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Football and Chronic Traumatic Encephalopathy: How Much Evidence Actually Exists?

Karam Moon and Nicholas Theodore

Chronic traumatic encephalopathy (CTE) has been in the news headlines in recent years, primarily due to increasing scrutiny of repetitive traumatic brain injury (TBI) suffered by football players. The media coverage has focused largely on high-profile autopsy studies of former National Football League players, such as Junior Seau, whose suicides have been attributed to CTE. The diagnosis and pathology are not new. The clinical syndrome was first described in the 1920s as dementia pugilistica (DP) by Martland in relation to a cohort of boxers, although gross neuroanatomic findings, such as cavum septum, cortical scarring, and degeneration of the substantia nigra, in DP have not been included in the modern-day characterization of CTE by Omalu et al. However, recent reviews have examined the individual case series of CTE reported to date and have questioned the association between CTE and sports-related concussion.

In particular, Davis et al. recently performed an extensive review of available clinical and pathologic evidence for sports-related CTE and concluded that much of the evidence has been inconsistent or poorly differentiated from evidence indicative of other neurodegenerative diseases. For example, Davis et al. argue that the index cases of modern CTE were ambiguous clinical accounts, with tau and amyloid deposition appropriate for the subjects’ ages and insufficient evidence of brain atrophy, all of which lends little support to a causal relationship between CTE and suicidal tendencies. Another recent series by McKee et al. compared a cohort
of concussed athletes with a control group of patients from the Framingham Heart Study—an inadequate control, given the significant differences in the cohort profile. Similarly, recent studies have largely failed to control for potentially confounding factors, such as underlying depression or anxiety, familial or genetic predisposition to psychiatric illness, or even opioid use, which has been correlated with hyperphosphorylated tau deposition.\(^8\) Finally, much of the overlapping clinical and pathologic findings described in CTE, Alzheimer disease (AD), and frontotemporal dementia have been based on small sample sizes, and the methodology of recent CTE studies does not allow us to accurately characterize CTE as a separate entity yet, especially given the complex nature of the proteins involved (i.e., tau, amyloid beta, and TDP-43).

The answer may be murkier, as Bailes et al.\(^9\) suggested in a recent article based on their 2014 CNS Annual Meeting presentation, given some striking similarities in the accounts of athletes diagnosed with CTE. First, they described a latency period of 6–12 years after retirement from a contact sport, followed by well-documented disorders of behavior, cognition, mood, and motor control. Second, they pointed out that the increased risk of suicide in athletes with CTE stands in stark contrast to that of patients with other tauopathies such as AD. Furthermore, whereas neurodegenerative diseases can often be comorbid, a recent report from the National Institutes of Health characterized several neuropathologic features seemingly unique to CTE, including topographic tau distribution and the absence of classic amyloid plaques and other pathognomonic changes of other tauopathies.\(^10\) This report reaffirmed CTE as a distinct neuropathologic diagnosis. As with susceptibility to any neurodegenerative disease, however, that of a repetitively concussed athlete to development of CTE is likely due, in large part, to genetics and environment. Although the apolipoprotein E (APOE) allele has been postulated as a potential risk factor, the e4 version of the APOE gene is also significantly associated with AD;
thus no definitive genetic marker for CTE yet exists. What remains difficult, however, is that, while recent laboratory studies have begun to characterize CTE as a distinct entity, an increasing body of evidence supports a delineated subset of clinical and neuropathologic features shared by CTE and neurodegenerative diseases such as AD and Parkinson disease (PD, Figure 1).11

Ultimately, there are likely numerous causes of dementia and cognitive decline in retired athletes, a patient population already at a higher independent risk for substance abuse, depression, and suicide. Immunohistochemical studies have come a long way but have much further to go, given the small numbers of CTE patients and potentially confounding variables, such as the involvement of tau in normal aging and opioid use, as well as environmental and genetic risk factors in concussed athletes. Future research will no doubt address causation. Furthermore, as we find more differences between CTE and other entities such as AD and PD, we also simultaneously find more shared characteristics, which raises the question of whether the diagnoses of CTE and AD or PD are mutually exclusive. Does genetic susceptibility to one increase the risk of developing the other? Longitudinal studies may one day answer such questions, provided they use appropriate cohort comparisons and control groups to evaluate variables such as the environmental factors, genetic predisposition, and confounders mentioned earlier. While we may understand more about TBI and concussion today than ever before, our understanding of CTE and its relation to sport remains in its infancy, underscoring the role of the neurosurgeon in interpreting the latest evidence and using it to advocate for a safer playing field for all.
References


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Figure 1. The clinical and pathologic findings of chronic traumatic encephalopathy have been found to overlap those of Alzheimer disease (AD) and Parkinson disease (PD). (From Bailes JE, Turner RC, Lucke-Wold BP, Patel V, Lee JM. Chronic traumatic encephalopathy: is it real? The relationship between neurotrauma and neurodegeneration. *Neurosurgery.* 2015;62:15-23. Used with permission from *Neurosurgery.*)