OXFORD
UNIVERSITY PRESS

Archives of Clinical Neuropsychology 33 (2018) 644–648

Archives of CLINICAL NEUROPSYCHOLOGY

Chronic traumatic encephalopathy is not a real disease

Christopher Randolph*

Neurology, Loyola University Medical Center, Maywood, IL, USA

*Corresponding author.
E-mail address: crandol@lumc.edu.

Editorial Decision 18 April 2018; Accepted 16 July 2018

Abstract

There was a long-lasting debate during the first half of the 1900s about whether boxers suffered from a condition called "dementia pugilistica". This included arguments as to whether there was such a distinct clinical condition, whether it was static or progressive, and whether boxers were actually at any increased risk of any neurological issues at all. The debate was never resolved, but was resuscitated in 2005 with the speculation that a similar condition, dubbed "chronic traumatic encephalopathy (CTE)" existed in retired National Football League (NFL) players. A specific pattern of p-tau deposition has been identified in the brains of NFL retirees, and also identifiable in the brains of at least a percentage of individuals exposed to contact sports in general. Advocates of CTE as a disease describe it as presenting with behavioral disturbance, increased suicidality and neurodegeneration leading to dementia. The evidence to date, however, does not rise to the level of a verifiable disease, and remains at the level of case report. To assume that CTE pathology represents a neurodegenerative disease flies in the face of a number of facts, including that traumatic brain injury does not cause neurodegeneration, protein deposits in the brain are a poor predictor of behavioral symptoms, p-tau is not necessarily toxic or self-propagating, and retired NFL players are actually much physically and mentally healthier than men of their demographic background. They have an all-cause mortality rate that is 50% of that expected, and a suicide rate that is 40% of that expected. The most parsimonious explanation of the evidence to date is that repetitive head trauma may result in p-tau deposition, but that this isoform of p-tau is inert and has no toxic or self-propagating effects.

Keywords: Head injury; Traumatic brain injury

Editor's Note

This paper was originally solicited as part of the Point – Counterpoint series. It received the standard peer review process. Unfortunately, the authors of the Counterpoint article did not submit a revision of their original manuscript. The editorial team decided that it would be unfair to penalize Dr. Randolph for this and that his paper could be published on its own merit.

Jacobus Donders
Associate Editor

Background

Over the first half of the 20th century, a debate was waged as to whether retired boxers were at increased risk for some type of chronic or progressive encephalopathy. Such a condition was neither firmly established on an epidemiological basis, nor was any unique clinical syndrome ever defined or validated. From a neuropathological standpoint, one of the most recent and commonly cited articles was by Corsellis, Bruton, and Freeman-Brown (1973), who examined the brains of 15 boxers who were institutionalized prior to their death, predominantly for dementia. There were no neuropathological findings that were consistent across all cases, but the most commonly observed findings were neurofibrillary tangles (NFT) in the cortex, loss of pigmented cells in the substantia nigra, cavum septum pellucida and cerebellar scarring. Amyloid plaques were observed in only four cases, suggested some difference from classic Alzheimer-type pathology. Roberts et al. (1990) followed

doi:10.1093/arclin/acy063

this study up by re-examining 14 of the 15 brains studied by Corsellis, adding six new cases of boxers, and compared these with 20 cases of patients diagnosed in life with Alzheimer's disease (AD), with an additional 20 age-matched normal controls. Immunocytochemical methods were utilized for identifying cerebral amyloid. The conclusion from this study was that "The molecular markers present in the plaques and tangles of dementia pugilistica (DP) are the same as those in AD. Similarities in the clinical symptoms, distribution of pathology and neurochemical deficits also exist". Their final conclusion was that "It is probable that DP and AD share common pathogenic mechanisms leading to plaque and tangle formation". This begs the question, of course, as to why these authors did not come to the more parsimonious conclusion that they were simply studying the brains of boxers who had developed AD.

Little more attention was paid to this topic for next 20 years or so. The term "chronic traumatic encephalopathy (CTE)", which had never gained much traction during the approximate 50-year debate about retired boxers was resurrected by Omalu and colleagues (2005, 2006) in neuropathological reports of two retired National Football League (NFL) players. One case had diffuse amyloid plaques in the cortex and sparse NFT, the other had little or no amyloid and diffuse NFT. Subsequently, McKee and colleagues at Boston University have redefined CTE pathologically as consisting of patterns of phosphorylated-tau (p-tau) around small vessels in the depths of the cortical sulci. In their most recent paper (Mez et al., 2017), they reported finding CTE in the brains of 110 of 111 (99%) retired NFL players in a sample of convenience; i.e., brains donated by concerned family members. McKee and colleagues conceptualize CTE as a progressive neurodegenerative disorder leading to dementia. In McKee et al. (2013), they described the hypothesized clinical syndrome of CTE as follows: "CTE is clinically associated with symptoms of irritability, impulsivity, aggression, depression, short-term memory loss and heightened suicidality that usually begins 8−10 years after experiencing repetitive mild traumatic brain injury". They go on to propose that this progresses to a degenerative dementing disorder.

Since the average retirement age for NFL players is around 30, according to McKee and colleagues, we should expect a very high percentage of retired NFL players to begin experiencing symptoms by the time they are 40, followed by increased rates of suicide and progressive dementia, presumably resulting in relatively early death. Even accounting for the fact that their sample was one of convenience, a 99% rate of CTE pathology would suggest that there still should be a high prevalence in an unbiased sample.

There are a number of scientific shortcomings to the CTE hypotheses tendered by McKee and colleagues at the "Boston CTE Center" (see below), but they have captured the popular imagination and their press releases have been widely covered in the media. It is reasonable to conclude that the general public believes that CTE is a real disease, afflicting retired athletes at a high rate, despite a number of cautionary peer-reviewed publications to the contrary (e.g., Karantzoulis and Randolph, 2013; Manley et al., 2017; Randolph, 2014). The primary problem with this approach to "discovering" a disease is that it is essentially repeats the mistakes made by researchers like Corsellis and Roberts, who explored the brains of individuals with premortem behavioral and/or cognitive abnormalities for pathology, then assumed that the pathological features they identified were associated with the premortem symptoms and moreover generalizable to others in the same occupational population. This is the neuropathological dog wagging the clinical in a most inappropriate and unjustifiable way. Here are the major reasons why CTE as hypothesized by McKee and colleagues is not only highly improbable, but essentially unsupportable as a true disease:

(1) **Traumatic brain injury does not cause neurodegenerative disease:** This is almost never discussed in articles about CTE, but is not even necessary to resort to literature citations to establish this as fact in a neuropsychology journal. The natural history of recovery from various levels of traumatic brain injury (TBI) at all ages is well understood, and follows a course of acute impairment, recovery to some level depending in large part upon the severity of the injury, and stabilization. This is true for mechanical injury, stroke, penetrating injuries, neurosurgical interventions and acute infectious processes. To assume that minor traumatic brain injury, even if repetitive, can trigger a neurodegenerative disease flies in the face of both logic and evolutionary forces. Mild TBI is ubiquitous, occurring well over a million times per year in the US alone (Bazarian et al., 2005), and repetitive mild cerebral trauma is nothing new to humans (or other animal species, for that matter) in the course of play, organized sport or physical conflicts. Any genetic mechanism that triggered a fatal neurodegenerative disease from a minor trauma, or multiple mild traumas, would be unlikely to survive evolutionary forces to exist in more than a small minority of a population, if at all. It is worth mentioning the concept of cognitive and cerebral reserve here, to note that any significant damage to the brain is likely to lower the threshold at which late-life neurodegenerative diseases become symptomatically evident. This is not, however, evidence of a "new" disease, or even of increased risk for an established disease. It is an increased risk for earlier clinical expression of an underlying neurodegenerative disease, due to diminished reserve. Both cognitive and cerebral reserve are well-established factors in determining the onset of symptomatology in neurodegenerative diseases like AD (e.g., Groot et al., 2017). It is conceivable that repetitive

cerebral trauma could reduce cerebral reserve, but it seems hardly credulous that it could trigger a neurodegenerative disorder for the reasons iterated above.

(2) **Pathological protein deposition in the brain is a poor predictor of symptoms:** There is an assumption among both the general public, and much of the scientific community that abnormal protein deposits in the brain are definitively indicative of a disease and must have some clinical effects. The reality is that this is far from the truth. Even in a well-established disorder like AD, neuropathology in terms of plaque and tangle burden are only loosely associated with clinical symptomatology. The best illustration of this comes from longitudinal cohort studies conducted at Rush University Medical Center in Chicago, involving blinded neuropathological examination. These studies included brain donation from subjects who underwent extensive annual examinations that included neurological and neuropsychological assessments. Bennet et al. (2006) reported that 37% of subjects who were determined to be cognitively normal within a year of death met pathological criteria for AD. This is actually slightly higher than the percentage of individuals in the same studies who had pure AD pathology at autopsy and were clinically diagnosed with dementia due to AD (Schneider, Arvanitikas, Bang & Bennett, 2007). In other words, the predictive value of definitive AD pathology for clinical symptoms during the year prior to death was no better than the flip of a coin. The advent of cerebral amyloid imaging and cerebrospinal fluid amyloid assays has provided *in vivo* correlative evidence that many individuals with high levels of cerebral amyloid remain clinically normal, and the predictive value of cerebral amyloid burden for the onset of clinical symptomatology remains largely unknown.

(3) **The p-tau deposits that characterize CTE may be inert and not self-propagating or neurotoxic:** There are many different isoforms of p-tau, and not all of them are associated with a neurodegenerative disorder. Hyperphosphorylation of tau can occur as a result of a number of conditions that do not involve progressive neurodegeneration, including brain trauma (Genis, Chen, Shohami & Michaelson, 2000), hypoxia (Gao, Tian, Gao & Xu, 2013) and stroke (Wen et al., 2007). If minor brain trauma results in deposition of p-tau, it is conceivable that this p-tau is inert and has no intrinsic clinical effect or self-propagating activity. It is also worth pointing out that NFTs are ubiquitous in individuals over a certain age: 97% of cognitively normal adults at autopsy have been reported to meet criteria for Braak Stage 1 or higher (Bennet et al., 2006). Therefore, it is abundantly clear that "abnormal" cerebral protein deposits may not actually be that abnormal, are not very predictive at all of clinical symptomatology, and cannot be assumed to be representative of a neurodegenerative disease that will ever become clinically evident. It is also important to point out here that the Boston University sample is a sample of convenience, consisting of brains donated by family members who were concerned about premortem behavioral and/or cognitive changes. Little attention has been paid to the fact that the majority of these brains contain evidence of known neurodegenerative disorders. In the Mez et al. (2017) report on CTE in deceased American football players, of those players with findings of CTE 61% had evidence of amyloid beta, 58% had diffuse amyloid plaques, 41% had neuritic amyloid beta plaques, 39% had amyloid angiopathy, 48% had TDP-43 and 24% had alpha-synuclein Lewy bodies. It is therefore conceivable that the premortem symptoms exhibited by these men were attributable to known neurodegenerative diseases (or other disorders), and that the CTE pathology did not contribute to symptomatology. This hypothesis is supported by the findings of Bieniek et al. (2015), who explored CTE in a neurodegenerative disorders brain bank. They found CTE in the brains of 21 of 66 former contact sports athletes, but not in the brains of 198 individuals without contact sports exposure. The athletes with CTE did not, however, differ with respect to any premortem clinical characteristics or levels or patterns of comorbid neuropathologies compared to the athletes without CTE. This paper certainly suggests an increased risk of CTE p-tau deposits associated with contact sports, but does not suggest that the presence of CTE is associated with different premortem symptoms or comorbid neuropathology. Again, the most parsimonious interpretation of these data would be that the CTE p-tau patterns are not contributing to symptoms or increasing the risk of neurodegenerative disease in general.

(4) **There is no evidence of increased central nervous system disease in retired NFL players, who are much mentally and physically healthier than their demographic cohort:** In the most rigorous epidemiological study of retired NFL players to date, Baron, Hein, Lehman, and Gersic (2012) examined mortality cause and rates in over 3,400 NFL retirees who were members of the pension plan, having played in at least five seasons. The all-cause mortality rate compared to men of their demographic background was approximately 50% of that expected, and their suicide rate was only 41% of that expected. This is directly at odds with the report by McKee et al. that 99% of retired NFL players have CTE, and their hypothesis that this is associated with symptom onset 8–10 years post-injury, with increased suicidality and progressive dementia following. Lehman, Hein, Baron, and Gersic (2012) reported on the same sample in a subsequent paper that death rates due to neurodegenerative diseases (specifically AD and amyotrophic lateral sclerosis) were somewhat higher than expected, but this was only seen in players at "speed" positions, and the absolute numbers were no more than a handful of cases, leading them to conclude that

"these results were highly imprecise because of the small numbers". Moreover, it is worth pointing out that when mortality rates due to causes like cardiovascular disease, suicide, and cancer are dramatically reduced, late-life causes of death should rise proportionally. Since the "speed" position players were found to be generally healthier, it is not surprising that they would be more likely to live to the point where they would be at increased risk of late-life neurodegenerative disease.

(5) **The clinical presentation of retired NFL players who do have cognitive problems is not unique, and is explainable by known diseases:** We examined the neurocognitive profile of 41 retired NFL players who were recruited for a treatment study of mild cognitive impairment (MCI; Randolph, Karantzoulis & Guskiewicz, 2013). These subjects were identified as having probable MCI on the basis of telephone interviews with subjects and spouses, along with a telephone cognitive screening. These 41 NFL retirees were compared to 41 health controls and 81 patients with a clinical diagnosis of amnestic MCI with respect to their profile across domains of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The profile of performance of the retired NFL players was essentially identical to that of the amnestic MCI sample. This suggests a common pathophysiology; i.e., that both the clinical sample and the NFL retirees were in the early symptomatic stage of AD. A second study recruited 34 NFL retirees for a study of depression and cognitive impairment (Hart et al., 2013). These retirees underwent extensive neuropsychological and neurological evaluations, and the investigators did not identify any unique clinical syndrome, concluding specifically that "none of the retired players fit the reported profile for CTE at the time of the examination" (p. 331).

Summary

The current reincarnation of "dementia pugilistica" is based upon a series of unblinded neuropathological examinations of a sample of convenience. McKee and colleagues have defined the pathological criteria of CTE as consisting of a pattern of p-tau deposition around small vessels in the depths of the cortical sulci, and established what they consider to be a staging system for severity. They have reported finding CTE in 99% of the brains of retired NFL players that they have examined. In addition, they have posited that the clinical symptoms.

This flies in the face of medical logic, known facts about recovery from cerebral trauma, and epidemiological data on retired NFL players, who retire on average at about age 30 and go on to have dramatically *reduced* suicide and all-cause mortality rates compared to men of their demographic background in the USA. In addition, the majority of the brains studied by McKee and colleagues had evidence of other known neuropathologies that could have accounted for premortem symptoms, to the extent that such symptoms existed. This hypothesis is supported by the findings of Bieniek et al. (2015), who found evidence of CTE in approximately a third of brains of individuals with contact sports exposure, but no difference between cases with or without CTE in terms of premortem diagnosis or comorbid neurodegenerative disease.

The scientific evidence for CTE as a putative disease remains at the lowest level of credibility; i.e., case reports. To establish a disease risk from occupational or lifestyle exposure requires epidemiological evidence and clinical diagnosis. Neither of those sources of evidence exist for CTE, and publicizing this as an established disease to the general public is not only scientifically unjustified, it is irresponsible. Webner and Iverson (2016) revisited suicide rates in retired NFL players over the past 95 years. They confirmed the Baron et al. (2012) findings that retired NFL players overall have much lower rates of suicide then men of their demographic background, but noted that this rate has increased since 2009. The authors speculated that the media coverage regarding CTE might have contributed to this. In other words, it is conceivable that some retired players with treatable diseases (e.g., depression) may have come to believe that they were suffering from a fatal neurodegenerative disease and chose the path of suicide as a result. It is incumbent upon the medical and scientific community to "first do no harm", and while concerns about the late-life effects of repetitive head trauma are legitimate, we must communicate the state of the evidence regarding potential risks to the general public in a balanced and responsible way. To date, there are absolutely no credible data to suggest a quantifiable increased risk of any neurological disorder in retired NFL players (or contact sports participants in general), and this is a message that needs to be delivered while research into the issue continues.

Conflict of interest

None declared.

References

Baron, S. L., Hein, M. J., Lehman, E., & Gersic, C. M. (2012). Body mass index, playing position, race, and the cardiovascular mortality of retired professional football players. *American Journal of Cardiology*, *109*, 889–896.

Bazarian, J. J., McClung, J., Shah, M. N., Cheng, Y. T., Flesher, W., & Kraus, J. (2005). Mild traumatic brain injury in the United States, 1998–2000. *Brain Injury*, *19*, 85–91.

Bennet, D. A., Schneider, J. A., Arvanitakis, Z., Kelly, J. F., Aggarwal, N. T., Shah, R. C., et al. (2006). Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology*, *66*, 1837–1844.

Bieniek, K. F., Ross, O. A., Cormier, K. A., Walton, R. L., Soto-Ortolaza, A., Johnson, A. E., et al. (2015). Chronic traumatic encephalopathy pathology in a neurodegenerative disorders brain bank. *Acta Neuropathology*, *130*, 877–899.

Corsellis, J. A., Bruton, C. J., & Freeman-Brown, D. (1973). The aftermath of boxing. *Psychological Medicine*, *3*, 270–303.

Gao, L., Tian, S., Gao, H., & Xu, Y. (2013). Hypoxia increases Abeta-induced tau phosphorylation by calpain and promotes behavioral consequences in AD transgenic mice. *Journal of Molecular Neuroscience*, *51*, 138–147.

Genis, L., Chen, U., Shohami, E., & Michaelson, D. M. (2000). Tau hyperphosphorylation in apoliprotein E-deficient and control mice after closed head injury. *Journal of Neuroscience Resarch*, *60*, 559–564.

Groot, C., van Loenhoud, A. C., Barkhof, F., Bart, N. M., van Berckel, B. N. M., Koene, T., et al. (2017). Differential effects of cognitive reserve and brain reserve on cognition in Alzheimer disease. *Neurology*, *90*, e149–e156.

Hart, J., Kraut, M. A., Womack, K. B., Strain, J., Didehbani, N., Bartz, E., et al. (2013). Neuroimaging of cognitive dysfunction and depression in aging retired National Football League players: a cross-sectional study. *JAMA Neurology*, *70*, 326–335.

Karantzoulis, S., & Randolph, C. (2013). Modern chronic traumatic encephalopathy in retired athletes: what is the evidence? *Neuropsychology Review*, *23*, 350–360.

Lehman, E. J., Hein, M. J., Baron, S. L., & Gersic, C. M. (2012). Neurodegenerative causes of death among retired National Football League players. *Neurology*, *79*, 1970–1974.

Manley, G. T., Gardner, A. J., Schneider, K. J., Gukiewicz, K. M., Bailes, J., Cantu, R. C., et al. (2017). A systematic review of the potential long-term effects of sport-related concussion. *British Journal of Sports Medicine*, *51*, 969–977.

McKee, A. C., Stein, T. D., Nowinski, C. J., Stern, R. A., Daneshvar, D. H., Alvarez, V. E., et al. (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain*, *136*, 43–64.

Mez, J., Daneshvar, D. H., Keiman, P. T., Abdolmohammadi, B., Alvarex, V. E., Huber, B. R., et al. (2017). Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. *Journal of the American Medical Association*, *318*, 360–370.

Omalu, B. I., DeKosky, S. T., Hamilton, R. L., Minster, R. L., Kamboh, M. I., Shakir, A. M., et al. (2006). Chronic traumatic encephalopathy in a National Football League player: Part II. *Neurosurgery*, *59*, 1086–1092.

Omalu, B. I., DeKosky, S. T., Minster, R. L., Kamboh, M. I., Hamilton, R. L., & Wecht, C. H. (2005). Chronic traumatic encephalopathy in a National Football League player. *Neurosurgery*, *57*, 128–134.

Randolph, C. (2014). Is chronic traumatic encephalopathy a real disease? *Current Sports Medicine Reports*, *13*, 33–37.

Randolph, C., Karantzoulis, S., & Guskiewicz, K. M. (2013). Prevalence and characterization of mild cognitive impairment in retired National Football League players. *Journal of International Neuropsychological Society*, *19*, 873–880.

Schneider, J. A., Arvanitikas, Z., Bang, W., & Bennett, D. (2007). Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*, *69*, 197–204.

Webner, D., & Iverson, G. (2016). Suicide in Professional American Football Players in the Past 95 Years. *Brain Injury*, *30*, 1718–1721.

Wen, Y., Yang, S. H., Liu, R., Perez, E. J., Brun-Zinkernagel, A. M., Koulen, P., et al. (2007). Cdk5 is involved in NFT-like tauopathy induced by transient cerebral ischemia in female rats. *Biochimica et Biophysica Acta*, *1772*, 473–483.