PATHOLOGY OF CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE)

PROGRAM SYLLABUS
CHRONIC TRAUMATIC ENCEPHALOPATHY:
CONCLUSIONS IN SEARCH OF EVIDENCE

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Introduction

Chronic traumatic encephalopathy (CTE) is the accepted term for a pattern of phosphorylated tau (ptau) deposition in the brain that differs from that of age-related accumulations and neurodegenerative diseases1. Specifically, ptau in CTE 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 layers 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 is said to vary from markedly atrophic to normal, while cavum septum pellucidum and septal fenestrations are common findings, although not invariable. Attempts at staging of the progression and severity of CTE have been proposed in the literature, although the two systems most often referred to either relate most closely to age 1, or comprise individual clinical phenotypes, each with a wide spectrum of possible pathological expressions2.

CTE is empirically associated with contact sports and is often considered a variation of so-called dementia pugilistica (DP) 3-5, a long known condition in boxers accompanied by neurological signs and neurofibrillary degeneration6. The nature of various sports implicated in CTE, along with the apparent increase in ptau in parenchymal brain tissue, has further suggested head trauma as the underlying biomechanical etiology. Concussion and subconcussive blows are an accepted clinical substrate, although it should also be pointed out that even classically described dementia pugilistica has been controversial since its description, with poorly documented prevalence, absence of prospective data7, surprisingly few studies with autopsy correlation5,8-12, and lack of accounting for co-morbidities such as substance abuse, infection, and genuine vascular or neurodegenerative disease13. Comparisons with more recently described CTE suggest certain differences between CTE and DP, such as clinical presentation, association with ApoE genotype8,14, age at onset, and tendencies for neurological signs, although none of the differences provides predictive value. Most neuropathologists who have studied both subtypes tend to believe that CTE and dementia pugilistica are the same condition for practical purposes – progressive tauopathy caused by concussion or subconcussive impact to the head1.

Prominent among the contact sports in recent years is American football, made even more prominent by several high profile cases involving suicide, violent death, or otherwise sudden unexpected death in relatively young professional athletes. Anecdotal cases have also been suggested in hockey players1, professional wrestlers, rugby players15, soccer players12, a professional baseball player15, and an achondroplastic dwarf who suffered occupational head trauma as a circus performer16.

The clinical correlate of reported CTE cases in non-pugilists is largely psychiatric, including aggression, explosive anger, impaired impulse control, domestic disarray, depression, and heightened suicidality1. Short-term memory complaints and Parkinsonism are among the neurological symptoms in some reported cases. Most cases of CTE reported in the literature are not progressive8, which suggests at the outset that CTE differs fundamentally from genuine neurodegenerative diseases (e.g., Alzheimer’s disease, amyotrophic lateral sclerosis).

Accepted CTE paradigm – TBI, neuroinflammation, ptau accumulation, and templating

The gaps in knowledge of CTE are substantial, and the collective data, which are retrospective, anecdotal, and based on self-selected cases, permit no conclusions as yet, particularly as regards its biomechanical precursor or even its existence as a clinicopathologic entity. Nevertheless, there has evolved a paradigm that is generally accepted.
TBI and Concussion. The paradigm begins with the heterogeneous, poorly understood, and imperfectly modeled condition termed traumatic brain injury (TBI). TBI most often signifies loss of consciousness and is arbitrarily termed ‘mild’ if the loss of consciousness is up to 30 minutes. Alteration in consciousness for up to 24 hours, or posttraumatic amnesia for up to 24 hours, is also accepted under the mild TBI umbrella17. On the other hand, the diagnosis of mild TBI may be entirely subjective, as it is often based on self-reported neurological symptoms18. Thus, while mild TBI is portrayed in the literature as a definable condition, it encompasses a wide spectrum of potential biomechanical precursors, including nature and type 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 the TBI terminology to be used for military related TBI, given the spectrum from mild to severe, whereas the civilian lesion is usually termed ‘concussion’ rather than “mild TBI.”

Concussion in contact sports, either objective or subjective, is exceedingly common and by no means limited to high-energy collision sports such as American football19. It should also be pointed out that 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 progress19.

Risk factors for concussion have been only obliquely addressed in the context of CTE. Among these are history of previous concussion, number of and severity of concussion, age, gender, pre-existing mood disorders, pre-injury learning disabilities such as attention deficit hyperactivity disorder, and history of migraines. 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 superficially uniform term. As such, terms like “multiple concussive events” or “repeated subconcussive blows to the head” by themselves have limited meaning as a precursor to chronic structural pathology.

It is of some passing interest that one high profile NFL football player who was found 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 has tends to de-emphasize the importance of concussion per se, and elevate the importance of subconcussive contact as the operant etiological factor. On the other hand, retrospective interviews in this case have called into question the absence of concussion, and, by extension, the reliability of clinical history even in carefully monitored athletes. One mainstream sports media report went so far as to publish a teammate’s view of a more meaningful definition of concussion: the grade 1 concussion, or “seeing stars.” By this definition, the decedent may have suffered as many as 1,500 “concussions,” and ostensibly explains the lack of concussion history. In either case, uncertainties regarding concussion and potential biomechanical antecedents to CTE are evident, notwithstanding the certainty of the widely held view that concussions cause CTE.

Biomechanical issues and potential sequelae of TBI. Understanding concussion in the acute state from the standpoint of neuropathology is problematic in that the neurological deficit is transient and without mass effect, i.e. the patients survive and do not require neurosurgery. The pathology and mechanics of concussion are therefore difficult to elucidate in vivo. Studies on brain contusion on the other hand (a lesion definable by its pathology) have led to the basic concept that shear stresses, or the movement of one tissue plane over another, are necessary for parenchymal brain injury20. As emphasized by Holbourne more than 70 years ago, the brain’s relative incompressibility and low modulus of rigidity necessitate shear stresses over compressive stresses, and rotational acceleration over linear acceleration21. One could reasonably speculate, therefore, that shear stresses and rotational acceleration are the basic physical precursors to concussion.

Purely biomechanical models in intact primates from the 1970’s and 1980’s may have also shed some initial light on concussion indirectly through the characterization of diffuse traumatic axonal injury (DAI). The biomechanics of DAI appear to follow that of concussion, albeit with more severe clinical and anatomic outcome. In early primate models, it was
determined among other factors that acceleration in the coronal plane\textsuperscript{22} and low strain rate (prolonged interval of acceleration) favored prolonged traumatic unconsciousness, poor outcome, and DAI at necropsy.

At the experimental level, the last 30 years has seen a proliferation of \textit{in vitro}\textsuperscript{23} and mammalian\textsuperscript{24} trauma models, which have led to an exponential expansion of data that implicate essentially all major molecular disease mechanisms. Thus, TBI and otherwise biomechanical forces result in pleiotropic deleterious, biochemical sequelae, encompassing single 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, induction of apoptosis, etc\textsuperscript{25-32}.

These processes \textit{in toto} may be referred to as 'neuroinflammation'. The neuroinflammation then leads to, or otherwise facilitates, tau phosphorylation via altered kinase-phosphatase metabolism\textsuperscript{33}. This causes microtubule instability and precipitation of ptau as toxic, insoluble intraneuronal and intra-astrocytic inclusions\textsuperscript{34}. Somewhat more concerning are the studies suggesting protein templating with cell to cell transmission\textsuperscript{35}, and the inclusion of tauopathies, including and especially CTE, in the lexicon of prion (or prion-like) diseases. Transgenic mice overexpressing P301L tau and inoculated with ptau, for example, demonstrate \textit{de novo} ptau anatomically distant from the site of inoculation\textsuperscript{36}.

Tau phosphorylation, as well as TDP-43 accumulation (an evolving, ancillary issue in CTE), thus "spreads" along neuroanatomic pathways, leading to disease progression and neurodegenerative disease. The frequent involvement of frontal and temporal lobes by the neurotoxic process is said to cause dysexecutive signs, including disordered impulse control, explosive aggressiveness, extreme impulsivity, impaired judgment and social function, and heightened suicidality. Medial temporal lobe involvement may cause short-term memory complaints, while involvement of the brainstem may further result in Parkinsonism and motor signs.

In short, TBI induces neuroinflammation, leading to tau phosphorylation, leading in turn to disease progression, possibly encompassing unfolded protein responses, ptau templating, trans-synaptic spread of toxicity, neurodegeneration, and a tendency toward neuropsychiatric disturbances and self-harm.

\textbf{Problems with the current paradigm}

The problem begins with TBI. At present, the \textit{biomechanical substrate of the ptau lesions seen post mortem is completely unknown}. It is reasonable to speculate that some form of head trauma may predispose to such lesions given the description of the changes in boxers and football players, but the simple fact is that there is no evidence that concussion, or subconcussion for that matter, results in the ptau lesions of CTE. One may even question the role of head trauma \textit{per se}, in light of studies showing perivascular neuroinflammatory changes in the absence of any head trauma, in a hydrodynamic pulse model in rats (Simard, JM et al, \textit{J Neurotrauma}, in press).

\textbf{Problems with Ptau as a mediator of disease}. Ptau as a toxic phenomenon is not a settled issue. An abundance of evidence supports ptau as a disease response, possibly even a beneficial disease response\textsuperscript{37}. A reduction of oxidative stress accompanying tau phosphorylation has been demonstrated. Neurofibrillary degeneration (morphologic correlate of tau phosphorylation) is associated with adducts of advanced glycation and lipid peroxidation, sequestration of toxic free radicals and heavy metals, and otherwise is known to accumulate in viable cells for decades. Their appearance in areas of biomechanical stress (e.g., depths of sulci, perivascular areas) is therefore not surprising, and less indicative of toxicity than they are of reactivity. Staging of ptau, such as in CTE, would thus stage the disease response and as such would have an unreliable and capricious relationship with clinical disease. More plausible is that ptau is an inert substance, occurring as a localized secondary event to a number of potential underlying causes (mechanical trauma, oxidative stress, chronic inflammation, age). Small punctate lesions at the depths of sulci and around blood vessels may represent more of a brain "decoration" in many cases than a pathological lesion.
The kinetics of ptau in apparent CTE during life is an additional unknown. Whether a non-progressive dynamic equilibrium is reached, whether ptau is elaborated and metabolized, whether ptau forms a nidus for progression, or whether it is some combination of the three, is not established. The spectrum of neuroinflammatory processes is certainly worthy of investigation but is still very much theoretical, as is tau templating in that the experimental constructs i) require overexpression of an aberrant, pathogenic mutation (P301L); ii) utilize supraphysiologic concentrations of ptau in the innocula; and iii) have a paucity of neurofibrillary change at necropsy.

The juxtaposition of two empirical human brain features may also cast doubt on ptau templating as an in vivo pathophysiologic event. Braak et al 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. If ptau templating, cell-to-cell transmission, and spreading toxicity were in vivo phenomena, it is reasonable to suggest that neurodegeneration would have selected the human species out of existence. Nevertheless, tau templating is increasingly accepted and promoted by internationally known scholars 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 (e.g., concussion), despite the fact that experimental models are poorly representative of the human condition.

Erroneously relating structural lesions to functional symptoms. The strict association between ptau lesions and dysexecutive symptoms including suicide, which experts are now proposing and the lay public now believes, may be unprecedented in neuropathology, and unwarranted. It should be kept in mind that autopsy brain examination, including ptau immunohistochemistry, is concerned with structural neuropathology. Neuropsychiatric signs, in contrast, are functional or biochemical. Neuropathology is thus a powerful diagnostic and research tool for defining the structural basis of disease across the spectrum of human maladies, including neurodegenerative, inflammatory, infectious, metabolic, neoplastic, and malformative conditions. Neuropathology is useless in defining such issues as impulsivity, aggression, depression, poor judgment, and mismanagement of personal circumstances. It should also be noted from the standpoint of “pretest probability” that there is no evidence that participation in contact sports represents any suicide risk at all.

In actuality, neuropathologists have considerable difficulty drawing conclusions about clinical signs as basic and easily tested as cognition, even with rigorously quantitated lesions and the availability of cognitive data obtained on a prospective basis. Neuropathology cannot, for example, distinguish intact cognition from dementia in the very old. Other clinical distinctions, such as clinical variants of frontotemporal dementia (e.g., semantic, behavioral, aphasic), Lewy body dementia versus Parkinson disease, and specific cortical variants of Alzheimer disease (e.g., visual variants), cannot be predicted on the basis of neuropathology. As we have commented upon previously, this touches on what may be a fundamental misadventure in the interpretation of pathology of chronic disease, namely assigning pathological changes to cause rather than effect, and equating neurodegenerative lesions with toxicity. We might also remind ourselves that we have collectively achieved nothing of therapeutic benefit in Alzheimer disease by the targeting of lesions, despite an exponential expansion of knowledge and potential therapeutic agents. The pathogenic significance of lesions (e.g., ptau) is therefore questionable.

No evidence of neurodegenerative disease risk and no denominator. Of additional importance and equal uncertainty, is the risk of TBI, or contact sports, in producing neurodegenerative diseases. One study that analyzed death certificates showed a slight relative risk of Alzheimer’s disease and amyotrophic lateral sclerosis in football players, but also showed an improved overall mortality. Neither finding constitutes epidemiological certainty, although the study does raise the issue of the health benefit of sport, which is rarely discussed. The simple fact, however, is that there is no evidence for a cause-effect relationship between contact sports and neurodegenerative disease, or conclusive evidence of even a small relative risk.

Among the most concerning issues in CTE is the absence of a denominator. We simply do not know the prevalence of the described CTE lesions. On this basis alone we have no idea
of the relationship between CTE and neuropsychiatric signs and symptoms, and therefore what to do to prevent them.

Index case of CTE. Ironically, one may find solace in a careful review of the index case of CTE in a professional football player that appeared in *Neurosurgery*. The athlete in question played 245 games on the offensive line including 150 straight games. He passed away at age 50 from myocardial infarct, in the setting of known atherosclerotic cardiovascular disease, cardiomegaly, and atrial fibrillation. No significant neurologic history was apparent during life, although postmortem questioning of family members suggested symptoms of depression and Parkinsonian symptoms. At autopsy, his brain was completely normal by gross examination, aside from attenuated pigment in the substantia nigra. This gross finding correlated only with mild to moderate loss of pars compacta (pigmented) and pars reticularis neurons, a semiquantitative finding and a potential variation of normal depending on the actual histologic presentation. Mild extraneuronal pigment was described, which is a normal finding in a 50 year old. In the cerebral cortex, he was noted to have diffuse plaques, rare neocortical neurofibrillary tangles, and rare neuropil threads, which were depicted in photomicrographs. Each of these is an incidental finding in a 50 year old. Thus, aside from some nonspecific changes in the substantia nigra, this index case of CTE could legitimately be interpreted as an entirely healthy 50 year-old brain.

In essence, the brain of a man whose head was subjected to unspeakable punishment over a period of more than 25 years showed no sequelae of head trauma whatsoever in the images available. Moreover, ApoE genotyping was reported as E3/E3 – the most common genotype that is neither protective of, nor predisposes to, neurodegeneration. Athletes across the US and abroad may therefore find optimism in the resilience and plasticity of the human brain, and its ability to resist physical punishment on an enormous scale in the setting of high-energy collision sports.

Conclusions

While the neuropathology community continues to elucidate brain changes that may be related to some form of trauma to the head during life, the humble recognition of ignorance as regards chronic sequelae of mild head trauma is now overdue. The sensationalism surrounding CTE may also be doing the athletes and their families a disservice of historical proportions. By extrapolating from anecdotal reports and samples of convenience, the media in collaboration with medical science has cast a broad net that may be inapplicable to the vast majority of athletes. This not only produces undue fear of a disease process that is poorly understood, it also trivializes potentially legitimate cases of trauma-induced chronic, progressive brain injury and dilutes any potential genetic susceptibility studies. Only by accepting the many uncertainties surrounding CTE will we progress toward meaningful understanding and prevention.
REFERENCES