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PATHOBIOLOGY IN FOCUS

Chronic traumatic encephalopathy: A paradigm in search of evidence?

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Chronic traumatic encephalopathy (CTE) has been in the medical literature since the 1920s. It is characterized clinically by diverse neuropsychiatric symptoms, and pathologically by variable degrees of phosphorylated tau accumulation in the brain. The evolving paradigm for the pathogenesis of CTE suggests that concussion or subconcussion from athletic participation initiates a cascade of pathologic events, encompassing neuroinflammation and protein templating with trans-synaptic neurotoxicity. The end result is neurologic and neurobehavioral deterioration, often with self-harm. Although these concepts warrant further investigation, the available evidence permits no conclusions as regards the pathogenesis of the reported findings. Investigations into the role of premorbid or co-morbid neurodegenerative diseases has been limited to date, and in-depth genetic analyses have not been performed. The role of concussion or subconcussion if any, whether and how the condition progresses over time, the extent of phosphorylated tau in clinically normal athletes, the role of phosphorylated tau as a toxic species *versus* an inert disease response, and whether protein templating has any *in vivo* relevance remain to be elucidated.

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Chronic traumatic encephalopathy (CTE) is the accepted term for a pattern of phosphorylated tau (ptau) deposition in the brain that appears to differ from age-related accumulations and neurodegeneration.[1] According to data from the largest CTE series to date, ptau tends to occur as localized accumulations in depths of sulci and perivascular areas of the cerebral cortex, particularly frontal, temporal, and insular cortices. CTE further tends to involve cortical laminae 2 and 3, relative to AD and aging where ptau predominates in laminae 3 and 5. Extensive medial temporal lobe involvement, and involvement of the brainstem tegmentum, may also be present. Axonal varicosities in the deep cortex and subcortical white matter are variously described. The gross brain varies from markedly atrophic to normal, while cavum septum pellucidum and septal fenestrations are common findings. Staging schemes have been proposed in recent years, in an attempt to understand the kinetics of the process as a function of time and clinical manifestations.[1,2]

CTE is associated with contact sports and is often considered a variation of so-called dementia pugilistica (DP),[3–5] a long known condition in boxers associated with neurologic decline and neurofibrillary degeneration at autopsy.[6] Although generally accepted as a distinct entity, DP has been controversial since its original description, with absence of prospective data,[7] surprisingly few studies with autopsy correlation[5,8–13] and lack of accounting for co-morbidities such as substance abuse, infection, and vascular or neurodegenerative disease.[13] In the only large-scale study of boxers to date, Roberts[14] investigated 250 boxers from a cohort of 16 781 boxers in the UK and found 37 with neurological lesions, suggesting an overall prevalence of 17%. Some differences between CTE and DP have been suggested in a recent review, including clinical presentation, age at onset, association with *APOE* genotype,[8] and tendencies for neurological *versus* psychiatric signs, although none of these features provide a clear separation. Both CTE and DP tend to be viewed as variants of the same condition—progressive tauopathy caused by brain trauma.[1]

The exposure to sport along with the increase in ptau in parenchymal brain tissue has suggested head trauma as the underlying biomechanical etiology of CTE. Indeed, the recent, heightened awareness of concussion and subconcussion as potentially important[15] comes from studies in National Football League (NFL) players. Rare cases of CTE have been suggested in hockey player,[1] professional wrestlers, rugby players,[16] soccer players,[12] a professional baseball player, and a circus performer.[17] The issue of CTE possibly resulting from combat-related traumatic brain injury (TBI) has also been

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raised; however, its existence as an entity in combat veterans and potential mechanisms of injury, have yet to be confirmed.[18]

The clinical manifestations associated with CTE in recently characterized cases are largely psychiatric, and include aggression, explosive anger, impaired impulse control, domestic disarray, depression, and heightened suicidality,[1] although cognitive impairment, short-term memory loss, and headache are also reported. The nature and rate of progression, however, remains an open question.[8]

ACCEPTED CTE PARADIGM

The gaps in the knowledge of CTE are substantial, and the collective human data, which are retrospective, and largely based on self-selected cases, permit no conclusions as yet, regarding etiology or its existence as a distinct clinicopathologic entity. Nevertheless, the CTE paradigm from TBI to neurodegeneration is generally accepted, with efforts directed more at identifying the molecular events responsible for the neurodegeneration, than confirming its existence.[19]

TBI and Concussion

The paradigm begins with the heterogeneous, imperfectly modeled, and complex condition termed TBI. In-depth reviews of TBI are available.[19] Briefly, TBI most often signifies loss of consciousness and is arbitrarily termed 'mild' if the loss of consciousness is up to 30 min. Alteration in consciousness for up to 24 h, or posttraumatic amnesia for up to 24 h, is also accepted under the mild TBI umbrella. The diagnosis of mild TBI may be entirely subjective, as it is often based on self-reported neurological symptoms.[20] Thus, although mild TBI is portrayed in the literature as a definable condition, it encompasses a wide spectrum of potential biomechanical precursors, including nature and type of impact, directionality of acceleration-deceleration phenomena, and individual susceptibilities, as well as the interpretation itself which is often subjective, and often provided by physicians and other personnel with wide variability in experience in the diagnosis of TBI. There is a tendency for 'TBI' to be used for military-related TBI, given the spectrum from mild to severe, and for 'concussion' to be used in sport, in place of mild TBI.

Concussion in contact sports, either objective or subjective, is a common and inevitable accompaniment of a range of sports.[21] Indeed, in high school sports in the US, the concussion rate in girls' soccer is comparable with that of boys' football.[22] The diagnosis of concussion often presents a challenge among sports medicine physicians and athletic trainers, just as mild TBI may be a challenge to the medical personnel in armed conflicts. Assessment by physicians with specific expertise in concussion is ideal, although this is often not available. Codified evaluation and management strategies are in progress.[21]

Risk factors for concussion have been only obliquely addressed in the context of CTE. Among these are history of previous concussion, number and severity of concussion, age, gender, pre-existing mood disorders, pre-injury learning disabilities such as attention deficit hyperactivity disorder, and history of migraines.[23] Prolonged concussive symptoms or post-concussive syndrome that may persist in a minority of patients for weeks or even years, adds an additional level of complexity and pathophysiological uncertainty to the concept of TBI.

It is of some passing interest that one high-profile NFL football player who was determined to have some degree of ptau deposition post-mortem had no documented concussions during his football career at any level prior to committing suicide at the age of 43. This case tends to de-emphasize the importance of concussion *per se*, and elevates subconcussive impact as a potential etiological factor. Regardless of the specific concussion history in athletes, however, uncertainties regarding concussion and potential biomechanical antecedents to CTE are evident, notwithstanding the certainty with which concussions are viewed as etiological in the media as well as the medical literature.[24]

Diffuse Traumatic Axonal Injury (DAI) and Biomechanics of Concussion

Understanding concussion in the acute state from the standpoint of neuropathology is problematic in that the neurological deficit is transient and without mass effect, ie, the patients survive and do not require neurosurgery, precluding pathological evaluation. The pathology and mechanics of concussion are therefore difficult to study *in vivo*. One study that looked at brain changes in individuals who expired from other causes shortly after concussion found evidence of axonal injury, including involvement of the fornix, suggesting similarities with DAI and involvement of memory circuitry.[25] Such data, however, are sparse. On the other hand, studies on brain *contusion*, a commonly observed lesion and one that is definable based on anatomic pathology have led to the basic concept that sheer stresses, or the movement of one tissue plane over another, are necessary for parenchymal brain injury.[26] As emphasized by Holbourne[27] more than 70 years ago, the brain's relative incompressibility and lack of rigidity necessitate shear stresses over compressive stresses and rotational acceleration over linear acceleration. One could reasonably speculate, therefore, that shear stresses, rotational acceleration, and axonal disruption or injury are the basic physical precursors to concussion.

Purely biomechanical models in primates from the 1970s and 1980s may have also shed some initial light on concussion indirectly through the characterization of DAI. In these early primate models, it was determined among other factors that acceleration in the coronal plane[28] and low strain rate (prolonged interval over which acceleration occurs) favored prolonged traumatic unconsciousness, poor outcome, and DAI at necropsy.[29,30] The biomechanics of DAI may therefore follow that of concussion, albeit with more severe clinical and pathological outcome. This is also consistent with

the clinical definition of DAI requiring 6 h of traumatic unconsciousness,[31] which differs from concussion largely on the basis of duration of the unconsciousness.

At the experimental level, the last 30 years has seen a proliferation of *in vitro*[32] and mammalian[33] trauma models, which have led to an exponential expansion of data implicating essentially all major molecular disease mechanisms. The collective data indicate that TBI and otherwise biomechanical forces acting on parenchymal brain tissue result in pleiotropic deleterious, biochemical sequelae, encompassing signal transduction, elaboration of toxic proteins, unfolded protein responses and ER stress, oxidative stress, dysfunction in mitochondria and energy metabolism, channelopathy effects with elaboration of pore forming molecular complexes, inflammatory cytokine production, perturbations in calcium and electrolyte metabolism, and induction of apoptosis, among other mechanisms.[34–41] With respect to CTE, however, these processes lead to, or otherwise facilitate, tau phosphorylation via altered kinase-phosphatase metabolism,[42] resulting in microtubule instability and precipitation of ptau as toxic, insoluble intraneuronal and intra-astrocytic inclusions.[43]

CTE as a Prion Disease

Somewhat concerning are the studies suggesting protein templating with trans-synaptic transmission[44] and the incorporation of the tauopathies in the lexicon of prion (or prion-like) diseases. Transgenic mice overexpressing P301L tau in the entorhinal cortex, for example, demonstrate *de novo* wild-type ptau in brain regions synaptically connected with the performant pathway.[45] Further, prion-like self-propagating 'strains' of tau appear along neuroanatomical pathways following intracerebral inoculation of experimental mice transgenic for human tau.[46] Similar strain propagation of amyloid-β has been demonstrated with synthetic peptides, and suggested as basis for phenotypic variability to human AD.[47,48] These data taken together make a sophisticated case for spreading toxicity in a prion-like manner.

Phosphorylated tau species according to this hypothetical paradigm thus 'spreads' along neuroanatomical pathways, leading to disease progression and neurodegenerative disease. The frequent involvement of frontal and temporal lobes by the neurotoxic process is said to cause neurobehavioral symptoms such as disordered impulse control, explosive aggressiveness, extreme impulsivity, impaired judgment and social function, and heightened suicidality.[1] Medial temporal lobe involvement may disrupt episodic memory, whereas the involvement of the brainstem implicates a number of functions.[49]

In short, TBI induces neuroinflammation, leading to tau phosphorylation, leading in turn to disease progression, possibly encompassing unfolded protein responses, ptau templating with trans-synaptic spread of toxic, self-propagating strains, and neurodegeneration in a distribution that favors neuropsychiatric disturbances, impaired cognition, and motor signs (Figure 1). Moreover, head trauma, even singular head trauma, may initiate this process according to reports,[2] and may set up a cellular milieu favoring neurodegeneration, including AD, frontotemporal lobar degeneration, and amyotrophic lateral sclerosis.

PROBLEMS WITH THE CURRENT PARADIGM

The DP Literature

The concept for present day CTE, including the naming of the condition, is based on DP, which, while broadly accepted as a clinicopathological entity, is comprised of a relatively small number of cases with remarkably heterogeneous pathology. Moreover, the few DP cases described in the literature have been examined over many decades using differing techniques, including dyes and silver impregnation, with a minority of cases assessed via immunohistochemistry for ptau and amyloid-beta.

The term 'punch drunk' appeared in the medical literature in a 1928 *JAMA* article by Martland, in which small hemorrhages were emphasized pathologically. The first case of DP with neurofibrillary degeneration was described by Brandenberg and Hallervorden[50], in a 51-year-old retired boxer (retired at age 28 after 11 years as an amateur boxer), although plaque pathology and cerebral amyloid angiopathy were also noted, as was death from intracerebral hemorrhage, raising the possibility of early onset AD. Courville[51] in 1962 reported an autopsy case of punch drunk syndrome, although no neurofibrillary degeneration or features presently ascribed to CTE were mentioned. Constantinides and Tissot in 1967[52] described severe degeneration of the substantia nigra with numerous neurofibrillary tangles in a 58-year-old man who had been retired from boxing for 34 years,[5] raising the possibility of co-morbid tauopathy. Payne[11] in 1968 described autopsy findings in six boxers in their forties, calling attention to septal abnormalities. CTE changes according to modern concepts (perivascular and superficial neurofibrillary change, neurofibrillary change in the depth of sulci) were not apparent, although 'early' neurofibrillary changes were observed in two brains, and were considered non-specific.

The largest series to date, however, was that of Corsellis *et al*,[5] who described findings in 15 boxers. In this seminal article, neurofibrillary degeneration out of proportion to plaque pathology was established as an integral pathological change, while also emphasizing septal changes, substantia nigra degeneration, and cerebellar scarring. Clinical findings often included speech abnormalities, ataxia, and movement disorders. A closer look at the cases, however, indicates a level of complexity and variability. At least 6 of the 15 cases were accompanied by heavy alcohol use. Co-morbidities such as hypertensive vascular disease with lacunar infarcts were evident in some cases. One patient had tabes dorsalis, another had a cavernous malformation of the globus pallidus, while others had little pathology and were neurologically normal during life. A number of the subjects boxed in the early part of the twentieth century, when several hundred fights were

not uncommon. The reduced exposure in boxers presently may significantly reduce the risk of chronic neurologic sequelae.[53] Also noteworthy is the subsequent examination of many of the original cases using immunohistochemistry to amyloid beta, which showed not only diffuse plaques, but also neuritic plaques which in some cases were sufficient in quantity to warrant the diagnosis of AD.[9,54] Extreme substantia nigra degeneration with neurofibrillary change in residual neurons also raises the possibility of sporadic tauopathy (e.g., corticobasal syndrome, progressive supranuclear palsy). Atrophy involving hypothalamus and mammillary bodies in some of these cases warrants discussion of thiamine deficiency and Wernicke–Korsakoff syndrome. It should also be noted, in light of the recently identified genetic lesions that cause FTLD/ALS, family history was not commented upon in any of the cases in this series. Thus, although the description of neurofibrillary degeneration was remarkable, the limited numbers, extensive head trauma exposure, and co-morbidities indicate a level of uncertainty even in the relatively well-accepted entity of DP.

More recent cases are fewer but perhaps more compelling. For example, Hof *et al*[55] described neurofibrillary tangle clusters in frontal and temporal cortices in a 24-year-old autistic patient who was prone to frequent and protracted self-injurious head-banging. The findings included a tendency for focal involvement of cortical laminae 2 and 3, now considered a feature of CTE. Geddes *et al*[12] noted neurofibrillary change with a tendency for basal cortical involvement by tau immunohistochemistry in two boxers in their twenties, and further called attention to perivascular tau, also considered a hallmark of CTE. Neither subject had clinical signs suggesting DP, however. About the same time, the *New England Journal of Medicine* presented a case of multisystem neurodegenerative disease, including involvement of the spinal cord and substantia nigra, in a 67-year-old retired boxer (10 year career with over 100 bouts).[56] Interestingly, probable amyotrophic lateral sclerosis was diagnosed in the patient's brother, raising the possibility of pathogenic mutation. Schmidt *et al*[57] examined brain tissue from this same patient and one additional retired boxer, aged 78, and noted that the tau isoform profile in soluble fractions resembled that of AD. The second patient, however, had Lewy bodies in the substantia nigra, again raising the issue of co-morbid neurodegenerative disease. Areza-Fegyveres *et al*[58] reported a case of DP with a clinical progression that was indistinguishable from AD.

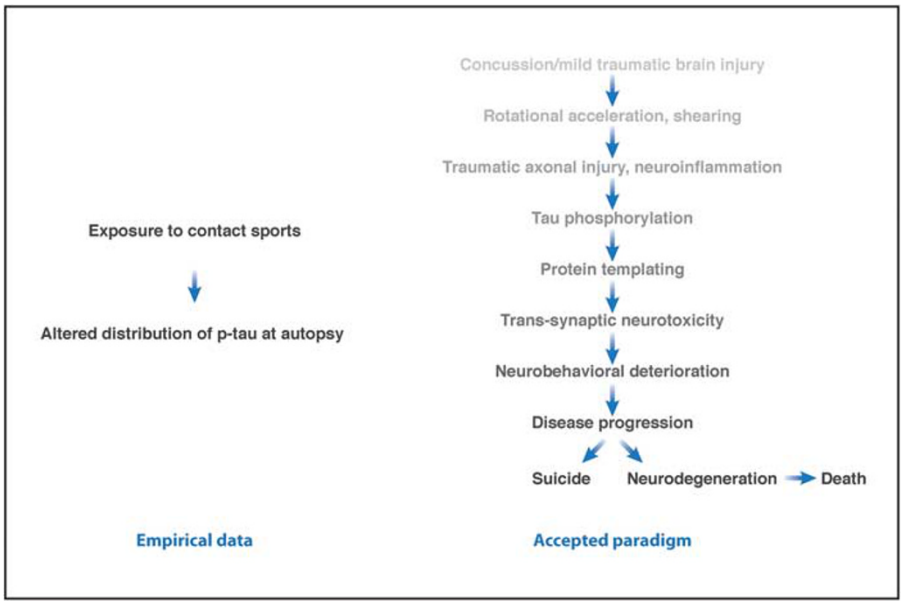

Figure 1 The empirical data regarding tauopathy and contact sports appear to indicate that certain contact sports may be associated with an altered distribution of phosphorylated tau when examined at autopsy years to decades following sports participation. The significance of this change and the correlation between such changes and clinical signs are matters of considerable uncertainty, as more research with more rigorous prevalence data is necessary even for this preliminary assertion. This is in contrast, however, to the accepted paradigm, none of which has been objectively demonstrated in humans. The accepted paradigm indicates that head trauma *per se* and in particular concussion, initiates the overall process, which in turn sets in motion neuroinflammatory processes that span a large spectrum of biology. Phosphorylation of tau via pathological alteration of kinase-phosphatase equilibrium subsequently occurs in brain regions vulnerable to mechanical stress. Soluble, low-n phospho-tau oligomers of altered conformation or 'strain' then spread along neuroanatomical pathways, effect conformational changes in other phospho-tau species via protein templating, and cause trans-synaptic neurotoxicity, which fosters disease progression. The tendency for frontotemporal involvement by phosphorylated tau further is suggested to be the basis for complex behaviors, such as impulse control, mood, and attention, as well as the reported psychiatric manifestations of CTE. Involvement of memory pathways is suggested to disrupt episodic memory. The overall neurotoxic cascade is said to overlap with, include, or even cause, pathology of Alzheimer's disease, frontotemporal lobar degeneration, and/or amyotrophic lateral sclerosis.

He had fought more than 60 bouts but had never been knocked out.

McKee and colleagues on the other hand more than doubled the cases of sport-associated tauopathy reported in the literature with a remarkable brain procurement effort, particularly targeting NFL athletes.[1] Emphasis was placed on the *pattern* of tauopathy, best illustrated by thick, sledge microtome whole-mount immunostains. Thus, the updated pathology of CTE includes: (i) localized neuronal and glial accumulations of phosphorylated tau involving perivascular areas of the cerebral cortex, sulcal depths, and with a preference for neurons within superficial cortical laminae; (ii) multifocal axonal varicosities involving deep cortex and subcortical white matter; (iii) relative lack of Aβ deposits; and (iv) TDP-43-positive inclusions and neurites. The first of the above findings is arguably the most robust, as these distributions are generally not described as incidental accumulations with age or as a prominent feature in AD. Axonal varicosities, relative lack of Aβ, and TDP-43 pathology may be difficult to distinguish from other diseases and controls in blinded analyses.

In a review of the CTE (including DP) literature to date, however, Gardner *et al*[8] noted that of the 61 pure athlete cases reported by McKee *et al*, 25% demonstrated no pathological features of CTE, and 25% had 'pure' CTE pathology. Of those with pure CTE pathology, clinical findings were sometimes absent or nonspecific. Noteworthy also was that only a minority of cases showed disease progression, contrary to the commonly held view that CTE is a neurodegenerative disease.

Both DP as classically defined, and modern day CTE, therefore span a wide spectrum from normal to advanced disease, from the standpoint of both clinical presentation and neuropathological findings, with disease progression being doubtful in many cases according to one review. The broad question of whether DP or CTE merits inclusion in the broad category of neurodegenerative disease may be debated in light of these data, although the low thresholds for exposure and diagnosis are understandable as information is still accumulating.

Ptau as a Mediator of Disease

Ptau accumulation occurs in a long list of conditions and is manifestly downstream in Alzheimer's disease according to the amyloid cascade hypothesis.[59] Some have suggested that ptau is not only a reactive phenomenon but possibly even a beneficial or adaptive disease response.[60] Neurofibrillary degeneration, for example, is associated with adducts of advanced glycation[61] and lipid peroxidation;[62] these chemical modifications contribute to protein insolubility, and target inert accumulations for degradation. Ptau has been shown to sequester toxic-free radicals and heavy metals,[63] and is known to accumulate in viable cells for decades.[64] Transgenic tauopathy models have further demonstrated lack of neurotoxicity associated with ptau.[65] The appearance of phosphorylated tau in areas of biomechanical stress or otherwise neuroinflammation (e.g., depths of sulci, perivascular areas) may therefore be less indicative of toxicity than of reactivity.

The kinetics of ptau accumulation during life is difficult to monitor, although research into tau-targeted positron-emission tomography is progressing,[66] and may provide insight into ptau progression over time, i.e., whether it progresses, stabilizes, or even regresses. The known age-related ptau accumulations will require rigorous attention to variations of normal, particularly in light of the recently described, but reportedly very common, primary age-related tauopathy.[67] In this aging pattern, ptau involvement of anterior-medial temporal lobe and brainstem tegmentum, often emphasized in CTE, is an expected finding.[68,69]

It should also be noted that the prion-like, tau templating concept, while raising novel issues about basic protein chemistry, confronts the shortcomings of the *in vitro* experimentation when applied to human disease, such as (i) requirement of one to several, pathogenic mutations; (ii) utilization of supraphysiologic concentrations of mutated or insoluble, phosphorylated protein; (iii) variable pathology; and (iv) variable behavioral correlates.[45,70,71] The juxtaposition of two pieces of human data may also cast doubt on ptau templating as an *in vivo* pathophysiologic event. Braak *et al*[69] note that ptau, as detected by AT8 immunohistochemistry, is found earliest in the locus ceruleus, and as early as the first decade of life. In turn, the locus ceruleus is said to be 'unsurpassed' in the diffuseness and ubiquity of its connections throughout the nervous system.[72] If ptau templating, cell-to-cell transmission, and spreading toxicity in a prion-like manner were *in vivo* phenomena, it is reasonable to suggest that clinically significant neurodegeneration would occur earlier in life and with greater regularity. Nevertheless, protein templating is increasingly accepted as an *in vivo* occurrence and has led to the palpable fear that a neurodegenerative process could result from a single blow to the head (http://www.psychologytoday.com/blog/invisible-wounds/201208/disturbing-new-study). This appears unwarranted from the standpoint of human data.

Genetic Predisposition to Chronic Neurodegeneration in Professional Athletes

It is commonly stated that genetic susceptibility (yet to be clarified) may underlie the sporadic appearance of CTE in athletes.[16] In the case of American football, however, CTE is reported in essentially all professional athletes examined to date. In the absence of subclassification, such a high percentage precludes genetic susceptibility studies, as no one is genetically resistant. That said, apolipoprotein E genotype (*APOE*) is often discussed, given its role as the major genetic risk for sporadic AD. In the largest series to date, *APOE* allelic frequencies were comparable with the general population.[1] An overrepresentation of the ε4 allele in boxers with neurological impairment was noted in one study, although autopsy findings were not available for correlation.[73]

Relevant to the discussion going forward may be the expanding list of pathogenic mutations and polymorphisms in frontotemporal dementia (FTD) and ALS,[74,75] particularly because (i) signs of FTD overlap with those reported in CTE; (ii) FTD typically presents in middle age; and (iii) co-occurrence of ALS and CTE is reported in some cases.[1] FTD is also the second most common type of presenile dementia after AD and, importantly, the percentages of FTD and ALS patients with known pathogenic mutations have increased substantially in recent years.[74] Among genetic variants, microtubule-associated protein tau (*MAPT*) and progranulin (*GRN*) mutation tend to favor an FTD presentation, while superoxide dismutase-1 (*SOD1*) mutations present as ALS.[76] Mutations involving *C9ORF72*, TAR DNA-binding protein-43 (*TARDP*), Valosin-containing protein (*VCP*), p62/sequestosome-1 (*SQSTM1*), and ubiquilin 2 (*UBQLN2*), may have mixed FTD-ALS phenotypes.

C9ORF72 mutation involves expanded hexanucleotide repeats on the non-coding portion of chromosome 9, and is now the most common mutation in both ALS and FTD, accounting for up to 46% and 29% of familial ALS and FTD cases, respectively, in European populations.[77] This recent finding may add to the understanding of CTE in that a subset of athletes presenting with signs of FTD and/or ALS may be excluded from the CTE category by genetic analysis. It also raises the issue of potential outcome in athletes with unrecognized genetic susceptibility to known diseases, ie, whether athletic participation influences neurodegeneration or is otherwise incidental in individuals with expanded *C9ORF72* repeats.

The assignment of TDP-43 immunohistochemistry to the cardinal pathological features of CTE may be problematic owing to morphologic heterogeneity of TDP-43 immunoreactivity apparent in a range of conditions. TDP-43 positivity is found to varying extents with age and AD.[78] In the FTD/ALS spectrum, TDP-43 positivity may be present in variable cell types (neurons *versus* glia), subcellular compartments (nucleus *versus* cytoplasm), distributions (superficial cortical *versus* diffuse *versus* subcortical), and morphologic expressions (perikaryal and nuclear inclusions of various morphologies *versus* neurites).[79] TDP-43 positivity is further observed in a subset of familial and sporadic FTD, with and without *TARDP*, *GRN*, and *C9ORF72* mutation.[74] The finding in CTE cases is therefore not surprising and appears to be an empirical phenomenon, rather than a pathogenic signature. Rigorous controls for age and other competing diagnoses are probably necessary before accepting TDP-43 reactivity as hallmark pathology.

MAPT mutation also may be relevant to CTE given that both FTD with *MAPT* mutation and CTE show increased ptau at autopsy, both are reported to show behavioral disturbances, and both are reported to show cognitive deterioration and parkinsonism, in at least some cases.[74] *MAPT* mutations account for 5–20% of familial FTD cases, which is significant given the tendency for pathogenic mutation in FTD overall. *MAPT* mutation screening therefore may be considered in athletes presenting with presenile onset of behavioral disturbances and parkinsonism. Likewise, as the frequency of presenilin-1 (*PSEN1*) mutation (the most common pathogenic mutation in AD) increases with early onset dementia and strength of family history,[50,80] autosomal dominant AD may be considered in middle-aged athletes presenting with dementia and possible family history. The occasional cases in the DP literature with middle age onset dementia and frank AD pathology,[5] for example, suggest early onset AD rather than DP.[5,50] Finally, although only 10% of Parkinson disease patients have a positive family history, some pathogenic mutations produce substantia nigra degeneration without synucleinopathy (e.g., LRRK, parkin),[81] which may be considered in athletes with early onset parkinsonism, substantia nigra degeneration at autopsy, and no Lewy bodies.

Neuropathology as a Predictor of Function in Degenerative Proteinopathies

The strict association between ptau lesions and behavioral or dysexecutive symptoms, and indeed the implied causal link between the two,[18,82] is problematic in that autopsy brain examination, including ptau immunohistochemistry, is useful for *structural* neuropathology. Neuropsychiatric signs, in contrast, are *functional* or biochemical. In point of fact, correlating basic neurologic dysfunction even with rigorously quantitated lesions and the availability of copious cognitive data is challenging.[83] Blinded neuropathologic examination, for example, cannot distinguish intact cognition from dementia in the very old.[84] Discerning clinical presentation among the FTD subtypes, or initial presentation in Lewy body diseases (cortical signs *versus* parkinsonism),[74,85–87] also cannot be carried out accurately with available methodology and consensus criteria. With this in mind, drawing mechanistic associations between tauopathy at autopsy, and psychiatric signs or complex behaviors such as suicide, explosive anger, impulse control, or posttraumatic stress disorder,[88] appears beyond the scope of neuropathological interpretation.

Neurodegenerative Disease Risk with Athletic Exposure

In a recent study of former NFL players by Lehman *et al*,[89] the mortality rate from neurodegenerative disease was three times greater than that of the general population, whereas the mortality rate overall of NFL players was about half that of the general population. The numbers in this study were relative small, with 334 former players, of which there were two cases of AD and six ALS cases. Moreover, none of these cases had autopsy confirmation or genetic screening. One study of professional Italian soccer players showed an increased risk of ALS,[90] although selection bias and possible confounding influences of dietary and environmental factors have been raised.[91] Physical activity in general has also been suggested as a risk for ALS,[92] but an association with physical activity *per se* has been generally refuted.[93] The only class II study of ALS incidence in American football found no risk.[94] The

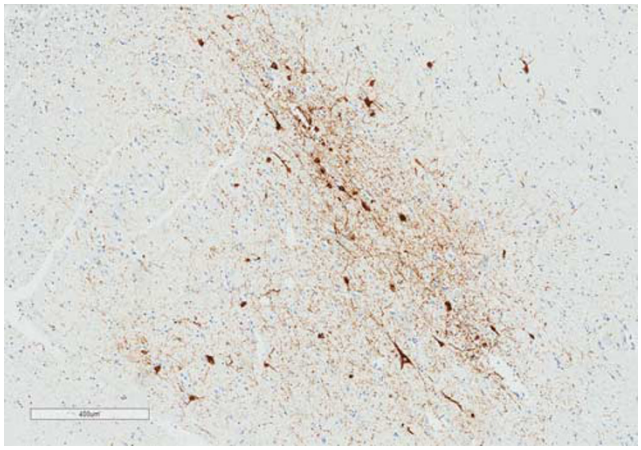

Figure 2 Focal neurofibrillary degeneration in the superficial amygdala was noted in this 41-year-old retired NFL offensive lineman who, by definition, suffered thousands of head impacts over the course of this career (scale bar = 400 μm). This was the only finding noted after an extensive examination for ptau (AT8) throughout the neuraxis, and is an incidental finding for age. This is the oldest NFL athlete reported to date with no CTE changes at autopsy.

improved mortality in the Lehman *et al* study is also interesting in that it raises the issue of health benefit of sport, which is only rarely discussed in the context of CTE.[16] Regardless, the available evidence does not support a cause–effect relationship between exposure to head trauma in contact sports and neurodegenerative disease.

Arguably, the most substantial shortfall of the autopsy studies on DP and CTE, and autopsy studies in general, is the lack of prevalence data. The relationship between CTE changes at autopsy and neuropsychiatric signs and symptoms is therefore an open question, as is the extent and impact of susceptibility factors, kinetics of progression, and whether CTE exists as a distinct clinicopathologic entity. It is also noteworthy that NFL athletes do not appear to have an increased risk of suicide compared with the general population (data suggest a decreased risk),[95,96] casting some doubt on the inference that concussive or subconcussive exposure leads to heightened suicidality.

The Role of Neuroplasticity in Repetitive Head Trauma

Parents, athletes, and perhaps combat veterans may find solace in the fact that one can survive a career in the NFL neurologically intact and with no significant proteinopathy. Figure 2, for example, depicts the only brain finding identified in a retired, middle-aged NFL player. This individual came to autopsy after passing away from natural causes, with no history of neurologic or psychiatric illness. He further played on the offensive line, a position that suffers the most frontal impacts of all positions in the sport.[97] He retired after several years in the NFL, having also played for 5 years at a major Division I university. A conservative estimate, based indirectly on accelerometer studies, is that he suffered as many as 10 000 head impacts exceeding 10 times *g*, over the course of just his collegiate and professional careers.[98] This athlete again had no neurologic or psychiatric disturbances during life, and, at autopsy, his brain was entirely normal by gross and microscopic examination. The only incidental finding, after extensive examination of the brain for ptau throughout the neuraxis was a small collection of neurofibrillary tangles and neuropil threads in the superficial amygdala, and a pretangle and rare neuropil threads in the locus ceruleus. This extent of ptau may be found in any individual of this age, irrespective of *APOE*, occupation, head trauma exposure, or other factors.

Although this negative case may not appear noteworthy on casual review, it should be pointed that this is the first reported middle-aged NFL athlete to date with no CTE changes.[1,2] This raises the issue of the much needed prevalence data and selection biases, if not the resilience and plasticity of the human brain, and its ability to endure protracted physical punishment in the setting of high-energy collision sports at the highest level.

CONCLUSIONS

The recent CTE literature has advanced the discussion beyond the preceding CTE literature, by codifying a specific distribution of proteinopathy, and laying out criteria for future studies. The criteria for CTE nevertheless appear overly inclusive, which may in turn hamper understanding of molecular-genetic underpinnings. It may also be acknowledged that there are more questions than answers about all aspects of the CTE concept, from biomechanical substrates to molecular pathogenesis to the existence of CTE as a distinct entity.

DISCLOSURE/CONFLICT OF INTEREST

The author declares no conflict of interest. The contents are solely the responsibility of the author and any opinions expressed herein are not necessarily the views of the editors, the United States and Canadian Academy of Pathology, or Nature Publishing Group.

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