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Chronic Traumatic Encephalopathy:

Diagnosing the Repetitively Injured Brains of Athletes and Soldiers

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In the past decade, it has become increasingly clear that chronic traumatic encephalopathy (CTE; previously known as dementia pugilistica) is associated with several high-impact sports (e.g., boxing, American football, soccer, hockey) and, on the battlefields of Iraq and Afghanistan, with exposure to explosive blasts that arise from improvised explosive devices (IEDs). The combination of support and concern for wounded soldiers and athletes has elevated the public profile of CTE. This is coupled with the disturbing news of six documented cases of CTE in high school football players (1). While the rising awareness of CTE has provoked an international discussion, the scarcity of evidence-based answers to many key questions has become apparent. Most importantly, there is a critical need for accurate measures of CTE prevalence as well as for reports of individuals who remain unaffected despite similar exposure. With these data in hand, it would be possible to derive estimates of the risk associated with each sport or type of military activity and, in turn, we would be able to provide true informed consent to adults grappling with this issue on behalf of themselves and/or their relatives.

A perspective on CTE and current prospects for diagnosis during life

By the time he died in 2005, NFL Hall of Famer and former Pittsburgh Steeler Mike Webster suffered from such profound emotional and cognitive dysfunction that he was destitute and living in his car. At autopsy, pathologist Bennet Omalu at the University of Pittsburgh recognized that Webster's brain was devastated by extensive accumulation of neurofibrillary tangles (NFT) (2). Omalu shared these observations with his colleagues, molecular neurologist Steven DeKosky and forensic examiner Cyril Wecht, both of whom confirmed Omalu's observations. Together they concluded that in Webster's brain, they were seeing the NFT pathology of dementia pugilistica (DP) (3-6). But Webster was a professional football player, not a boxer. Because of this, the diagnosis of DP was set aside in favor of an earlier, more general term, "chronic traumatic encephalopathy (CTE)" (2).

In the entire worldwide literature, about 100 athletes have shown extensive postmortem NFT accumulation in their brains, and most of these cases have suffered from neuropsychological ailments consistent with clinically probable CTE. Because the major component of NFT is a protein called tau, this pathology is more properly described as a tauopathy. Omalu and colleagues raised many questions that we are only beginning to answer:

- Was Webster's illness only the tip of an iceberg that would represent a much larger problem relevant to most or all contact sports in which the brain is repeatedly impacted against the inner table of the skull?
- How common is this pathology in football? Soccer? Hockey? Rugby?

- Is this pathology ever seen in individuals with no history of repetitive head trauma?
- How does this pathology differ from that seen in individuals with a history of a single TBI?
- What quantity, severity, and frequency of head impacts are associated with CTE?
- Could insults acquired during childhood, adolescence, and young adulthood stimulate the development of this form of dementia decades later?
- Should asymptomatic players be screened for subtle neuropsychological deficits? At what ages?
- Does everyone with pathological evidence of CTE also have clinical symptoms consistent with CTE? Which comes first, the clinical syndrome or the pathology? Are there identifiable genetic factors?
- Can we develop appropriate informed consent procedures for children and adults who wish to engage in this class of high-risk behavior?

The most robust environmental risk for dementia is a history of traumatic brain injury (TBI) (7). If sports played by young people are associated with clinically important tauopathy, the implications for the culture of sports worldwide may be profound. Evidence-based answers to the questions above and other related issues are now urgently needed so that athletes can make informed decisions about their risk tolerance. There is a significant need to identify in-vivo marker(s) of CTE that correlate with postmortem evidence of CTE, as well to accurately estimate the prevalence of persons affected with CTE. While this involves expensive and time consuming methodology, it is necessary for establishing clinical CTE diagnostic criteria. To investigate potential criteria, the affected group would be compared against a second needed group — individuals who remain *unaffected* despite exposure to repetitive head trauma identical to that which those manifesting symptoms were exposed. Such data would allow us to derive estimates of CTE risk associated with each contact sport.

This commentary is occasioned by the development of several positron emission tomography (PET) ligands that provide, for the first time, *in vivo* brain scan-based diagnosis of protein aggregation pathology such as tauopathy and a related aggregation pathology known as cerebral amyloidosis (8-10). While the emerging tau PET ligands have not yet had the validation that will be required for routine clinical utilization (as is already the case for cerebral amyloidosis PET markers), such studies are underway. On a related note, a new blood test has been described that enables the detection in the blood of tau released from acutely damaged brain neurons (11). The achievement of these milestones in molecular detection now necessitates consensus about which questions are answerable and which questions hold the highest priority. Our goals herein are to highlight key turning points in the history of CTE and to focus the current questions in light of early experiences with tauopathy and amyloidosis ligands.

Neurodegenerative sequelae of boxing, dementia pugilistica

In 1973, John Corsellis and colleagues (12) brought CTE to its modern conceptualization with their definitive documentation of the delayed, progressive neurodegeneration associated with exposure of

professional boxers to repetitive head trauma. Their report sparked the persisting controversy regarding the role of society in regulating the potential for head injury in voluntary activities, and the liability of organizations that oversee such exposure that continues despite the absence of any meaningful informed consent. In turn, informed consent is largely absent because we have no evidence-based and population-based estimates of risk.

Corsellis' neuropathological examination of the brains of three retired professional boxers demonstrated that the primary CTE lesion involved multifocal intracellular aggregates of hyperphosphorylated tau protein, apparently identical to the NFTs found in individuals with Alzheimer's disease (AD). However, as shown in the 1990s by Hof (13), and later on by McKee (14) and others, the anatomical patterns of NFT distribution in CTE differ from those observed in AD. There is greater involvement of the superficial layers of the association neocortex in cases with CTE, most notably in the depths of the cortical sulci (13, 14). This difference may reflect a unique way in which NFT are formed, and in the manner in which the cortex is stretched and stressed by the repeated trauma. Perivascular tauopathy is also prominent (14).

In 1991, several groups re-examined 14 out of the original 15 CTE cases from the 1973 Corsellis study using improved methods for immunohistochemistry and formic acid pretreatment of tissue sections to recover antigenic epitopes (15). The primary antibody used for this re-evaluation was directed against the amyloid β (Aβ) peptide, the main component of the extracellular amyloid deposits that are characteristic of AD. Although Corsellis (12) had observed no amyloid in the brains of CTE patients using less sensitive histochemical dyes, re-examination with immunocytochemistry revealed that every brain had both NFT pathology and Aβ-immunoreactive amyloid plaques. These data established that CTE is often associated with *both* NFT- and Aβ-related pathologies. McKee and colleagues estimate that amyloid, either as diffuse or neuritic plaques, is present in about half of the cases of CTE that they have examined (14). This is especially significant since it is now possible to induce potentially meaningful therapeutic benefits from the infusion of anti-Aβ antibodies (16).

Involvement of Aβ deposition in the pathogenesis of CTE

Diffuse axonal injury (DAI) is the single most consistently reported neuropathological feature following head trauma (17-20). DAI is associated with focal, intra-axonal accumulation of aggregated forms of a number of proteins that normally anterogradely traverse the axon, e.g., tau, the Aβ-precursor protein (APP), chromogranin A, cathepsin D, ubiquitin, and α-synuclein (20, 21). DAI has been experimentally described in the absence of anterogradely transported proteins. However, it is believed this is a more severe form of injury, resulting in rapid degradation of axonal segments (17, 22). As an acute reaction to TBI, there is up-regulation of APP transcription and increased Aβ generation due to metabolism of the excess APP (23). The Aβ (especially the longer Aβ42 form) is deposited in diffuse plaques after both acute severe TBI (20) and in boxers with CTE (15, 24). Data from surgical craniectomy subjects (20) indicate that about 30% of severe

TBI patients show evidence of Aβ plaques in the acute post injury stage. These can occur in relatively young adults and develop within hours to days after TBI.

In AD, amyloid imaging using PET is positive for as long as to three decades before symptoms begin (25). That interval of presymptomatic cerebral amyloidosis is now being targeted in AD prevention trials using agents such as solanezumab and aducanumab (16). Aβ imaging in TBI and CTE has primarily been positive in the chronic phase of recovery from moderate to severe TBI, although Menon and colleagues have recently demonstrated positive Aβ image in the acute phase of moderate to severe TBI (26, 27). The development of Aβ lesions may depend on several factors, including age of the patient, severity of TBI, time interval since any prior TBI, and genetic factors. *APOE ε4* plays an obvious role in enhancing Aβ pathology (28), especially in women. Given the encouraging results with aducanumab, it is plausible that an Aβ imaging-guided trial of amyloid reduction therapy might be clinically beneficial in moderate to severe TBI. The potential effects of Aβ deposits in CTE have received less attention due to the preponderance of tauopathy by the time affected individuals have expired. Conceivably, each acute TBI could be associated with a burst of submicroscopic Aβ generation. One observation that points to a role for Aβ is the link of *APOE ε4* to clinical dementia in CTE (29, 30). This link was unexpected because in AD, *APOE ε4* modulates Aβ accumulation but not tauopathy (28). The rate of clearance of Aβ from brain is also retarded by *APOE ε4* (31) and perhaps by polymorphisms in the Aβ-degrading enzyme, neprilysin (32). Efficient removal of Aβ deposits for the decades that usually pass between sports careers and death may explain why little evidence of Aβ deposition is found in many CTE brains at autopsy. *APOE ε4* carriers may be more impaired because they have had longer exposure to Aβ because of its slower rate of removal in the presence of *APOE ε4*. Additionally, inflammation may play a key role. Interleukin 1β (IL-1β) has long been believed to be responsible for the elevation of amyloid precursor protein immediately after injury. Long-term IL-1β signaling could propagate CTE pathogenesis because sustained elevation of IL-1β levels in animal models of AD causes regression of amyloidosis and exacerbation of tauopathy (33).

Detection of brain tau protein in the blood following TBI

In 2014, Zetterberg and Blennow demonstrated a method for detection of the appearance of tau in the blood of professional hockey players (11). Blood levels were highest immediately following games but remained elevated for the entire season (months). Most importantly, the blood levels of tau immediately after games were strongly predictive of neurological recovery from the acute injury. This breakthrough in clinically relevant biomarker discovery holds great promise for setting rational standards for return-to-play and return-to-learn policies for athletes and return-to-duty policies for the military. These measurements might also aid in prediction of the risk for later life neurodegeneration and subsequent dementia or other clinical manifestations.

Tauopathy imaging

In addition to this progress in blood biomarkers, 2014 also marked the year in which tauopathy ligands for PET began to emerge in human research. The first widely-studied tau-specific PET tracer, termed T807, was developed by Siemens and acquired by Avid/Lilly (8-10). The figure shows a PET-obtained image using the T807 tracer to show evidence of tau presence. Since T807 development, at least two other series of tau ligands have emerged, suggesting that this area of investigation will move forward rapidly. A mixed specificity ligand, FDDNP, has also been employed to assess CTE (34).

At the same time that these data were emerging, however, an entity termed primary aging-related tauopathy (PART) has been defined and codified in the literature (35). PART is a pathological condition in which tau and NFT are found in the medial temporal lobe, the severity of which correlates with amnestic cognitive impairment. PART may bear some important relationship with CTE in that it may confound the detection of CTE in the elderly (6, 7). Alternatively, PART might arise from very mild repetitive traumatic brain injury caused by medial temporal lobe damage (35). Now investigators are accumulating experience with clinicoradiological and clinicopathological correlation using these ligands.

Summary

Amyloid imaging, tau imaging, and blood tau levels are all in their early days. Investigators with interests in various tauopathies are now acquiring access to these ligands and/or the tau blood test and applying one, another, or all three measurements to various clinical populations of interest. Accumulation of sufficient numbers of subjects in each clinical category will be the next important step before we can formulate how to approach CTE with blood tau levels and/or tauopathy or amyloid PET imaging in such a way as to derive accurate, meaningful results. The availabilities of patients and these specialized scans and assays are somewhat limited at the moment, but both the need and interest are intense, and we anticipate that there will be substantial progress toward *in vivo* diagnosis of CTE over the coming few years. When we understand better the risks and how they are specified, the next challenge will begin when we bring these data on CTE risk to athletes of all ages, parents, school boards, and coaches as well as to veterans and military populations.

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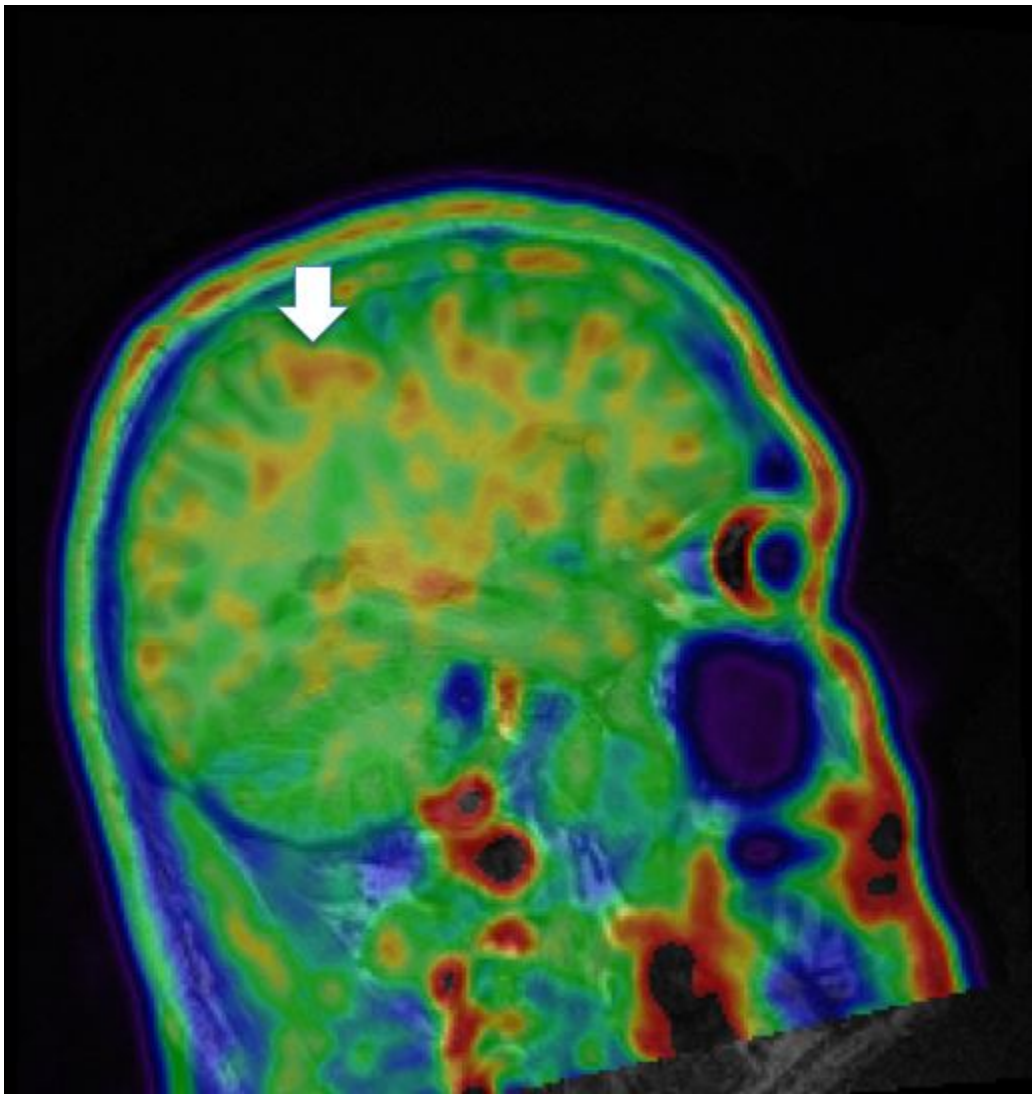
Figure legend

Figure. T807 PET with MRI overlay of brain of former athlete with clinically probable CTE. Serpentine red-yellow signal (e.g., at white arrow) localized to white matter, especially at gray matter-white matter junction, is consistent with consensus criteria for diagnosis of CTE at autopsy (36). A complete case report of this subject is in preparation (Dickstein et al.).



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