tau pathology. Among older football players with CTE, more years of football participation corresponded to more severe WM rarefaction and greater burden of tau pathology.[81] Overall, dementia in CTE may result from multiple neuropathologies linked to RHI, including WM rarefaction and tau pathology, as well as pathologies not related to TBI or RHI, such as arteriolosclerosis and other age-related disease (►Fig. 1).

Primary Tauopathies

CTE is just one of several pathological entities and contexts in the brain associated with the presence of abnormal tau aggregates.[82] Among these entities, the frequency varies considerably and would thus be expected to exist comorbidly with CTE to varying degrees. The term tauopathy was originally coined to describe a subset of frontotemporal lobar

degeneration (FTLD) patients with germline autosomal dominant *MAPT* gene mutations, but these patients are very rare.[83] Subsequently, the term tauopathy has come to encompass all brain diseases where tangles occur.

Neurofibrillary tangles and gliofibrillary tangles are nearly ubiquitous in usual aging by about the age of 50 years old.[84] Remarkably, cross-sectional studies have revealed that the very first evidence of tau abnormalities can occur in the teen years in the brain stem.[85] These changes progress though the lifespan, involving midbrain and forebrain structures to varying degrees and leading to a wide spectrum of clinical and neuropathological outcomes. This heterogeneity is thought to depend on several intrinsic and extrinsic factors, including environment and genetics. Thus, depending on age, some degree of tau pathology is expected and differentiating CTE from common age-related changes is critical. Various factors contribute to the heterogeneity in tau pathology, including selective vulnerability of brain regions and cell types, and understanding these mechanisms is key to rendering diagnoses. In the absence of a *MAPT* mutation, the approach to differentiating tauopathies relies heavily on three factors: (1) regional (i.e., neuroanatomical) vulnerability, (2) cellular vulnerability (mainly neurons and glia), and (3) biochemical differences in tau isoform expression. Other factors, such as tau filament ultrastructure and tau hyperphosphorylation, are not currently useful as differentiating factors.

Primary Age-Related Tauopathy

Primary age-related tauopathy (PART) is a term used to describe AD type neurofibrillary tangle pathology appearing in a limited neuroanatomical distribution, predominantly the medial temporal lobe and other structures, in the absence amyloid plaques.[86] PART is commonly observed in cognitively normal individuals after the age of 50, but it is generally not very severe. The frequency and severity of tau pathology increases with age. Interestingly, but not surprisingly, it was recently found in a supercentenarian.[87] With increased burden of neurofibrillary pathology and neurodegeneration in PART, the likelihood of cognitive impairment is higher.[88] Symptomatic PART is generally manifested as amnestic mild cognitive impairment (MCI) or dementia,[89] but other symptoms may occur. PART patients are often clinically diagnosed with AD, given the prominent amnestic component, but they may have some clinical features that diverge. For example, recent studies suggest that cognitive impairment declines more slowly in PART[90,91] and that these patients may have relative preservation of certain cognitive domains, such as semantic memory.[92] This remains unclear, however, as some studies have suggested that higher stages of neurofibrillary tangle burden in PART might be associated with more rapid decline on tasks involving episodic and semantic memory along with tests of processing speed and attention.[93]

Postmortem examination in PART has revealed that the tangles are regionally, morphologically, biochemically, and ultrastructurally very similar to those seen in AD.[86] They are present in neurons in the entorhinal cortex and hippocampus proper and variably present in other temporal lobe regions. There may be preferential involvement of CA2. Outside the medial temporal lobe, neurofibrillary tangles in PART can be seen in the brainstem, including the locus coeruleus and substantia nigra, as well as inferior frontal

cortex and nucleus accumbens. These tangles are present in neurons, structurally similar to the classic flame-shaped tangles in AD that accumulate and take on the shape of the pyramidal neurons in which they commonly develop. Biochemical studies have consistently demonstrated an isoform profile that is similar to AD, with both tau isoforms containing 3 and 4 microtubule binding domain repeats. Ultrastructurally, they contain Alzheimer-type paired helical filaments. Just as in all tauopathies, the tau contains numerous secondary modifications, including hyperphosphorylation, but there are no specific markers for PART at this time.

The genetics of PART is not fully explored, although emerging evidence suggests that individuals with PART have divergent genetic risk from AD.[94] There is no increase in the frequency of the *APOE ε4* allele which is strongly associated with amyloid deposition and AD. Instead, PART is associated with an increased allele frequency of the protective *APOE ε2* allele.[95] Theoretically, individuals with PART may harbor other genetic variations that protect from amyloid deposition alongside risk for tau accumulation, such as the *MAPT* 17q21.31 H1 haplotype.[95,96]

Differentiating PART from CTE can be accomplished as the regional tau accumulation in the neocortical sulcal and perivascular lesions that define CTE are not a component of PART. However, medial temporal lobe pathology is common in the late stages of CTE, and the regional pattern of the two diseases overlaps and may be difficult to discriminate if the hippocampal formation is examined in isolation. Thus far, the differential involvement of the subfields of the hippocampus between PART and CTE is unknown, though CTE may preferentially affect CA4.[27] For this reason, we recommend extensive sampling of neocortical regions when suspicion merits.

Aging-Related Tau Astrogliopathy

Aging-related tau astrogliopathy (ARTAG) is a term coined to describe a morphological spectrum of pathological accumulation of abnormal tau protein in astrocytes in aging.[97] ARTAG is mainly observed in subjects over the age of 60 years where it has been observed in up to 38% of brains in one series.[98] The ARTAG spectrum includes thorn-shaped astrocytes at the glial limitans and in the WM as well as granular fuzzy astrocytes in the gray matter. It is not clear whether these different glial fibrillary forms represent different or single pathological processes. ARTAG is distinct from the pathology seen in other tauopathies with prominent glial changes, such as progressive supranuclear palsy (PSP) and cortical basal degeneration, which are characterized by tufted astrocytes[99] and astrocytic plaques,[100] respectively.

ARTAG is most readily observable using immunohistochemistry, especially 4R isoform-specific antisera. Connection 43 and aquaporin 4 expression are also strongly correlated with ARTAG.[101] These abnormal astrocytes can be seen in various compartments, including subpial, subependymal, perivascular, WM, and gray matter. ARTAG can be seen diffusely throughout the central nervous system, but the peri-amygdala WM is preferentially vulnerable.[102] While ARTAG may spread through the brain in a similar pattern as has been

proposed for neurofibrillary tau, the propagation is more complex with only some forms of ARTAG showing clear hierarchical progression.[101]

Understanding of the clinical implications of ARTAG is minimal. Early studies revealed argyrophilic thorny astrocyte clusters in primary progressive aphasia associated with AD pathology.[103] Later, thorn-shaped astrocytes were linked to cognitive symptoms, but this was variable.[104,105] Intriguingly, one recent study found evidence that cortical ARTAG is associated with dementia, but limbic and brainstem ARTAG was not.[106] Further studies are required to clarify the clinical impact of ARTAG.

Given its prevalence, ARTAG would be expected to be observed comorbidly with numerous other diseases, and reports have documented it in numerous and disparate contexts, including human immunodeficiency virus,[107] FTLD,[108] and Huntington's disease.[109] The relationship between CTE and ARTAG is worth noting. Astrogliosis in CTE patients can be robust.[110] In addition, there are significant morphological overlaps. This includes localization of tau pathology to subpial, perivascular, and gray matter astrocytes, as with ARTAG. The key feature of the CTE-associated lesions is neuronal tau, however, so the presence of pure astrocyte tau, even in a perivascular distribution, should not be considered diagnostic of CTE. Studies of ARTAG progression have invited speculation that ARTAG may be a precursor lesion for CTE, however further investigation is required.[101]

Argyrophilic Grain Disease

Argyrophilic grain disease (AGD) was first reported as a neurodegenerative disease with late-onset displaying small spindle- or comma-shaped, silver stain positive lesions, termed argyrophilic grains.[111] Follow-up studies revealed that these lesions were composed of hyperphosphorylated-tau. These are observed in combination with oligodendroglial coiled bodies and numerous pretangles. While AGD is commonly seen in the context of MCI and aging, it is very commonly comorbid with other neurodegenerative diseases, and identifying a distinctive clinical correlate has been challenging.[112,113] One understudied aspect of CTE is the dot-like lesion.[114] These lesions are common in CTE and track the other thread and tau pathology in CTE. They have been proposed to be related to AGD, but this requires further investigation.[115]

Frontotemporal Lobar Degeneration

FTLD is the neuropathological category that is the counterpart to the clinical term frontotemporal dementia, a heterogeneous group of syndromes, including behavioral variant FTD, progressive nonfluent aphasia, semantic dementia, and corticobasal syndrome. These diseases have a range of neuropathological changes, with the most common being accumulation of TDP-43 termed FTLD-TDP43. This is followed by tau pathology, termed FTLD-tau, which can be familial in kindreds with autosomal dominant *MAPT* mutations, or sporadic. Other forms of FTLD have been reported, but these are very rare.

CTE has been reported to occur comorbidly with FTLD-tau. For example, sporadic PSP was observed in a 75-year-old ex-professional boxer.[116] This finding was intriguing because, unlike autosomal dominant genetic forms of FTLD where causality is established,

the pathogenesis of sporadic FTLD remains less clear and it raises the possibility that mechanical injury may play a role. As discussed previously, TBI and RHI are likely risk factors for other neurodegenerative diseases beyond CTE, including AD, PD, and ALS, but a link with PSP has not yet been established and further studies are required.[117]

Other Neurodegenerative and Brain Diseases

In addition to the entities described above, CTE has been reported comorbidly with several neurodegenerative and psychiatric illnesses. For example, CTE has been seen alongside prion disease, with three cases of histopathologically validated CTE with coexisting sporadic Creutzfeldt–Jakob disease.[118] Features consistent with stage I CTE were also demonstrated in comorbid in a single case of Huntington's disease (i.e., rare perivascular aggregates of tau-positive neurons, astrocytes, and processes were identified at sulcal depths).[109] This patient did not have a history of contact sport play, but did have documented falls. Similarly, CTE was found in approximately 6% of patients with multiple systems atrophy,[119] another disorder associated with frequent falls. Finally, CTE has also been seen in the context of schizophrenia,[120] where TBI might be a risk factor.[121]

Conclusion

Altogether, comorbid pathology is common in CTE and likely influenced by both age and the severity and type of exposure to RHI as well as underlying genetic predisposition. Recent studies suggest that RHI may lead to or alter the presentation of multiple neuropathologies including Aβ deposition, CAA, LBD, and WM degeneration. Age and *APOE* genotype further contribute to the development and progression of pathology. The prevalence of rare diseases such as ALS comorbid with CTE suggests a possible association, but better powered and prospective studies are necessary. Overall, recognition of risk factors and detection of comorbid pathology will be important for prevention, diagnosis, and treatment.

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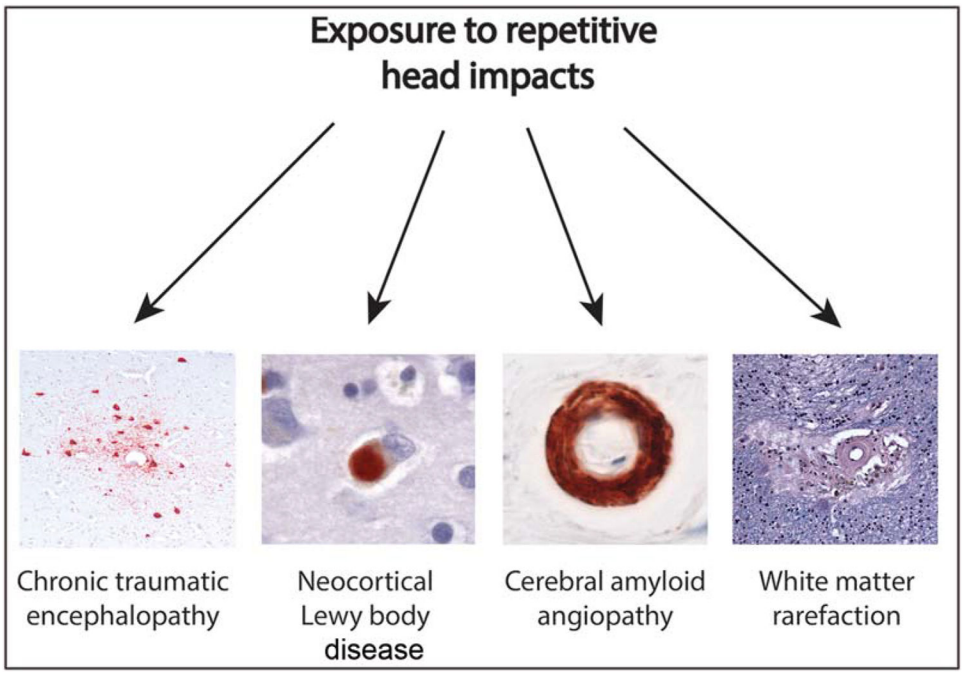

Fig. 1.

Recent studies have linked total years of exposure to repetitive head impacts from contact sports to a variety of neuropathologies including chronic traumatic encephalopathy (CTE),[27,58,122] neocortical Lewy body disease,[58] severity of cerebral amyloid angiopathy,[46] and white matter rarefaction.[81] Examples of each pathology in subjects with CTE are shown.

Table 1

Neuropathological comorbidities and reported frequencies in CTE

	Frequency[a]	Mean age (y)	Reference
Beta-amyloid plaques			
- Diffuse	59/55 (52%)	60	Stein et al 2015[28]
- Neuritic	41/73 (36%)	60	Stein et al 2015[28]
Cerebral amyloid angiopathy	72/179 (29%)	60	Standring et al 2019[46]
Alzheimer disease[b]	23/154 (13%)	67	Mez et al 2017[63]
Lewy body disease			
- Any	53/86 (38%)	57	Adams et al 2018[58]
- Neocortical	13/238 (5.2%)	60	Standring et al 2019[46]
Amyotrophic lateral sclerosis	11/166 (6%)	67	Mez et al 2017[63]
Arteriolosclerosis (moderate-severe)	85/95 (47%)	68	Alosco et al 2019[81]
Primary age-related tauopathy (PART)	Unknown	–	–
Age-related tau astrogliopathy (ARTAG)	Unknown	–	–

Abbreviation: CTE, chronic traumatic encephalopathy.

[a]Data are presented as with/without (% with).

[b]Based on NIA-Reagan criteria.