REFERENCES

1. Matthews TJ, MacDorman MF, Thoma ME. Infant mortality statistics from the 2013 period linked birth/infant death data set. *Natl Vital Stat Rep*. 2015;64(9):1-30.

2. Willinger M, Hoffman HJ, Wu KT, et al. Factors associated with the transition to nonprone sleep positions of infants in the United States: the National Infant Sleep Position Study. *JAMA*. 1998;280(4):329-335.

3. Moon RY; Task Force on Sudden Infant Death Syndrome. SIDS and other sleep-related infant deaths: evidence base for 2016 updated recommendations for a safe infant sleeping environment. *Pediatrics*. 2016;138(5):e20162940.

4. Colson ER, Levenson S, Rybin D, et al. Barriers to following the supine sleep recommendation among mothers at four centers for the Women, Infants, and Children program. *Pediatrics*. 2006;118(2):e243-e250.

5. Moon RY, Oden RP, Joyner BL, Ajao TI. Qualitative analysis of beliefs and perceptions about sudden infant death syndrome in African-American mothers: implications for safe sleep recommendations. *J Pediatr*. 2010;157(1):92-97.e2, e92.

6. Moon RY, Hauck FR, Colson ER, et al. The effect of nursing quality improvement and mobile health interventions on infant sleep practices: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2017.8982

7. Smith LA, Geller NL, Kellams AL, et al. Infant sleep location and breastfeeding practices in the United States, 2011-2014. *Acad Pediatr*. 2016;16(6):540-549.

8. Shapiro-Mendoza CK, Colson ER, Willinger M, Rybin DV, Camperlengo L, Corwin MJ. Trends in infant bedding use: National Infant Sleep Position study, 1993-2010. *Pediatrics*. 2015;135(1):10-17.

9. Ostfeld BM, Schwartz-Soicher O, Reichman NE, Teitler JO, Hegyi T. Prematurity and sudden unexpected infant deaths in the United States. *Pediatrics*. 2017;140(1):e20163334.

10. Moon RY, Hauck FR, Colson ER. Safe infant sleep interventions: what is the evidence for successful behavior change? *Curr Pediatr Rev*. 2016;12(1):67-75.

11. Colson ER, Joslin SC. Changing nursery practice gets inner-city infants in the supine position for sleep. *Arch Pediatr Adolesc Med*. 2002;156(7):717-720.

12. Parks SE, Erck Lambert AB, Shapiro-Mendoza CK. Racial and ethnic trends in sudden unexpected infant deaths: United States, 1995-2013 [published online May 15, 2017]. *Pediatrics*. doi:10.1542/peds.2016-3844

13. Hawkins RP, Kreuter M, Resnicow K, Fishbein M, Dijkstra A. Understanding tailoring in communicating about health. *Health Educ Res*. 2008;23(3):454-466.

Advances and Gaps in Understanding Chronic Traumatic Encephalopathy

From Pugilists to American Football Players

Gil D. Rabinovici, MD

Traumatic brain injury (TBI) is a major public health concern, affecting an estimated 10 million people worldwide per year and more than 40% of US residents over the course of a lifetime.[1,2] Mild TBI, also referred to as concussion, is defined as blunt, nonpenetrating head trauma associated with transient symptoms (eg, headache, nausea, dizziness, visual changes, confusion, or difficulty concentrating) and accounts for more than 80% of all TBI cases. Beyond the morbidity of the immediate trauma, patients who experience mild TBI are at increased risk of developing neurological and psychiatric disorders later in life.[3] The majority of TBI is caused by motor vehicle crashes and falls, although brain injuries also occur during participation in contact sports, with an estimated 1.6 million to 3.8 million sports-related concussions occurring in the United States per year.[4]

Related article page 360

In a report published in *JAMA* in 1928, Martland[5] introduced the term *punch drunk* to describe a syndrome of motor slowing and neuropsychiatric decline affecting boxers exposed to repetitive head trauma. Work over the following decades provided additional evidence for a unique neurodegenerative syndrome associated with repetitive TBI.[6] The condition was renamed dementia pugilistica and later chronic traumatic encephalopathy (CTE), the currently preferred term. In 2005, Omalu et al[7] published the first report of CTE in a retired professional American football player, an observation that was soon replicated in additional case series and extended to include athletes exposed to repetitive TBI in other contact sports, as well as military veterans, survivors of intimate partner violence, and persons exposed to other TBI-associated conditions.[8]

In this issue of *JAMA*, Mez and colleagues report neuropathological findings from 202 deceased players of American football who were assessed as part of a brain bank established to study the neuropathological sequelae of repetitive TBI.[9] This study represents the largest CTE cohort published to date. To put the size of the cohort in perspective, a comprehensive review published in 2009 identified a total of 48 cases of confirmed CTE (due to any cause) in the medical literature.[6]

The diagnosis of CTE in the present study was made blinded to clinical information, applying recently published consensus criteria developed by a panel of experts convened by the National Institutes of Health.[10] Postmortem diagnosis of CTE hinges on the presence of phosphorylated tau aggregates in neurons, astrocytes, and cell processes around small blood vessels, often present at the depths of cortical sulci. Tau is a neuronal protein that under normal conditions binds to microtubules and plays a role in cytoskeletal support, axonal transport, and cell-signaling pathways.[11] Under pathological conditions, tau undergoes phosphorylation and acetylation and tends to aggregate, initially into toxic soluble oligomers and ultimately into insoluble fibrillar aggregates. Phosphorylated tau aggregates are a core feature of a variety of neurodegenerative conditions including Alzheimer disease, frontotemporal lobar degeneration, and others. One of the features that distinguishes the phosphorylated tau lesions of CTE from those found in other disorders is the unique distribution of aggregates in perivascular regions and at the depths of cortical sulci.

Biomechanical models suggest that these regions are particularly susceptible to stress and strain forces when exposed to rapid acceleration/deceleration in mild TBI, providing a potential mechanistic link between acute injury and the distribution of tau aggregation in CTE.[12] Because CTE can presently only be diagnosed at autopsy, the evidence linking repetitive TBI to the disease is by necessity cross-sectional and correlative. However, to date there have been no reported cases of CTE in the literature occurring in the absence of antecedent TBI, and as knowledge of the disorder increases, a relationship that is not founded on cause and effect becomes increasingly implausible.

The primary finding in the present report is that 177 (87%) of 202 former football players, including 117 (98.3%) of 119 who played professionally in the United States or Canada, met neuropathological criteria for CTE. This result, while concerning, needs to be interpreted with some caveats. First, the cohort represents a convenience sample of former players whose brains were donated for research (usually by next of kin). As the investigators acknowledge, such a sample is likely to be biased to include more impaired individuals who experienced significant neuropsychiatric decline during life, thus prompting their family members to pursue brain donation.

Indeed, in semistructured interviews between the researchers and patient informants (both blinded to pathology), the prevalence of cognitive and behavioral symptoms in the autopsy cohort was 88% and 95%, respectively. In contrast, questionnaire-based ascertainment of neuropsychiatric symptoms among retired National Football League players found that the prevalence of memory symptoms and depression was 5% to 20%.[13,14] Acknowledging that questionnaires are an insensitive method for detecting neurodegenerative disease, the large discrepancy between these rates and those found in brain donors suggest that the rates of symptomatic CTE may be lower in an unselected cohort of former players. Furthermore, 69% of players in the present sample played professional or semiprofessional football and only 3% participated only in high school or youth football. Thus, the sample is heavily weighted toward individuals with very high exposure to football in terms of duration of play and frequency and magnitude of TBI. In the general population, the vast majority of individuals who play football do not participate beyond high school. Early-stage CTE was found in 3 of 14 high school football players, suggesting that high school football exposure can be sufficient to yield associations with early neuropathological features of the disease. However, it is important to note that a link between high school football participation and neurological decline later in life is not well established.[15]

In addition to characterizing tau pathology, the investigators performed an extensive evaluation for other protein aggregates associated with neurodegeneration, including amyloid-β, α-synuclein, and transactive response DNA binding protein 43. They found a high prevalence of these co-pathologies, with only 55% of patients showing isolated CTE and the remainder meeting additional neuropathological criteria for Alzheimer disease, Lewy body disease, frontotemporal lobar degeneration, or motor neuron disease. The high prevalence of these co-pathologies raises the possibility that repetitive TBI represents a risk factor for multiple neurodegenerative proteinopathies. Previous studies have described the extent and contribution of these co-pathologies to the course of CTE in greater detail.[16,17] Axonal injury and neuroinflammation are key elements in the pathophysiology of acute and chronic TBI[18] and may contribute to clinical manifestations in CTE, particularly in early pathologic stages, when tau pathology appears patchy and sparse in comparison with the gravity of neuropsychiatric impairment.

The retrospective informant interviews conducted in the present study, in conjunction with prospective assessments of high-risk patients,[19,20] contribute to the current understanding of the clinical features of CTE. Patients can present with a primary psychiatric syndrome characterized by impulsive, explosive, and sometimes violent behavior; depression; and a tendency to suicidality. This phenotype is associated with younger age and an earlier stage of CTE pathology. Older patients often present with a primary cognitive disorder involving memory loss and executive dysfunction that can mimic Alzheimer disease, may be accompanied by parkinsonism and other motor features, and is associated with more advanced tau pathology. Most often, patients present with a mix of cognitive, mood, and behavioral features. Potentially treatable contributing factors are found in many patients, including high rates of substance abuse, affective disorders, headaches, and sleep disturbances. Thus, at-risk patients may benefit from a multidisciplinary medical team to optimize symptomatic treatment and maximize patient function and quality of life.

Nearly 90 years following Martland's seminal report, there has been substantial progress in describing the neuropathology of CTE, and the study by Mez and colleagues represents a major contribution to this effort. Nevertheless, fundamental questions about the disorder remain unresolved. What is the incidence and prevalence of CTE in population-based samples? What is the magnitude of risk associated with participating (and allowing children to participate) in various contact sports? Are there individual susceptibility and resilience factors that modify the risk or expression of the disease? What are the mechanisms that link acute TBI to a latent neurodegenerative process, and what is the best way to intervene? Addressing these questions will require improved disease models, and prospective studies in at-risk populations using an expanding armamentarium of biomarkers.[18] Increased medical and public awareness around the diagnosis and prevention of TBI remains paramount. Toward the conclusion of his article, Martland stated "The condition can no longer be ignored by the medical profession or the public." This assertion remains as relevant today as when first written in 1928.

ARTICLE INFORMATION

Author Affiliation: Memory and Aging Center, Department of Neurology, University of California San Francisco, California.

Corresponding Author: Gil D. Rabinovici, MD, Memory and Aging Center, MC 1207, University of California, San Francisco, 675 Nelson Rising Ln, Ste 190, San Francisco, CA 94158 (gil.rabinovici@ucsf.edu).

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Rabinovici receives research support from Avid Radiopharmaceuticals, Eli Lilly, GE Healthcare,

and Piramal. He has received consulting or speaking honoraria from Eisai, Genentech, Lundbeck, Merck, Putnam, and Roche and receives an honorarium for his duties as an Associate Editor for *JAMA Neurology*.

REFERENCES

1. Whiteneck GG, Cuthbert JP, Corrigan JD, Bogner JA. Risk of negative outcomes after traumatic brain injury: a statewide population-based survey. *J Head Trauma Rehabil*. 2016;31(1):E43-E54.

2. Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC. The impact of traumatic brain injuries: a global perspective. *Neurorehabilitation*. 2007;22(5):341-353.

3. Perry DC, Sturm VE, Peterson MJ, et al. Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis. *J Neurosurg*. 2016;124(2):511-526.

4. Daneshvar DH, Nowinski CJ, McKee AC, Cantu RC. The epidemiology of sport-related concussion. *Clin Sports Med*. 2011;30(1):1-17.

5. Martland HS. Punch drunk. *JAMA*. 1928;91:1103-1107.

6. McKee AC, Cantu RC, Nowinski CJ, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol*. 2009;68(7):709-735.

7. Omalu BI, DeKosky ST, Minster RL, Kamboh MI, Hamilton RL, Wecht CH. Chronic traumatic encephalopathy in a National Football League player. *Neurosurgery*. 2005;57(1):128-134.

8. McKee AC, Stern RA, Nowinski CJ, et al. The spectrum of disease in chronic traumatic encephalopathy. *Brain*. 2013;136(Pt 1):43-64.

9. Mez J, Daneshvar DH, Kiernan PT, et al. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. *JAMA*. doi:10.1001/jama.2017.8334

10. McKee AC, Cairns NJ, Dickson DW, et al; TBI/CTE Group. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathol*. 2016;131(1):75-86.

11. Morris M, Maeda S, Vossel K, Mucke L. The many faces of tau. *Neuron*. 2011;70(3):410-426.

12. Cloots RJ, Gervaise HM, van Dommelen JA, Geers MG. Biomechanics of traumatic brain injury: influences of the morphologic heterogeneities of the cerebral cortex. *Ann Biomed Eng*. 2008;36(7):1203-1215.

13. Guskiewicz KM, Marshall SW, Bailes J, et al. Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery*. 2005;57(4):719-726.

14. Guskiewicz KM, Marshall SW, Bailes J, et al. Recurrent concussion and risk of depression in retired professional football players. *Med Sci Sports Exerc*. 2007;39(6):903-909.

15. Janssen PH, Mandrekar J, Mielke MM, et al. High school football and late-life risk of neurodegenerative syndromes, 1956-1970. *Mayo Clin Proc*. 2017;92(1):66-71.

16. Stein TD, Montenigro PH, Alvarez VE, et al. Beta-amyloid deposition in chronic traumatic encephalopathy. *Acta Neuropathol*. 2015;130(1):21-34.

17. McKee AC, Gavett BE, Stern RA, et al. TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. *J Neuropathol Exp Neurol*. 2010;69(9):918-929.

18. Blennow K, Brody DL, Kochanek PM, et al. Traumatic brain injuries. *Nat Rev Dis Primers*. 2016;2:16084.

19. Montenigro PH, Baugh CM, Daneshvar DH, et al. Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome. *Alzheimers Res Ther*. 2014;6(5):68.

20. Gardner RC, Possin KL, Hess CP, et al. Evaluating and treating neurobehavioral symptoms in professional American football players: lessons from a case series. *Neurol Clin Pract*. 2015;5(4):285-295.