The Armageddon Fall 2017
LAW 744-001-17C
Expert Evidence
Klick

You are a junior associate for a firm brought in to defend the Pop Warner organization in a wrongful death suit brought on behalf of a former Pop Warner football player (Randy). Randy played wide receiver and kick returner in the league from the age of 10 through 14 and then continued to play two years of (non-Pop Warner) high school football. At the age of 17, Randy committed suicide after an extended period where he exhibited signs of depression, memory loss, and erratic behavior. In an autopsy performed after his death, Randy's brain tested positive for chronic traumatic encephalopathy (CTE). There is no history of depression or suicide in Randy's family.

Pop Warner is the oldest (started in 1929) and largest (approximately 250,000 participants per year) youth football program in the United States. It is organized as a non-profit headquartered in Langhorne, PA. In terms of safety precautions, Pop Warner has adhered to strict player weight limitations as described here http://www.popwarner.com/Default.aspx?tabid=1476162 . Similar weight restrictions are not used in other youth football leagues (e.g., CYO football) or in high school football. Pop Warner also uses state of the art football helmets, continually replacing its equipment any time a new safety technology is introduced in the helmet market, and the organization requires its coaches to be trained in "heads up" football (https://usafootball.com/programs/heads-up-football/youth/), which stresses the importance of avoiding head-to-head contact while teaching proper tackling and blocking techniques.

You are told to examine the arguments made by Pop Warner's general counsel, Tony Corleto, in the attached National Law Review essay. You are also directed to examine three articles (also attached) that have been offered by the plaintiff's experts as supporting the wrongful death claim: 1) PET Scanning of Brain Tau in Retired National Football League Players: Preliminary Findings [refer to it as the PET study]; 2) Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football [refer to it as the JAMA study]; and 3) Neurodegenerative causes of death among retired National Football League players [refer to it as the Neurology study]. The study "High School Football and Risk of Neurodegeneration: A Community-Based Study" [refer to it as the Community study] cited by Corleto is also attached. Corleto also invokes suicide statistics in his argument. Data on suicide rates (including rates by age and race, which may be relevant) are available at https://wonder.cdc.gov/ucd-icd10.html .

Focusing on just the attached articles, you are asked to draft a memo laying out Pop Warner's legal risks and counter arguments (from an expert evidence standpoint) in Randy's wrongful death case. You should also specifically address the arguments made by Corleto. Although the case is brought in Pennsylvania state court (and, therefore, Frye applies), you are asked to also discuss whether any of your analysis would differ under Daubert, since Pop Warner has reason to believe it will face similar claims in other courts.

THE
NATIONAL LAW REVIEW

0.44% of NFL Brains

Article By
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Client Alert Entertainment, Art & Sports
Health Law & Managed Care
All Federal

Wednesday, August 16, 2017

When *The New York Times* reports that 110 out of 111 NFL brains (99.09%) have chronic traumatic encephalopathy (CTE), everyone pays attention. Mothers worry about their kids. Some worry about their jobs. Senate subcommittees investigate. The Times article covers Dr. Ann McKee's recent article in the Journal of the American Medical Association, "Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football" (JAMA. 2017;318(4):360-370) in dramatic fashion, illustrated with pathology slides of tissue samples from the brains of former football players and anecdotal information about them. Such claims are certain to be fuel for CTE litigation and cries to ban tackle football.

Let's put this in perspective. About 25,000 men have played American professional football. So, 110 is roughly 0.44%. Even if the real number is double, the outcome remains a statistical nonentity.

In all fairness, the study points out some of its limitations; for example, "Ascertainment bias associated with participation in this brain donation program." Inclusion was based entirely on exposure to repetitive head trauma eliminating any form of "control" group, a necessary element of any scientific study. The authors also disclose that "public awareness of a possible link" between head trauma and CTE "may have motivated" some participants. Finally, the authors acknowledge that the study is not representative of the population of all American football participants, as most play only at the youth or high school level, whereas the majority of the donors played at the professional level. The study data somewhat illustrates that point: CTE was found in none of two pre−high school participants and three of 14 high school participants (21%).

Breaking It Down

The 800-pound gorilla in this room is suicide. Suicide among former football players gets major media attention (Junior Seau and Aaron Hernandez) and has spawned a cottage industry of CTE litigation against every level of the sport from NFL down to Pop Warner. The study tries to correlate neuropathology with "clinical observations" − information drawn from "retrospective interviews" with family members of deceased donors. Observations are grouped as cognitive, behavioral or mood or both, and signs of dementia. Suicide was identified as the cause of death in 10% of the study group. "Suicidality" (ideation, attempts or completion) is identified among 33% of the study group. Some might conclude that if you play football you are 33% more likely to contemplate or attempt suicide and 10% more likely to succeed.

In fact, the rate of suicide mortality among retired NFL players is substantially lower than in the general population. An investigation performed at the National Institute for Occupational Safety and Health (NIOSH) and published in 2016 (Lehman, et al.) found that among players retired since 1987, the suicide rate is 6.1 / 100,000. Among players retired since 2005, it's 12.5 / 100,000. Among average American men, the rate since 2014 is 20.1 / 100,000. One would conclude that since 2005, NFL players are 48% less likely to commit suicide than the general population, and since 1987, 70% less likely. The study covered those who played for five years or more.

Of note, drugs are assessed by standardized mortality ratio – the increase or decrease in mortality with respect to the general population. "If playing in the NFL (for a minimum of five seasons) were treated like taking a drug, it would reduce the standardized mortality (measured 30 years later) by half!" Samadani, Brain Injury and Football, Reality v. Perception. THSCA presentation, 2016.

Similar studies have been done at the college level where the NCAA maintains a robust database. A nine-year study published in October 2015 (Rao, et al.) observed that as against a rate of 12 / 100,000 among 18−22-year-old non-college individuals, the suicide rate among college students was 7.5 / 100,000. Among male NCAA athletes, the suicide rate was 2.25 / 100,000.

Another study dispels the notion that CTE is a path to neurological deficit. Published in Acta Neuropathol, "Histological Evidence of CTE in a Large Series of Neurodegenerative Diseases" (Ling, et al., 2015) observed that (1) CTE prevalence in people with neurodegenerative diseases (11.8%) was the same as in controls (12.8%); (2) patients with CTE died at a mean age of 81 years and "most positive cases [were] likely to be clinically asymptomatic"; and (3) CTE is found under the microscope in equal proportions of healthy, normal, asymptomatic people as it is in people with dementia and other diseases. For those worried about doing the right thing by their kids, a study published in December 2016 in Mayo Clinic Proceedings (Savica, et al., "High School Football and Risk of Neurodegeneration: A Community-Based Study") found that among 438 football players followed for 50 years, the risk of dementia was the same as for members of the chorus, glee club or band.

Facts and Findings

Fortunately, in court science matters. The notion that football causes CTE has been rejected by at least one United States District Court, the Eastern District of Pennsylvania, and the Third Circuit Court of Appeals. See In re NFL Players Concussion Injury Litig., 307 F.R.D. 351 (EDPA, 2015), aff'd 821 F.3d 410 (3d Cir. 2016). Judge Brody's key findings, based on current scientific knowledge and affirmed by the appellate court, negate causation: (1) the study of CTE is nascent, and the symptoms of the disease, if any, are unknown; (2) medical research has not reliably determined which events make a person more likely to develop CTE; and (3) research has not determined what symptoms individuals with CTE typically suffer from while they are alive. In re NFL Players Concussion Injury Litig., 821 F.3d at 441.

The point: Media should not lead science. The health and psychosocial benefits of athletic activity at all ages far outweigh any perceived risk. As parents, we should encourage healthy activity. As professionals, we need to peel back what the media pushes, read the literature and understand the fundamentals.

The renowned neurosurgeon, Uzma Samadani, M.D., Ph.D., FACS, graciously provided additional medical literature and keen insight for this article.

Disclosures and Acknowledgments: Tony Corleto serves as general counsel for Pop Warner football. He defends concussion litigation. The renowned neurosurgeon, Uzma Samadani, M.D., Ph.D., FACS, graciously provided additional medical literature and keen insight for this article.

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MAYO CLINIC

ORIGINAL ARTICLE

High School Football and Risk of Neurodegeneration: A Community-Based Study

Rodolfo Savica, MD, MSc; Joseph E. Parisi, MD; Lester E. Wold, MD; Keith A. Josephs, MD, MST, MSc; and J. Eric Ahlskog, PhD, MD

Abstract

Objective: To assess whether high school football played between 1946 and 1956, when headgear was less protective than today, was associated with development of neurodegenerative diseases later in life.

Methods: All male students who played football from 1946 to 1956 in the high schools of Rochester, Minnesota, plus a non–football-playing referent group of male students in the band, glee club, or choir were identified. Using the records-linkage system of the Rochester Epidemiology Project, we reviewed (from October 31, 2010, to March 30, 2011) all available medical records to assess later development of dementia, Parkinson disease (PD), or amyotrophic lateral sclerosis (ALS). We also compared the frequency of dementia, PD, or ALS with incidence data from the general population of Olmsted County, Minnesota.

Results: We found no increased risk of dementia, PD, or ALS among the 438 football players compared with the 140 non–football-playing male classmates. Parkinson disease and ALS were slightly less frequent in the football group, whereas dementia was slightly more frequent, but not significantly so. When we compared these results with the expected incidence rates in the general population, only PD was significantly increased; however, this was true for both groups, with a larger risk ratio in the non–football group.

Conclusion: Our findings suggest that high school students who played American football from 1946 to 1956 did not have an increased risk of later developing dementia, PD, or ALS compared with non–football-playing high school males, despite poorer equipment and less regard for concussions compared with today and no rules prohibiting head-first tackling (spearing).

 ■ Mayo Clin Proc. 2012;87(4):335-340

Multiple concussive head injuries incurred in sporting activities previously have been associated with progressive neurodegenerative disease later in life. Initially, it was reported in boxers (dementia pugilistica),[1] but an evolving literature now suggests that this risk extends to other sports in which concussions are common. The term *chronic traumatic encephalopathy* (CTE) has been used to define this condition, with dementia being the primary delayed outcome.[2] Besides fighting sports, American football, soccer, and hockey predispose players to head trauma and have been implicated in the later development of CTE.[3,4] Moreover, head trauma and sport-related trauma have been reported as risk factors for development of Parkinson disease (PD),[5] dementia,[6] and amyotrophic lateral sclerosis (ALS).[7,8]

Although repeated concussive head trauma is a purported risk factor for later neurodegenerative disease, few studies have evaluated long-term risks in a cohort of athletes participating in a sport that is often associated with concussions.[9] American football as played several decades ago often put participants at risk for concussion, which at the time was commonly disregarded ("bell rung"); moreover, the protective headgear of that era was marginally protective against concussions (Figure 1). We chose to analyze the long-term medical outcomes of a cohort of high school football players from Rochester (Olmsted County), Minnesota, using the medical records linkage system of the Rochester Epidemiology Project (REP).[10,11] We hypothesized that athletes playing football during the decade 1946-1956 would be more likely to develop a neurodegenerative condition later in life than non–football players. Because CTE has been linked to dementia, PD, and ALS, we specifically assessed the frequency of these 3 conditions from the historical medical records. We compared outcomes in the high school football cohort with outcomes in male classmates from the same years who participated in band, glee club, or choir but did not participate in any sport activity. We also compared our results with the expected frequency of dementia, PD, and ALS as determined by using previously published sex- and age-adjusted incidence rates of the general population of Olmsted County.

From the Departments of Neurology (R.S., J.E.P., K.A.J., J.E.A.) and Laboratory Medicine and Pathology (J.E.P.), Mayo Clinic, Rochester, MN; and the Department of Pathology, Mayo Clinic Health System, Austin, MN (L.E.W.).

METHODS

Study Population and Medical Records Abstraction

During the years of interest, 1946-1956, Rochester had only 2 high schools: Lourdes High School and

FIGURE 1. One of the football players from Rochester Lourdes High School in 1946 wearing a "dog-ear" leather helmet. Photo courtesy of Lourdes High School, Rochester, MN. Used with permission.

Rochester High School. Yearbooks were available for these high schools, documenting rosters of football players, as well as members of the band, glee club, and choir (non–football players). We created lists of the male members of these respective groups; football players who also participated in band, glee club, or choir were included only in the list of football players. The yearbooks contained at least the following information: full name, year of graduation, and the activities performed during the previous years in high school. Soccer, tennis, boxing, and hockey were not available sports during these study years.

We linked the individuals in these 2 groups to their medical records, taking advantage of the REP browser. The REP is a unique medical records linkage system that encompasses the care delivered to residents of Olmsted County (including the city of Rochester). All individuals visiting any county care provider are present in the system. This is an active records linkage system that spans from the early 1900s to the present. Further details on the REP have been reported elsewhere.[10,11] The REP includes a tool that allows one to search for individuals on the basis of their first and last names and the year of birth. We searched for each person on our compiled lists, using his full name and the approximate year of birth (assuming that students graduated at age 18±2 years).

The study population was limited to only those individuals who had a medical record in the records linkage system and for whom we could confirm a match with our compiled lists. Individuals were included in the REP if they had at least one medical visit in their lifetime at any of the medical facilities in Olmsted County. Therefore, those who left Olmsted County before generating any medical records were not included.

A 2-step process was used to abstract the medical record. First, we screened the electronic medical indexes of the records linkage system using the REP tools. We focused our search on dementia of any type, parkinsonism of any type, and ALS. Second, a neurologist (R.S.), unaware of the status of the individuals (football players vs non–football players), reviewed the complete available medical charts of all those who ever received one of the diagnoses in order to confirm the electronic-based diagnosis. To determine the reliability of the clinical diagnosis of the abstractor, we compared his diagnoses with a set of electronic codes that already had been used in a previous study on the incidence of parkinsonism in the same population.[12] There were no differences between the diagnoses made by the neurologist and the cases identified by the electronic codes.

In addition, we reviewed autopsy reports and stored brain tissues when available. The study protocol and all procedures were approved by the institutional review boards of Mayo Clinic and Olmsted Medical Center. The study was performed from October 31, 2010, to March 30, 2011.

Data Analyses

We calculated the median, 25th percentile, and 75th percentile for the years of follow-up and the age at follow-up. To compare groups for length of follow-up and age at follow-up, we reported *P* values from the Wilcoxon rank sum test. We performed 2 separate analyses to determine if playing football increased the risk of dementia, PD, or ALS. First, we compared the football cohort directly to the cohort of students who participated in band, choir, or glee club. Individuals were followed up until the time of last available medical record information or until the time of onset of one of the outcomes of interest (dementia, PD, or ALS). We then performed Cox proportional hazards analysis and calculated a hazards ratio (HR) and 95% confidence interval (CI).

We calculated separately for the football cohort and the non–football cohort the expected

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number of persons with the outcomes of interest (dementia, PD, and ALS) based on incidence rates previously published for the population of Olmsted County.[12-14] Specifically, the expected number of outcomes was calculated by applying incidence rates to the age- and sex-specific person-years of follow-up in our study in the same years covered by the historical rates. We then calculated standardized incidence ratios (SIRs) to summarize this comparison. All analyses were performed by a statistician (not a coauthor) at the conventional 2-tailed α level of .05 using SAS version 9 (SAS Institute Inc, Cary, NC).

RESULTS

We identified 512 male football players and 203 male members of the band, glee club, or choir from high school classes between 1946 and 1956. Among these, we were able to successfully match 438 football players (86%) and 140 band, glee club, or choir members (69%) to a record in the REP system (Figure 2).

The median period of follow-up in the system was 50.2 years (interquartile range [IR], 13.7-57.5) for the football players and 42.7 years (IR, 8.8-55.4) for the non–football players. The age at the last follow-up was 68.4 years (IR, 31.5-75.6) for the football players and 59.1 years (IR, 26.7-73.4) for the band, glee club, and choir members.

We identified 13 cases of dementia of any type among the football players and 2 cases among the non–football players; the difference between groups was not significant (HR, 1.58; 95% CI, 0.36-7.01; P=.55). Our observed cases were fewer than expected in both groups, compared with Olmsted County incidence data (expected number of dementia cases in the football cohort, 18.2; expected number of dementia cases in the non–football cohort, 4.3). However, the differences between observed and expected were not significant (SIR, 0.72; 95% CI, 0.38-1.23 in the football players and SIR, 0.47; 95% CI, 0.05-1.68 in the non–football cohort). The median age at the onset of dementia was 72.4 years (IR, 69.3-77.0) in the football players and 76.0 years (IR, 75.0-77.0) in the non football cohort.

Parkinson disease was identified in 10 football players and 5 band, glee club, or choir members, which was statistically similar (HR, 0.48; 95% CI, 0.17-1.42; P=.19). Olmsted County incidence data predicted a PD frequency of 4.2 cases in football players and 1.0 case in band, glee club, or choir members; although comparison of observed frequency with this population-based data showed a statistically significant difference, this was true for both groups (SIR, 2.36; 95% CI, 1.13-4.34 in the football players and SIR, 4.94; 95% CI, 1.61-11.51 in the non–football cohort). The median age at onset of PD was 70.5 years (IR, 58.9-77.4) in the football players and 67.7 years (IR, 55.5-78.1) in the band, glee club, or choir members.

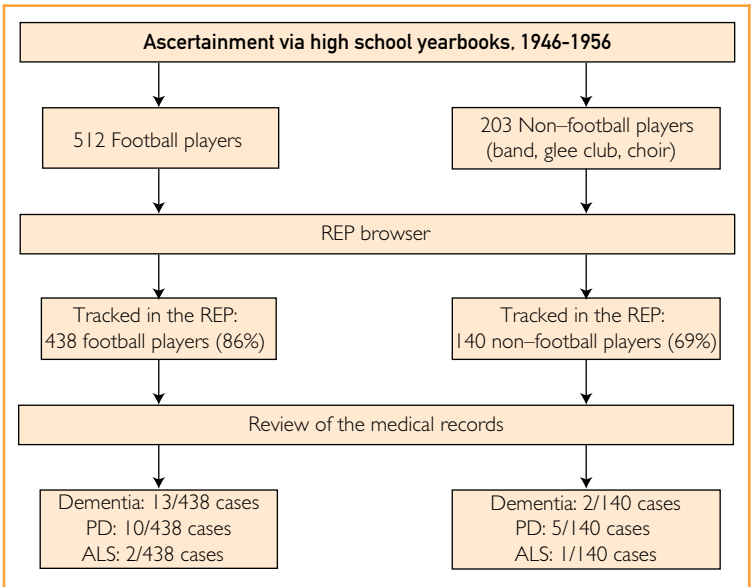

FIGURE 2. Flowchart of the study. ALS = amyotrophic lateral sclerosis; PD = Parkinson disease; REP = Rochester Epidemiology Project.

Amyotrophic lateral sclerosis was the only motor neuron disease subtype that we identified, and it was diagnosed in 2 football players and 1 band, glee club, or choir member (HR, 0.52; 95% CI, 0.05-5.68; P=.59). We also found no significant difference between observed and population-based expected number of cases for either group (SIR, 3.15; 95% CI, 0.38-11.33 in the football players and SIR, 6.44; 95% CI, 0.16-35.7 in the non–football cohort) (Tables 1 and 2).

Only a single brain was available for neuropathologic examination. This was a case of motor neuron disease that occurred in the football group. Routinely processed formalin-fixed tissues from multiple neocortical and subcortical areas were stained by a variety of techniques, including antibodies to β-amyloid, tau, alpha-synuclein, and TDP-43. Review of this material revealed that tau pathology was minimal and limited to medial temporal areas, which is consistent with nonspecific age-associated changes. We did not observe any pathologic findings supportive of CTE.

DISCUSSION

Our findings suggest that playing American football in high school between 1946 and 1956 did not increase the long-term risk of developing dementia, PD, or ALS later in life. Indeed, the frequency of PD and ALS was lower in the football group than in the

TABLE 1. Historical Cohort Study of Football Players vs Non–Football Players and Risk of Neurodegenerative Diseases[a]

	Football players (N=438)	Band/glee club/choir members (N=140)	HR	95% CI	*P* value[b]
Follow-up					
Years of follow-up[c]	50.2 (13.7, 57.5)	42.7 (8.8, 55.4)	...	...	.03
Age at follow-up[c]	68.4 (31.5, 75.6)	59.1 (26.7, 73.4)	...	...	.01
Outcome					
Dementia	13	2	1.58	0.36-7.01	.55
Parkinson disease	10	5	0.48	0.17-1.42	.19
Amyotrophic lateral sclerosis	2	1	0.52	0.05-5.68	.59

[a] HR = hazards ratio; CI = confidence interval.
[b] *P* values are for the Wilcoxon rank sum test.
[c] Values are median (25th percentile, 75th percentile).

band, glee club, and choir group; however, the 2 groups did not differ statistically. Although the dementia frequency was higher in the football group (3% vs 1.4%), the difference was not significant (*P*=.55).

Our concern was that the repetitive head trauma associated with high school football may have predisposed players to development of neurodegenerative disease similar to CTE.[4] Chronic traumatic encephalopathy is an insidiously developing neurodegenerative disorder beginning many years after multiple concussive brain injuries, best described in professional athletes, and characterized by progressive dementia and parkinsonism.[3] Chronic traumatic encephalopathy neuropathology is distinct from Alzheimer disease and other neurodegenerative diseases.[3,4,15] Moreover, several epidemiological studies have found that prior brain trauma is a risk factor for dementia,[6,16] PD,[5,17] and ALS.[15,18] In particular, ALS has been found to be increased in professional Italian soccer players[7] and professional American football players.[8]

Ideally, we would have been able to document specific instances of concussions in our football cohort. However, in that era, all but the most severe concussions were largely ignored, and players often returned to the game after injury (being said to have had their "bell rung"). Thus, medical records provide few references to such injuries.

Although the body weight and bulk of athletes from the investigated era (1946-1956) were, on average, less than those of modern athletes, the helmets and football rules put the earlier athletes at greater concussive risk. Figure 1 shows a common helmet of that era, which would hardly protect the player from a concussive blow. Not until 1973 did the National Operating Committee on Standards for Athletic Equipment (NOCSAE) implement the first football helmet standards, initially for professional football[19,20] and then college (1978), with high school standards not being adopted until 1980. Moreover, it was not until 1976 that rules prohibited spearing (leading with the head when blocking or tackling). Illustrating the risks to the brain, a study of American football fatalities reported that from 1945 through 1999 the major cause of death was brain injury (69%) and that most fatalities occurred from 1965 to 1969. With the adoption of NOCSAE standards, fatalities decreased by 74% and head injuries decreased from 4.25 per 100,000 to 0.69 per 100,000.[21] In summary, the evolution of better helmet technology, together with further rule changes and head injury management guidelines, has further reduced football head injuries.[22]

For this analysis to be valid, adequate follow-up is necessary. Neurodegenerative diseases typically develop among elderly persons, although CTE may occur much earlier.[4] In our study, follow-up was approximately 50 years of observation after high school graduation (median for dementia, 55 years; PD, 52.4 years; ALS, 47.6 years). The median age at last follow-up in the football group was 68.4 years, which may not extend sufficiently to ascertain all neurodegenerative diseases; however, premature neurodegenerative disease should have surfaced by that time. In addition, our analyses were adjusted either directly for age (via a matched non–football cohort) or indirectly for age (age-specific incidence rates) and did not rely on complete lifetime ascertainment.

This study has certain other limitations. Although we were able to track the vast majority of students in our system, it is possible that we have limited medical information regarding the later medical outcomes in some of them. Moreover, almost 35% of the non–football players never entered the system, either because they had no medical visits or because they no longer lived in the county; this

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could have led to selection bias. In addition, we can only speculate about the severity of concussions in the football cohort, as we have no direct documentation, and we were unable to include information regarding football players' time on the field, positions, or number of years played. Thus, we considered all players of equal likelihood to have suffered concussive trauma. The study sample size is relatively small, despite 10 years of ascertainment; thus, the study may be underpowered and a type II error cannot be excluded. Data were not available for other factors that might have influenced outcomes—smoking, use of caffeine, exposure to pesticides, family history, and so forth. Also, it may be noted that follow-up duration and age were greater in the football group, which should have biased toward identifying more, rather than less, neurodegenerative disease among the football players. Finally, we were able to identify only 3 cases of ALS (2 in the football group and 1 in the non–football group). Therefore, our findings should be interpreted cautiously, in light of the rarity of the outcome.

Compared with general residents of Olmsted County from the same birth year and sex, both groups, football and non–football, were less likely to develop dementia but more likely to be diagnosed with PD or ALS. Although the difference was significant only for PD, this was true for both high school groups and seems paradoxical. However, that these comparisons to population-expected cases ran parallel in our 2 high school groups suggests that other population variables affected these results. Possibly, differences in methodology between our study and the prior Olmsted County incidence studies[12-14] may have contributed to these findings. For example, this might have included differences in case ascertainment. Also, individuals moving out of Olmsted County after 1 or 2 medical visits would have reduced the denominators in the prior incidence studies. Additionally, we did not collect information on death rates in our 2 groups. Finally, note that this study assessed high school males in the immediate World War II era. The prior population-based incidence study likely captured a broader group of young males, many of whom had quit or deferred high school to serve in the military. Thus, our 2 male high school groups had different demographic characteristics than males of similar age in the prior incidence studies.

TABLE 2. Historical Cohort Study of Football Players and Non–Football Players vs General Population and Risk of Neurodegenerative Diseases

	Football players (N=438)	Band/glee club/choir members (N=140)	*P* value[a]
Dementia			
Observed	13	2	
Expected[b]	18.1	4.3	
SIR vs expected[c]	0.72 (0.38-1.23)	0.47 (0.05-1.68)	
Years after index[d]	55.3 (51.5, 59.4)	57.8 (57.2, 58.5)	.44
Age at outcome[d]	72.4 (69.3, 77.0)	76.0 (75.0, 77.0)	.35
Parkinson disease			
Observed	10	5	
Expected[b]	4.2	1.0	
SIR vs expected[c]	2.36 (1.13-4.34)	4.94 (1.61-11.51)	
Years after index[d]	52.4 (42.4, 59.6)	49.8 (37.4, 60.2)	.95
Age at outcome[d]	70.5 (58.9, 77.4)	67.7 (55.5, 78.1)	.95
Amyotrophic lateral sclerosis			
Observed	2	1	
Expected[b]	0.64	0.16	
SIR vs expected[c]	3.15 (0.38-11.33)	6.44 (0.16-35.7)	
Years after index[d]	47.6 (46.3, 48.8)	42.8 (42.8, 42.8)	.67

[a] *P* values are for the Wilcoxon rank sum test.
[b] Expected numbers of cases are calculated from age-specific person-years and previously published incidence rates in the Olmsted County population.
[c] Standardized incidence ratios (SIRs) are calculated on the basis of observed number of cases and expected number of cases. Values are SIR (95% confidence interval).
[d] Values are median (25th percentile, 75th percentile).

CONCLUSION

Our findings suggest that high school football players from a well-defined community who played from 1946 to 1956 did not have an increased risk of dementia, PD, or ALS compared with non–football players. These data should be interpreted in light of the many differences between today's high school football players and those of the distant past. Although today's players have better equipment, trainers and physicians who are more knowledgeable about concussions, and rules against spearing, they also tend to be larger and quicker than athletes in the prior era, increasing the force of impact. Moreover, although dramatically different from the marginally protective headgear of this earlier era, current helmets certainly do not eliminate concussions and may provide players with a false sense of protection. Although these results should be somewhat reassuring to high school players from 50 years ago, they should give no reassurance to today's players.

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Statistical analyses were conducted by B. R. Grossardt, MS, Division of Biomedical Statistics and Informatics, Department of Health Sciences Re-

search, College of Medicine, Mayo Clinic, Rochester, MN.

Abbreviations and Acronyms: **ALS** = amyotrophic lateral sclerosis; **CTE** = chronic traumatic encephalopathy; **PD** = Parkinson disease; **REP** = Rochester Epidemiology Project

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PET Scanning of Brain Tau in Retired National Football League Players: Preliminary Findings

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Objective: *Mild traumatic brain injury due to contact sports may cause chronic behavioral, mood, and cognitive disturbances associated with pathological deposition of tau protein found at brain autopsy. To explore whether brain tau deposits can be detected in living retired players, we used positron emission tomography (PET) scans after intravenous injections of 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP).* **Methods:** *Five retired National Football League players (age range: 45 to 73 years) with histories of mood and cognitive symptoms received neuropsychiatric evaluations and FDDNP-PET. PET signals in subcortical (caudate, putamen, thalamus, subthalamus, midbrain, cerebellar white matter) and cortical (amygdala, frontal, parietal, posterior cingulate, medial and lateral temporal) regions were compared with those of five male controls of comparable age, education, and body mass index.* **Results:** *FDDNP signals were higher in players compared with controls in all subcortical regions and the amygdala, areas that produce tau deposits following trauma.* **Conclusions:** *The small sample size and lack of autopsy confirmation warrant larger, more definitive studies, but if future research confirms these initial findings, FDDNP-PET may offer a means for premorbid identification of neurodegeneration in contact-sports athletes.* (Am J Geriatr Psychiatry 2013; 21:138–144)

Key Words: Positron emission tomography, FDDNP, tau, amyloid, mood disorder, depression, mild cognitive impairment, dementia

According to recent CDC estimates, 1.6–3.8 million sports-related traumatic brain injuries (TBIs) occur each year, including those never reported to healthcare professionals.[1] Most are minor concussions; many are repeated injuries and subconcussive blows.[1]

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Repetitive mild TBI due to contact sports may lead to chronic mood, behavioral, and cognitive changes.[2] Studies of retired contact-sport athletes, such as National Football League (NFL) players, show a higher rate of personality, behavioral, and mood disturbances (e.g., depression, irritability, impulsiveness), mild cognitive impairment (MCI, a risk state for dementia), and dementia compared with controls. Professional athletes exposed to repetitive mild TBIs are prone to develop chronic impairment, and available evidence suggests a possible dose response.[3] Retired NFL players with three or more reported concussions during their career were three times more likely to be diagnosed with depression and five times more likely to be diagnosed with MCI.[3,4]

Several investigators have described chronic traumatic encephalopathy (CTE), a clinicopathological entity that includes mood, personality, cognitive, and behavioral changes (e.g., suicidality), and motor symptoms (e.g., abnormal gait, tremor) associated with a range of autopsy findings, particularly widespread accumulation of phosphorylated tau protein as neurofibrillary tangles (similar to those observed in Alzheimer disease), astrocytic tangles, neurites, diffuse axonal injury, white matter abnormalities, inflammation, and immune proinflammatory cytokine responses in traumatized brain regions.[5] Immunoreactive deposits are found in neocortical, subcortical (e.g., thalamus, caudate, putamen, midbrain, and cerebellar white matter), and medial temporal (hippocampus, entorhinal cortex, and amygdala) regions, where neuronal loss may be observed.[5] TDP-43 proteinopathy may accompany tauopathy in CTE cases and is more prominent in motor neuron disease cases.[6] Amyloid deposition has been reported in approximately 40% of CTE cases and generally consists of diffuse plaques with relatively few cortical neuritic plaques.[5] Currently, CTE in former football players is only diagnosed at autopsy.

Our group invented 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP)-positron emission tomography (PET) for measuring both tau tangle and amyloid plaque deposition in living brains.[7] FDDNP signals differentiate Alzheimer disease from MCI and normal aging and predict future cognitive decline in nondemented subjects.[8,9] Although other tau tracers have been tested in human brain tissue sections and animal models,[10,11] FDDNP is the only PET probe of tau that has been studied in vivo in human imaging trials. FDDNP is not specific for tauopathies, but previous autopsy follow-up studies indicate regional specificity in patients with Alzheimer disease, wherein FDDNP-PET shows high signals in medial temporal regions where autopsy studies indicate a preponderance of tau tangles, as well as high signal in lateral temporal regions, where amyloid plaques are highly concentrated.[8]

Despite the devastating consequences of TBIs due to contact sports and the large number of people at risk, no method for early detection of brain pathology has yet been established. To address this issue, we performed PET scans after intravenous injections of FDDNP to explore whether brain tau deposits could be detected in a small group of retired NFL players with cognitive and mood symptoms and compared them with a group of male controls of comparable age, educational achievement, and body mass index (BMI).

METHODS

Neuropsychiatric evaluations were performed on five retired players aged 45 years or older who were recruited for this study because of a history of cognitive or mood symptoms. Through organizational contacts, NFL retirees with MCI-like symptoms were referred for testing. Of the 19 potential volunteers, 14 did not participate because of non-response or disinterest (N = 11), age (too young; N = 2), or medical illness (N = 2).

Subjects had screening laboratory tests and structural imaging scans (computed tomography [CT] or magnetic resonance imaging [MRI]) to rule out other causes of mental symptoms (e.g., stroke, tumor) and for co-registration with PET scans for region-of-interest (ROI) analyses. One player and two control subjects had CT scans because they could not tolerate MRI (claustrophobia, body metal, body size).

The Mini-Mental State Examination (MMSE), Hamilton Rating Scale for Depression (HAM-D), and a neuropsychological test battery[8,9] were administered to confirm diagnoses. Clinical assessments were performed within 4 weeks of scanning, and clinicians were blinded to scan results. Informed consent was obtained in accordance with UCLA Human Subjects Protection Committee procedures. Cumulative radiation dosimetry was below the mandated

maximum annual dose and in compliance with state and federal regulations.

PET scans were performed using an ECAT HR+ PET or Biograph PET/CT camera (both Siemens/CTI, Knoxville, TN) as detailed previously.[8,9] In brief, subjects were injected with 10 mCi of FDDNP. FDDNP binding data were quantified using Logan graphical analysis: The slope of the linear portion of the Logan plot is the relative distribution volume (DVR) of the tracer in an ROI divided by that in the reference region (cerebellum). ROIs were traced on co-registered MRI or CT scans for subcortical (caudate, putamen, thalamus, subthalamus, midbrain, cerebellar white matter) and cortical (amygdala, frontal, parietal, posterior cingulate, and medial and lateral temporal) regions.[8,9] Each DVR or binding value was expressed as an average of left and right regions. All scans were read and ROIs drawn by individuals blinded to clinical assessments.

Given the small number of players available for analyses, only non-parametric tests were performed. Controls for comparisons with players were identified using a propensity score matching method, wherein pairs of subjects are matched through a minimum distance estimator that can encompass several covariates.[12] This method thus mitigates potential biases and ensures that controls and players are as similar as possible in other characteristics that can affect FDDNP regional binding levels. FDDNP scans were available for 35 normally aging males from previous studies. We chose age, BMI, years of education, and dementia family history as covariates to match players and controls and used the greedy matching algorithm to identify controls to compare with players. Descriptive statistics were computed for players and controls, and the two-sample Wilcoxon test was used to compare groups on FDDNP binding levels, a global cognitive score (MMSE), and a depression measure (HAM-D). We explored possible relationships between FDDNP binding values and the number of concussions in the players using plots and Spearman correlations in those regions that showed higher signals in players compared with controls.

RESULTS

The players represented a range of positions and diagnoses (linebacker with MCI; quarterback with normal aging; guard with dementia/depression; defensive lineman with MCI/depression; center with MCI) and played professionally from 10−16 (median, 14) years (Fig. 1). Players and controls were comparable in age (median age for players [controls]: 59 [60]; range: 45−73 [45−66], BMI (players [controls]: 32 [34], 28−42 [28−38]), years of education (players [controls]: 17 [15], 15−18 [13−22]) and dementia family history (present in 3 players and 3 controls) (Table 1). Players had significantly higher HAM-D scores (median: 8, range: 5−17) compared with controls (0, 0−3; $p = 0.03$) and a trend towards lower MMSE scores (median: 28, range: 17−30 versus 30, 29−30, $p = .09$) (Table 1).

Players had significantly higher FDDNP signals compared with controls in caudate (median levels: 1.48 versus 1.23, $p = 0.03$), putamen (1.47 versus 1.20, $p = 0.05$), thalamus (1.48 versus 1.29, $p = 0.03$), subthalamus (1.45 versus 1.25, $p = 0.03$) midbrain (1.31 versus 1.14, $p = 0.03$), and cerebellar white matter (1.15 versus 1.09, $p = 0.05$) regions. The two groups did not differ significantly in FDDNP binding in cortical regions except for the amygdala (1.30 versus 1.14, $p = 0.03$) (Table 1; Figs. 1, 2).

Plots of FDDNP binding values versus number of concussions in regions that showed higher signals in players compared with controls are presented in Figure 3. Although none of the Spearman correlations reached statistical significance (as expected due to the small sample size), the plots show an increase in FDDNP binding levels with increase in number of concussions.

DISCUSSION

These initial FDDNP-PET findings in retired NFL players with histories of cognitive and mood symptoms demonstrate high signals in the amygdala and subcortical regions compared with controls. Although the subject groups were matched for important variables, such as age, BMI, and educational achievement, these preliminary results need interpretation with caution given the small sample size and multiple uncorrected statistical comparisons. Also, not all subjects had MRI scans for co-registration with PET, which could influence ROI values, although comparable numbers of players and controls had MRI scans (4 and 3, respectively). Other factors that could influence the results would be differences in cerebrovascular health and genetic risk between players and

FIGURE 1. **FDDNP-PET scan results for NFL players and a control. Coronal and transaxial FDDNP-PET scans of the retired NFL players include:**
NFL1: 59-year-old linebacker with MCI, who experienced momentary loss of consciousness after each of two concussions;
NFL2: 64-year-old quarterback with age-consistent memory impairment, who experienced momentary loss of consciousness and 24-hour amnesia following one concussion;
NFL3: 73-year-old guard with dementia and depression, who suffered brief loss of consciousness after 20 concussions, and a 12-hour coma following 1 concussion;
NFL4: 50-year-old defensive lineman with MCI and depression, who suffered two concussions and loss consciousness for 10 minutes following one of them;
NFL5: 45-year-old center with MCI, who suffered 10 concussions and complained of light sensitivity, irritability, and decreased concentration after the last two.
The players' scans show consistently high signals in the amygdala and subcortical regions and a range of cortical binding from extensive to limited, whereas the control subject shows limited binding in these regions. Red and yellow areas indicate high FDDNP binding signals.

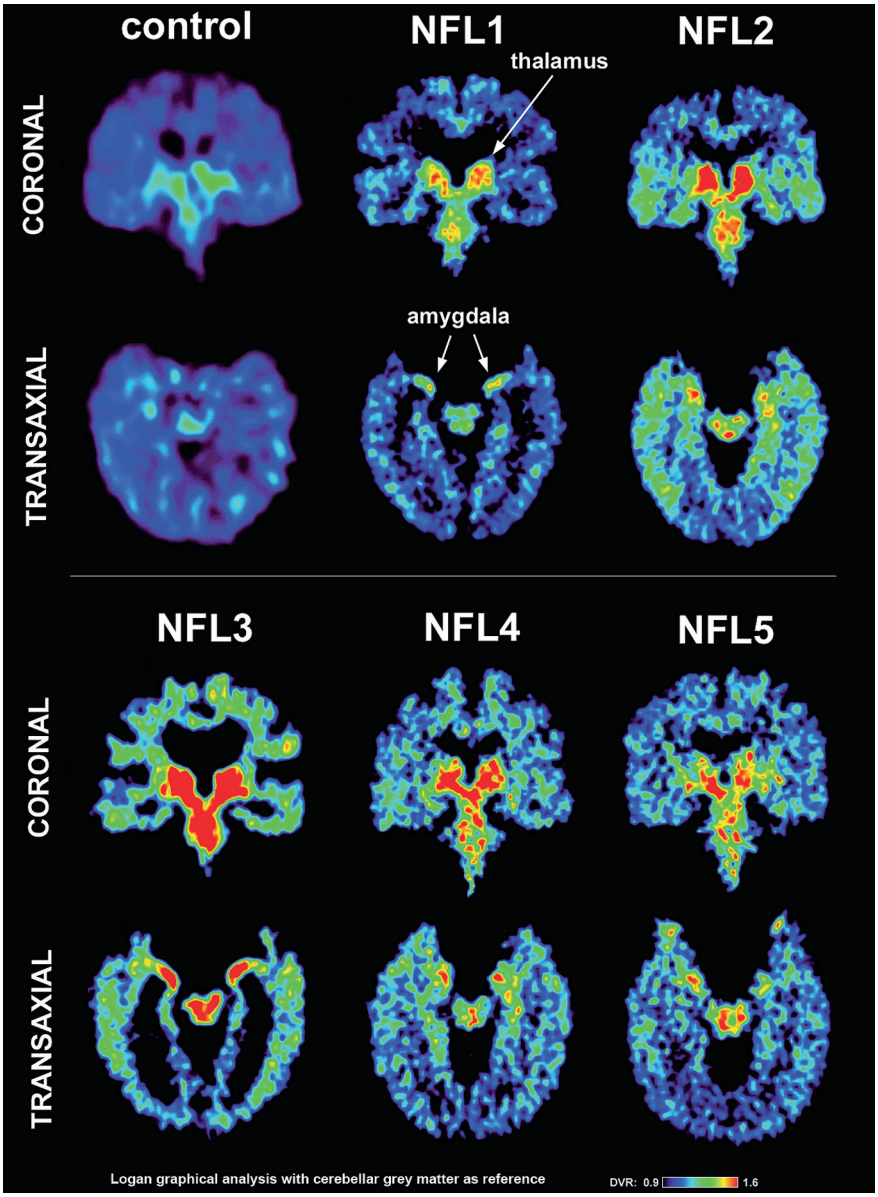


TABLE 1. Subject Characteristics and Regional FDDNP Binding Values

Characteristic[a]	Players (N = 5)	Controls (N = 5)
Age—yr	59 (45–73)	60 (45–66)
Education—yr	17 (15–18)	15 (13–22)
AD family history—none (%)	3 (60)	3 (60)
Body Mass Index	32 (29–42)	34 (28–38)
Mini Mental State Exam	28 (17–30)	30 (29–30)
HAM-D[b]	8 (5–17)	0 (0–3)
FDDNP binding values[c]		
Amygdala	1.30 (1.27–1.45)	1.14 (1.09–1.17)
Caudate	1.48 (1.46–1.81)	1.23 (1.16–1.34)
Putamen	1.47 (1.35–1.60)	1.20 (1.14–1.35)
Thalamus	1.48 (1.41–1.54)	1.29 (1.07–1.39)
Subthalamic	1.45 (1.31–1.51)	1.25 (1.09–1.30)
Midbrain	1.31 (1.27–1.39)	1.14 (1.10–1.18)
Cerebral white matter	1.15 (1.12–1.27)	1.09 (1.08–1.12)
Frontal	1.12 (0.97–1.16)	1.03 (0.98–1.13)
Parietal	1.05 (0.96–1.12)	1.04 (0.98–1.07)
Medial temporal	1.15 (1.07–1.19)	1.12 (1.08–1.18)
Lateral temporal	1.09 (1.00–1.13)	1.08 (1.03–1.13)
Posterior cingulate	1.08 (1.00–1.17)	1.09 (1.05–1.11)

Notes: [a]Data are presented as median (range) unless specified otherwise.

[b]Hamilton Rating Scale for Depression-21 item version; groups were significantly different: Wilcoxon statistic U = 15, p = 0.03.

[c]Significant differences between groups in the following regions: amygdala: U = 15, p = 0.03; caudate: U = 15, p = 0.03; putamen: U = 16, p = 0.05; thalamus: U = 15, p = 0.03; subthalamic: U = 15, p = 0.03; midbrain: U = 15, p = 0.03; cerebellar white matter: U = 16, p = 0.04.

controls. Despite such limitations, these elevated amygdala and subcortical FDDNP binding patterns in players are consistent with the fibrillary tau deposition patterns observed at autopsy in CTE cases.[5] Only patchy cortical tau deposits have been reported in mild CTE cases, except for the amygdala, where they are dense.[4]

The pattern of higher FDDNP binding values in players with a greater number of concussions (Fig. 3) suggests a link between the players' history of head injury and FDDNP binding. Moreover, these binding patterns (high subcortical and low cortical binding except for the amygdala) are consistent with tau deposition patterns observed in autopsy studies of CTE[5] and differ from those observed in patients with cognitive and mood symptoms without prior head trauma, who mainly present with increased cortical FDDNP binding. In patients with geriatric depression, FDDNP binding is highest in the posterior cingulate and lateral temporal regions,[14] whereas patients with Alzheimer dementia show high binding values throughout the cortex (parietal, medial and lateral temporal, frontal and posterior cingulate regions).[7–9] In patients with MCI, FDDNP binding is high in medial temporal, frontal, and parietal regions.[8]

FDDNP binds to both fibrillary tau and amyloid, but neuropathological studies indicate that amyloid plaques (mostly diffuse cortical) are observed in less than a third of CTE cases in retired football players.[5,13] This suggests that a high proportion of the FDDNP signal in the players represents fibrillary tau deposition. Using a tau marker for detection and tracking of neurodegenerative disease is critically important because severity of tau load, rather than amyloid burden, correlates with rates of neuronal loss.[9] To date, FDDNP is the only available imaging probe that provides in vivo measures of tau in humans.

Players had greater depressive symptoms than controls, as well as evidence of cognitive impairment (3 MCI, 1 dementia). Elevated FDDNP binding is associated with depressive symptoms in normal aging[14] and geriatric depression,[15] and with cognitive symptoms in normal aging, MCI, and dementia.[8,9] Thus, these increased FDDNP signals appear to reflect a range of mental symptoms that have been observed in CTE cases.

Despite the devastating consequences of mild TBI from contact sports and military exposure to explosive blasts and the large group of those exposed, the syndrome has only recently received heightened attention. Specific treatments have not been developed, and no method for early detection has yet been established. Early recognition and identification of those at high risk would allow clinicians to develop strategies and interventions to protect those with early symptoms rather than attempt to repair damage once it becomes extensive.

Previous studies in patients with MCI show that FDDNP-PET patterns may predict future cognitive decline and development of dementia.[9] Large-scale longitudinal studies are necessary to determine the utility of detecting tau pathology in head trauma victims who are not yet experiencing mood or cognitive symptoms and whether this technology will facilitate development of prevention strategies. Further, the added health benefits of FDDNP scanning on a large scale remains to be addressed. Previous analysis, however, indicates that appropriate use of PET for evaluating early dementia in geriatric patients can add valuable information to the clinical work-up,

FIGURE 2. Scatter plots of FDDNP binding values in players and controls. FDDNP binding scatter plots for the 5 players (red circles) and 5 controls (blue circles) in the amygdala, midbrain, thalamus, and caudate regions illustrate the significantly higher values in players compared with controls. FDDNP binding is expressed in terms of the DVR derived by the Logan graphic method, with the cerebellum as the reference region.

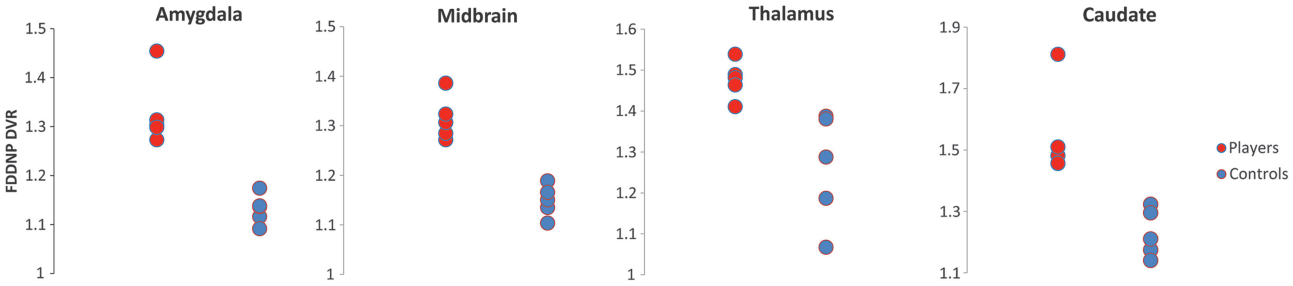
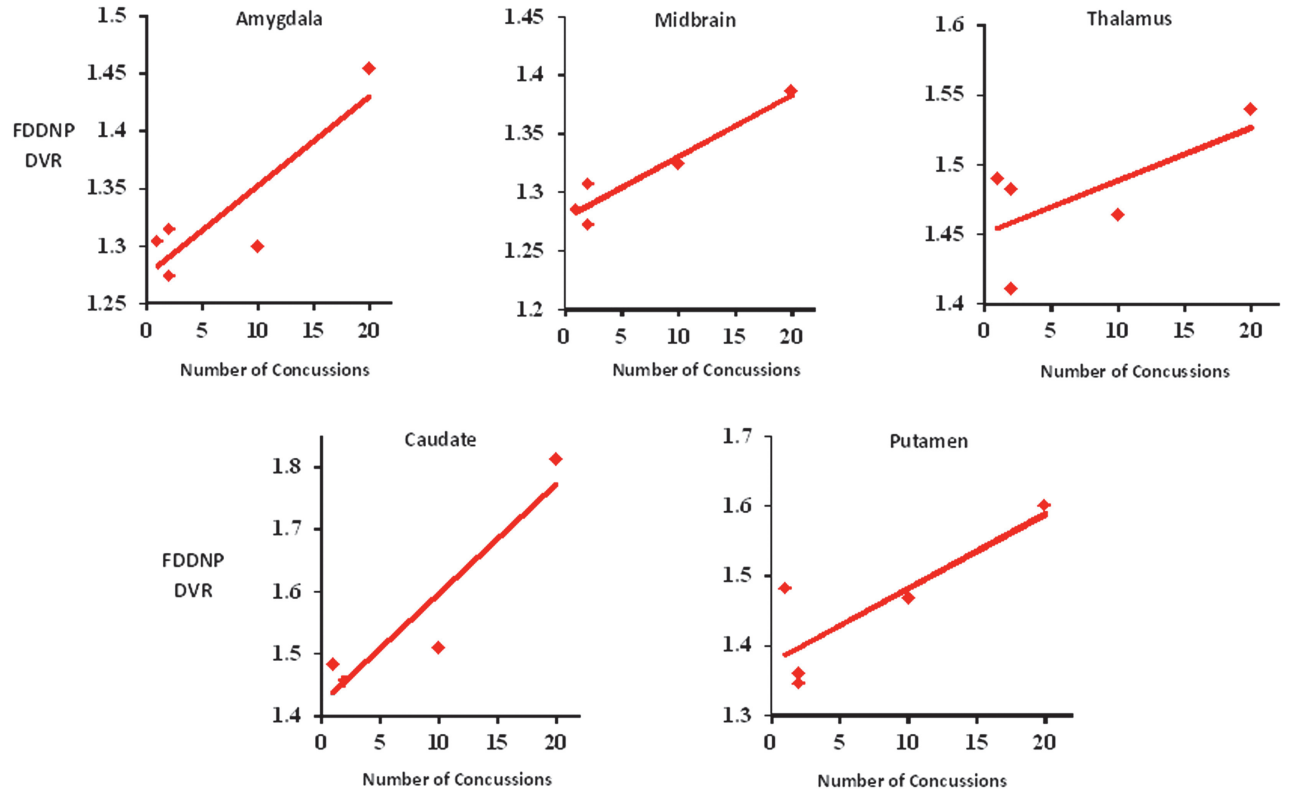


FIGURE 3. FDDNP binding levels versus number of concussions in retired players. Examination of plots showing FDDNP DVR binding values according to number of concussions in retired players suggests an association between a greater number of concussions and higher binding in regions that were found to show significantly higher FDDNP binding in players compared with controls. FDDNP binding is expressed in terms of the DVR derived by the Logan graphic method, with the cerebellum as the reference region.



without adding to the overall costs of evaluation and management, resulting in a greater number of patients being accurately diagnosed for the same level of financial expenditure.[16]

These findings suggest that FDDNP-PET could facilitate early recognition and intervention of trauma-related neurodegeneration through premorbid detection. Providing a non-invasive means of early

detection is a critical first step to developing interventions to prevent symptom onset and progression. Direct and indirect costs of TBI totaled an estimated $77 billion in the United States in 2000.[17] Given the large number of people at risk—not just athletes but military personnel, auto accident victims, and others—the potential public health impact is considerable.

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JAMA | Original Investigation

Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football

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IMPORTANCE Players of American football may be at increased risk of long-term neurological conditions, particularly chronic traumatic encephalopathy (CTE).

OBJECTIVE To determine the neuropathological and clinical features of deceased football players with CTE.

DESIGN, SETTING, AND PARTICIPANTS Case series of 202 football players whose brains were donated for research. Neuropathological evaluations and retrospective telephone clinical assessments (including head trauma history) with informants were performed blinded. Online questionnaires ascertained athletic and military history.

EXPOSURES Participation in American football at any level of play.

MAIN OUTCOMES AND MEASURES Neuropathological diagnoses of neurodegenerative diseases, including CTE, based on defined diagnostic criteria; CTE neuropathological severity (stages I to IV or dichotomized into mild [stages I and II] and severe [stages III and IV]); informant-reported athletic history and, for players who died in 2014 or later, clinical presentation, including behavior, mood, and cognitive symptoms and dementia.

RESULTS Among 202 deceased former football players (median age at death, 66 years [interquartile range, 47-76 years]), CTE was neuropathologically diagnosed in 177 players (87%; median age at death, 67 years [interquartile range, 52-77 years]; mean years of football participation, 15.1 [SD, 5.2]), including 0 of 2 pre–high school, 3 of 14 high school (21%), 48 of 53 college (91%), 9 of 14 semiprofessional (64%), 7 of 8 Canadian Football League (88%), and 110 of 111 National Football League (99%) players. Neuropathological severity of CTE was distributed across the highest level of play, with all 3 former high school players having mild pathology and the majority of former college (27 [56%]), semiprofessional (5 [56%]), and professional (101 [86%]) players having severe pathology. Among 27 participants with mild CTE pathology, 26 (96%) had behavioral or mood symptoms or both, 23 (85%) had cognitive symptoms, and 9 (33%) had signs of dementia. Among 84 participants with severe CTE pathology, 75 (89%) had behavioral or mood symptoms or both, 80 (95%) had cognitive symptoms, and 71 (85%) had signs of dementia.

CONCLUSIONS AND RELEVANCE In a convenience sample of deceased football players who donated their brains for research, a high proportion had neuropathological evidence of CTE, suggesting that CTE may be related to prior participation in football.

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Author Video Interview and JAMA Report Video

Supplemental content

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Chronic traumatic encephalopathy (CTE) is a progressive neurodegeneration associated with repetitive head trauma.[1-8] In 2013, based on a report of the clinical and pathological features of 68 men with CTE (including 36 football players from the current study), criteria for neuropathological diagnosis of CTE and a staging scheme of pathological severity were proposed.[6] Two clinical presentations of CTE were described; in one, the initial features developed at a younger age and involved behavioral disturbance, mood disturbance, or both; in the other, the initial presentation developed at an older age and involved cognitive impairment.[9] In 2014, a methodologically rigorous approach to assessing clinicopathological correlation in CTE was developed using comprehensive structured and semistructured informant interviews and online surveys conducted by a team of behavioral neurologists and neuropsychologists.[10] In 2015, the neuropathological criteria for diagnosis of CTE were refined by a panel of expert neuropathologists organized by the National Institute of Neurological Disorders and Stroke and the National Institute of Biomedical Imaging and Bioengineering (NINDS-NIBIB).[8]

Using the NINDS-NIBIB criteria to diagnose CTE and the improved methods for clinicopathological correlation, the purpose of this study was to determine the neuropathological and clinical features of a case series of deceased football players neuropathologically diagnosed as having CTE whose brains were donated for research.

Key Points

Question What are the neuropathological and clinical features of a case series of deceased players of American football neuropathologically diagnosed as having chronic traumatic encephalopathy (CTE)?

Findings In a convenience sample of 202 deceased players of American football from a brain donation program, CTE was neuropathologically diagnosed in 177 players across all levels of play (87%), including 110 of 111 former National Football League players (99%).

Meaning In a convenience sample of deceased players of American football, a high proportion showed pathological evidence of CTE, suggesting that CTE may be related to prior participation in football.

Methods

Study Recruitment

In 2008, as a collaboration among the VA Boston Healthcare System, Bedford VA, Boston University (BU) School of Medicine, and Sports Legacy Institute (now the Concussion Legacy Foundation [CLF]), a brain bank was created to better understand the long-term effects of repetitive head trauma experienced through contact sport participation and military-related exposure. The purpose of the brain bank was to comprehensively examine the neuropathology and clinical presentation of brain donors considered at risk of development of CTE. The institutional review board at Boston University Medical Campus approved all research activities. The next of kin or legally authorized representative of each brain donor provided written informed consent. No stipend for participation was provided. Inclusion criteria were based entirely on exposure to repetitive head trauma (eg, contact sports, military service, or domestic violence), regardless of whether symptoms manifested during life. Playing American football was sufficient for inclusion. Because of limited resources, more strict inclusion criteria were implemented in 2014 and required that football players who died after age 35 years have at least 2 years of college-level play. Donors were excluded if postmortem interval exceeded 72 hours or if fixed tissue fragments representing less than half the total brain volume were received (eFigure in the Supplement).

Clinical data were collected into a Federal Interagency Traumatic Brain Injury Research–compliant database. Since tracking began in 2014, for 98 (81%) brain donations to the VA-BU-CLF Brain Bank, the next of kin approached the brain bank near the time of death. The remaining brain donors were referred by medical examiners (11 [9%]), recruited by a CLF representative (7 [6%]), or participated in the Brain Donation Registry during life (5 [4%]) (eFigure in the Supplement).

Clinical Evaluation

Retrospective clinical evaluations were performed using online surveys and structured and semistructured postmortem telephone interviews between researchers and informants. Researchers conducting these evaluations were blinded to the neuropathological analysis, and informants were interviewed before receiving the results of the neuropathological examination. A behavioral neurologist, neuroscientist, or neuropsychologist (J.M., D.H.D., T.M.S., M.L.A., or R.A.S.) obtained a detailed history, including a timeline of cognitive, behavioral, mood, and motor symptomology. Additionally, other neuropsychiatric symptoms, exposures and symptoms consistent with posttraumatic stress disorder, features of a substance use disorder, neurodegenerative diagnoses made in life (Alzheimer disease [AD], frontotemporal dementia, vascular dementia, dementia with Lewy bodies, Parkinson disease, CTE, or dementia of unknown etiology), headaches that impaired function, symptoms and diagnoses made in life of sleep disorders, and causes of death were assessed. Clinicians qualitatively summarized the participants' clinical presentation (eg, presence and course of symptoms, functional independence) into a narrative and presented the case to a multidisciplinary consensus team of clinicians, during which it was determined whether the participant met criteria for dementia. To resolve discrepancies in methods that evolved over time, only clinical variables ascertained after January 2014 using a standardized informant report were included because of the larger subset of participants recruited during this time frame (n = 125).

Prior to January 2014, demographics, educational attainment, athletic history (type of sports played, level,

position, age at first exposure, and duration), military history (branch, location of service, and duration of combat exposure), and traumatic brain injury (TBI) history (including number of concussions) were queried during the telephone interview. Beginning in January 2014, demographics, educational attainment, and athletic and military history were queried using an online questionnaire. Informant-reported race was collected as part of demographic information so that neuropathological differences across race could be assessed. To be considered a National Football League (NFL) athlete, a participant must have played in at least 1 regular-season NFL game. Professional position and years of play were verified using available online databases (http://www.pro-football-reference.com, http://databasefootball.com, http://www.juststatsstats.com). History of TBI was queried using informant versions of the Ohio State University TBI Identification Method Short Form[11] and 2 questionnaires adapted from published studies that address military-related head injuries and concussions.[12,13] With the addition of these questionnaires, informants were read a formal definition of concussion prior to being asked about concussion history, which was not the case prior to January 2014.

Neuropathological Evaluation

Pathological processing and evaluation were conducted using previously published methods.[14,15] Brain volume and macroscopic features were recorded during initial processing. Twenty-two sections of paraffin-embedded tissue were stained for Luxol fast blue, hematoxylin and eosin, Bielschowsky silver, phosphorylated tau (ptau) (AT8), α-synuclein, amyloid-β, and phosphorylated transactive response DNA binding protein 43 kDa (pTDP-43) using methods described previously.[16] In some cases, large coronal slabs of the cerebral hemispheres were also cut at 50 µm on a sledge microtome and stained as free-floating sections using AT8 or CP-13.[16,17]

A neuropathological diagnosis was made using criteria for CTE recently defined by the 2015 NINDS-NIBIB Consensus Conference[8] and well-established criteria for other neuropathological diseases, including AD,[18,19] Lewy body disease,[20] frontotemporal lobar degeneration,[21-25] and motor neuron disease.[26,27] Neuropathological criteria for CTE require at least 1 perivascular ptau lesion consisting of ptau aggregates in neurons, astrocytes, and cell processes around a small blood vessel; these pathognomonic CTE lesions are most often distributed at the depths of the sulci in the cerebral cortex and are distinct from the lesions of aging-related tau astrogliopathy.[8] Supportive features for the diagnosis of CTE include ptau pretangles and neurofibrillary tangles (NFTs) in superficial cortical layers (layers II/III) of the cerebral cortex; pretangles, NFTs or extracellular tangles in CA2 and CA4 of the hippocampus; subpial ptau astrocytes at the glial limitans; and dot-like ptau neurites.[8]

Chronic traumatic encephalopathy ptau pathology was classified into 4 stages using previously proposed criteria.[6] Briefly, stage I CTE is characterized by 1 or 2 isolated perivascular epicenters of ptau NFTs and neurites (ie, CTE lesions) at the depths of the cerebral sulci in the frontal, temporal, or parietal cortices. In stage II, 3 or more CTE lesions are found in multiple cortical regions and superficial NFTs are found along the sulcal wall and at gyral crests. Multiple CTE lesions, superficial cortical NFTs, and diffuse neurofibrillary degeneration of the entorhinal and perirhinal cortices, amygdala, and hippocampus are found in stage III CTE. In stage IV CTE, CTE lesions and NFTs are densely distributed throughout the cerebral cortex, diencephalon, and brain stem with neuronal loss, gliosis, and astrocytic ptau pathology. Chronic traumatic encephalopathy pathology in stages I and II is considered to be mild and in stages III and IV is considered to be severe.

Neuropathological evaluation was blinded to the clinical evaluation and was reviewed by 4 neuropathologists (V.A., B.H., T.D.S., and A.M.); any discrepancies in the neuropathological diagnosis were solved by discussion and consensus of the group. In addition to diagnoses, the density of ptau immunoreactive NFTs, neurites, diffuse amyloid-β plaques, and neuritic amyloid-β plaques; vascular amyloid-β; pTDP-43; and α-synuclein immunoreactive Lewy bodies were measured semiquantitatively (0-3, with 3 being most severe) across multiple brain regions.

Descriptive statistics were generated using SPSS software version 20 (IBM Inc).

Results

Among the 202 deceased brain donors (median age at death, 66 years [interquartile range [IQR], 47-76 years]), CTE was neuropathologically diagnosed in 177 (87%; median age at death, 67 years [IQR, 52-77 years]; mean years of football participation, 15.1 [SD, 5.2]; 140 [79%] self-identified as white and 35 [19%] self-identified as black), including 0 of 2 pre-high school, 3 of 14 high school (21%), 48 of 53 college (91%), 9 of 14 semiprofessional (64%), 7 of 8 Canadian Football League (88%), and 110 of 111 NFL (99%) players.

The median age at death for participants with mild CTE pathology (stages I and II) was 44 years (IQR, 29-64 years) and for participants with severe CTE pathology (stages III and IV) was 71 years (IQR, 64-79 years). The most common cause of death for participants with mild CTE pathology was suicide (12 [27%]) and for those with severe CTE pathology was neurodegenerative (ie, dementia-related and parkinsonian-related causes of death) (62 [47%]). The severity of CTE pathology was distributed across the highest level of play, with all former high school players having mild pathology (3 [100%]) and the majority of former college (27 [56%]), semiprofessional (5 [56%]), Canadian Football League (6 [86%]), and NFL (95 [86%]) players having severe pathology. The mean duration of play for participants with mild CTE pathology was 13 years (SD, 4.2 years) and for participants with severe CTE pathology was 15.8 years (SD, 5.3 years) (**Table 1**).

In all cases, perivascular clusters of ptau immunoreactive NFTs diagnostic for CTE (ie, CTE lesions)[8] were found in

Table 1. Demographic and Exposure Characteristics of 177 American Football Players Diagnosed With CTE, Stratified by Neuropathological Severity[a]

Characteristics	No. (%) of Brain Donors[b]		
	Mild CTE (n = 44)	Severe CTE (n = 133)	Total (n = 177)
Men	44 (100)	133 (100)	177 (100)
Race			
White	35 (80)	105 (79)	140 (79)
Black	8 (18)	27 (20)	35 (19)
Pacific Islander	0	1 (1)	1 (1)
Asian	0	0	0
Other	0	0	0
Unknown	1 (2)	0	1 (1)
Age at death, median (IQR), y	44 (29-64)	71 (64-79)	67 (52-77)
Cause of death			
Neurodegenerative[c]	7 (16)	62 (47)	69 (39)
Cardiovascular disease	5 (11)	29 (22)	34 (19)
Suicide	12 (27)	6 (5)	18 (10)
Cancer	2 (5)	10 (8)	12 (7)
Motor neuron disease	4 (9)	7 (5)	11 (6)
Unintentional overdose	3 (7)	4 (3)	7 (4)
Injury	2 (5)	3 (2)	5 (3)
Other	9 (21)	12 (9)	21 (12)
Concussion count, median (IQR)[d]			
Definition provided (n = 99)	90 (22-150)	50.5 (12-163)	70 (12-150)
No definition provided (n = 61)	2.5 (0-5)	8 (1-19)	5 (1-13)
Age at first exposure to football, median (IQR), y	10 (8-14)	13 (10-14)	12 (10-14)
Duration of play, mean (SD), y	13 (4.2)	15.8 (5.3)	15.1 (5.2)
Highest level of play			
Youth	0	0	0
High school	3 (7)	0	3 (2)
College	21 (48)	27 (20)	48 (27)
Semiprofessional	4 (9)	5 (4)	9 (5)
Canadian Football League	1 (2)	6 (5)	7 (4)
National Football League	15 (34)	95 (71)	110 (62)
Primary position at highest level of play			
Offensive lineman	8 (18)	29 (22)	37 (21)
Defensive lineman	8 (18)	27 (20)	35 (20)
Running back	4 (9)	27 (20)	31 (18)
Linebacker	12 (27)	14 (11)	26 (15)
Defensive back	4 (9)	18 (14)	22 (12)
Quarterback	2 (5)	11 (8)	13 (7)
Tight end	1 (2)	6 (5)	7 (4)
Wide receiver	3 (7)	1 (1)	4 (2)
Kicker or punter	2 (5)	0	2 (1)
Other special teams	0	0	0
Military veteran	5 (11)	40 (30)	45 (25)

Abbreviations: CTE, chronic traumatic encephalopathy; IQR, interquartile range.

[a] Mild CTE (CTE neuropathological stages I and II) is characterized by sparse to frequent perivascular CTE lesions at the sulcal depths of the cerebral cortex. Severe CTE (CTE neuropathological stages III and IV) consists of multiple CTE lesions in the cerebral cortex and moderate to severe neurofibrillary degeneration of medial temporal lobe, diencephalon, and brain stem.

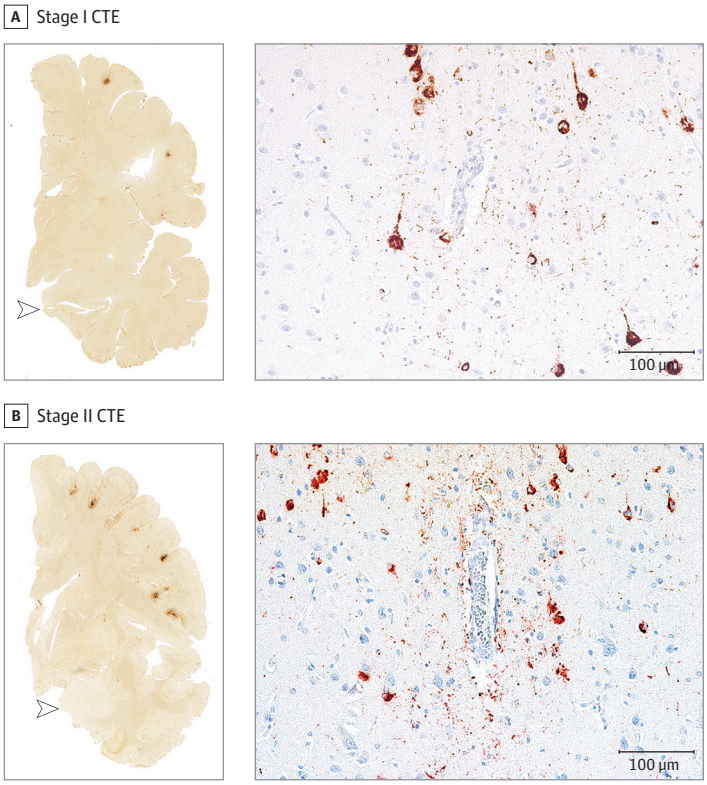
[b] Data are expressed as No. (%) unless otherwise indicated.

[c] Includes dementia-related and parkinsonian-related causes of death.

[d] Median estimates of the number of concussions reported per participant. Beginning in 2014, informants were read a formal definition of concussion prior to being asked about concussion history.

the cerebral cortex (**Figure 1** and **Figure 2**). In cases with mild CTE pathology (stages I and II), isolated perivascular CTE lesions were found at the sulcal depths of the cerebral cortex, most commonly in the superior and dorsolateral frontal cortices, but also in the lateral temporal, inferior parietal, insula, and septal cortices (Figure 1). Neurofibrillary tangles were sparse in other cortical regions, and there was no diffuse neurofibrillary degeneration of the medial temporal lobe structures (Figure 1, open arrowheads). Neurofibrillary tangles were also found in the locus coeruleus, substantia nigra, and substantia innominata (**Figure 3**) in mild CTE. In cases with severe CTE pathology, perivascular CTE lesions were large and confluent (Figure 2). Neurofibrillary tangles were widely distributed in the superficial laminae of cortical regions and there was severe neurofibrillary degeneration of the medial temporal lobe structures,

Figure 1. Representative Images of Phosphorylated Tau Pathology at CTE Pathological Stages I and II



CTE indicates chronic traumatic encephalopathy; NFT, neurofibrillary tangle; ptau, phosphorylated tau. For all images, 10-µm paraffin-embedded tissue sections were immunostained with microscopic mouse monoclonal antibody for phosphorylated tau (AT8) (Pierce Endogen). Positive ptau immunostaining appears dark red, hematoxylin counterstain; calibration bar indicates 100 µm. Stage I CTE is characterized by 1 or 2 isolated perivascular epicenters of ptau NFTs and neurites (ie, CTE lesions) at the depths of the cortical sulci. In stage II, 3 or more cortical CTE lesions are found. All hemispheric tissue section images are 50-µm sections immunostained with mouse monoclonal antibody CP-13, directed against phosphoserine 202 of tau (courtesy of Peter Davies, PhD, Feinstein Institute for Medical Research; 1:200); this is considered to be an early site of tau phosphorylation in NFT formation.[28] Positive ptau immunostaining appears dark brown. A, Former college football player with stage I CTE. Two perivascular ptau CTE lesions are evident at sulcal depths of the frontal cortex; there is no neurofibrillary degeneration in the medial temporal lobe (open arrowhead). Perivascular CTE lesion: neurofibrillary tangles and dot-like and threadlike neurites encircle a small blood vessel. B, Former NFL player with stage II CTE. There are multiple perivascular ptau CTE lesions at depths of sulci of the frontal cortex; there is no neurofibrillary degeneration in the medial temporal lobe (open arrowhead). Perivascular CTE lesion: a cluster of NFTs and large dot-like and threadlike neurites surround a small blood vessel.

including the hippocampus, amygdala, and entorhinal cortex (Figure 2, black arrowheads, and Figure 3). Neurofibrillary tangles were also frequent in the thalamus, nucleus basalis of Meynert, substantia innominata, substantia nigra, and locus coeruleus in severe CTE (Figure 3).

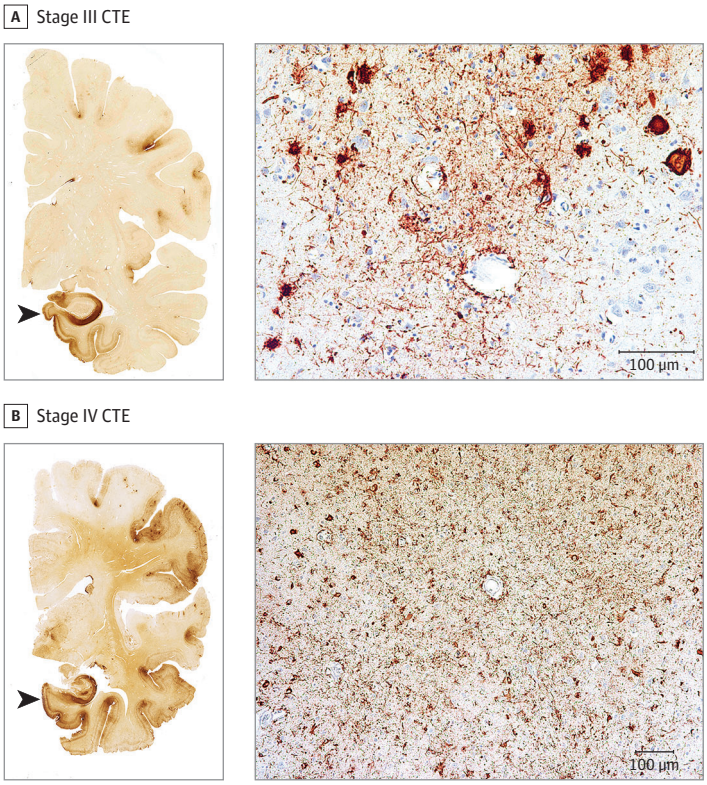
Deposition of amyloid-β was present in a subset of participants at all stages of CTE pathology, predominantly as diffuse amyloid-β plaques, but neuritic amyloid-β plaques and amyloid angiopathy were also present. In stage IV CTE, amyloid-β deposition occurred in 52 cases (91%). Deposition of TDP-43 and α-synuclein were found in all stages of CTE pathology; TDP-43 deposition occurred in 47 (83%) and α-synuclein deposition occurred in 23 (40%) stage IV CTE cases (**Table 2**).

Among the 25 football players without CTE, 9 showed no pathological abnormalities and 7 showed nonspecific changes; eg, hemosiderin-laden macrophages (n = 7) and axonal injury (n = 5). Other diagnoses included vascular pathology (n = 4), unspecified tauopathy not meeting criteria for CTE (n = 3), AD (n = 2), argyrophilic grain disease (n = 1), and Lewy body disease (n = 1).

Data on informants were collected beginning in 2014. The median number of participating informants was 2 (IQR, 1-3) per participant. Among all of the interviews, 71 (64%) included a spouse/partner, 56 (51%) included an adult child, 27 (24%) included a sibling, 16 (14%) included a parent, 13 (12%) included a non-first-degree relative, 8 (7.2%) included a neighbor or friend, and 4 included other informants. Among the informants who knew the participant the longest, the mean relationship length was 45.8 years (SD, 1.5 years).

Among the 111 CTE cases with standardized informant reports on clinical symptoms, a reported progressive clinical course was common in participants with both mild and severe CTE pathology, occurring in 23 (85%) mild cases and 84 (100%) severe cases (**Table 3**). Behavioral or mood symptoms were common in participants with both mild and severe CTE pathology, with symptoms occurring in 26

Figure 2. Representative Images of Phosphorylated Tau Pathology at CTE Pathological Stages III and IV



CTE indicates chronic traumatic encephalopathy; NFT, neurofibrillary tangle; ptau, phosphorylated tau. For all images, 10-µm paraffin-embedded tissue sections were immunostained with microscopic mouse monoclonal antibody for phosphorylated tau (AT8) (Pierce Endogen). Positive ptau immunostaining appears dark red, hematoxylin counterstain; calibration bar indicates 100 µm. In stage III CTE, multiple CTE lesions and diffuse neurofibrillary degeneration of the medial temporal lobe are found. In stage IV CTE, CTE lesions and NFTs are widely distributed throughout the cerebral cortex, diencephalon, and brain stem.[6] All hemispheric tissue section images are 50-µm sections immunostained with mouse monoclonal antibody CP-13, directed against phosphoserine 202 of tau (courtesy of Peter Davies, PhD, Feinstein Institute for Medical Research; 1:200); this is considered to be an early site of tau phosphorylation in NFT formation.[28] Positive ptau immunostaining appears dark brown. A, Former NFL player with stage III CTE. There are multiple large CTE lesions in the frontal cortex and insula; there is diffuse neurofibrillary degeneration of hippocampus and entorhinal cortex (black arrowhead). Perivascular CTE lesion: a dense collection of NFTs and large dot-like and threadlike neurites enclose several small blood vessels. B, Former NFL player with stage IV CTE. There are large, confluent CTE lesions in the frontal, temporal, and insular cortices and there is diffuse neurofibrillary degeneration of the amygdala and entorhinal cortex (black arrowhead). Perivascular CTE lesion: a large accumulation of NFTs, many of them ghost tangles, encompass several small blood vessels.

(96%) mild cases and 75 (89%) severe cases. Impulsivity, depressive symptoms, apathy, and anxiety occurred in 23 (89%), 18 (67%), 13 (50%), and 14 (52%) mild cases and 65 (80%), 46 (56%), 43 (52%), and 41 (50%) severe cases, respectively. Additionally, hopelessness, explosivity, being verbally violent, being physically violent, and suicidality (including ideation, attempts, or completions) occurred in 18 (69%), 18 (67%), 17 (63%), 14 (52%), and 15 (56%) mild cases, respectively. Substance use disorders were also common in participants with mild CTE, occurring in 18 (67%) mild cases. Symptoms of posttraumatic stress disorder were uncommon in both groups, occurring in 3 (11%) mild cases and 9 (11%) severe cases.

Cognitive symptoms were common in participants with both mild and severe CTE pathology, with symptoms occurring in 23 (85%) mild cases and 80 (95%) severe cases. Memory, executive function, and attention symptoms occurred in 19 (73%), 19 (73%), and 18 (69%) mild cases and 76 (92%), 67 (81%), and 67 (81%) severe cases, respectively. Additionally, language and visuospatial symptoms occurred in 54 (66%) and 44 (54%) severe cases, respectively. A premortem diagnosis of AD and a postmortem (but blinded to pathology) consensus diagnosis of dementia were common in severe cases, occurring in 21 (25%) and 71 (85%), respectively. There were no asymptomatic (ie, no mood/behavior or cognitive symptoms) CTE cases. Motor symptoms were common in severe cases, occurring in 63 (75%). Gait instability and slowness of movement occurred in 55 (66%) and 42 (50%) severe cases, respectively. Symptom frequencies remained similar when only pure CTE cases (ie, those with no neuropathological evidence of comorbid neurodegenerative disease) were considered (eTable in the Supplement).

Among the 111 CTE cases with standardized informant reports on clinical symptoms, 47 (42.3%; median age at death, 76 years [IQR, 63-81 years]) initially presented with cognitive symptoms, 48 (43.2%; median age at death, 66 years [IQR, 54-73 years]) initially presented with behavior or

Figure 3. Phosphorylated Tau Pathology for Each Brain Region by CTE Neuropathological Stage

		Brain Region												
CTE Stage	No. of Donors	Frontal	Temporal	Parietal	Septal	Insula	Entorhinal	Amygdala	Hippocampus	Thalamus	SI	SN	LC	Cerebellum
1	11	1.1	0.6	0.2	0.4	0.3	0.6	0.4	0.1	0.3	0.5	0.6	0.9	0
2	33	1.6	1.4	1.3	1.2	1.1	1.4	1.1	0.7	0.9	1.3	1.0	2.0	0.2
3	76	2.2	2.1	1.6	2.0	2.1	2.6	2.3	2.1	1.4	2.3	1.8	2.5	0.3
4	57	2.8	2.7	2.6	2.7	2.8	2.8	2.8	2.4	2.2	2.7	2.5	2.5	0.6
Total	177	2.2	2.1	1.8	2.0	2.1	2.3	2.1	1.8	1.5	2.1	1.8	2.3	0.3

CTE indicates chronic traumatic encephalopathy; NFT: neurofibrillary tangle, SI: substantia innominata, SN: substantia nigra; LC: locus coeruleus. Cerebellum indicates dentate nucleus of the cerebellum. In each region, 0 = no NFTs (yellow); 1 = 1 NFT per 20× field (orange); 2 = 2 to 3 NFTs per 20× field (amber); and 3 = ≥4 NFTs per 20× field (red). The color scale is based on the distribution of all values, not by each individual stage. Values represent means of phosphorylated tau pathology among participants in each stage.

mood symptoms, and 16 (14.4%; median age at death, 65.5 years [IQR, 39-78]) initially presented with both cognitive symptoms and behavior or mood symptoms. Forty (85%) of those initially presenting with only cognitive symptoms were reported to have behavior or mood symptoms at the time of death and 43 (90%) of those initially presenting with only behavior or mood symptoms were reported to have cognitive symptoms at the time of death. Dementia was present at the time of death in 36 (77%) of those initially presenting with cognitive symptoms, 33 (69%) of those initially presenting with behavior or mood symptoms, and 11 (69%) of those initially presenting with both cognitive and behavior or mood symptoms.

The most common primary cause of death was neurodegenerative for all 3 groups (cognitive, 26 [55%]; behavior or mood, 16 [33%]; both cognitive and behavior or mood, 6 [38%]). Substance use disorders, suicidality, and family history of psychiatric illness were common among those who initially presented with behavior or mood symptoms, occurring in 32 (67%), 22 (47%), and 23 (49%) cases, respectively.

Discussion

In a convenience sample of 202 deceased former players of American football who were part of a brain donation program, a high proportion were diagnosed neuropathologically with CTE. The severity of CTE pathology was distributed across the highest level of play, with all former high school players having mild pathology and the majority of former college, semiprofessional, and professional players having severe pathology. Behavior, mood, and cognitive symptoms were common among those with mild and severe CTE pathology and signs of dementia were common among those with severe CTE pathology.

Nearly all of the former NFL players in this study had CTE pathology, and this pathology was frequently severe. These findings suggest that CTE may be related to prior participation in football and that a high level of play may be related to substantial disease burden. Several other football-related factors may influence CTE risk and disease severity, including but not limited to age at first exposure to football, duration of play, player position, cumulative hits, and linear and rotational acceleration of hits. Recent work in living former football players has shown that age at first exposure may be related to impaired cognitive performance[29] and altered corpus callosum white matter[30] and that cumulative hits may be related to impairment on self-report and objective measures of cognition, mood, and behavior,[31] although it is unclear if any of these outcomes are related to CTE pathology. Furthermore, it is unclear if symptomatic hits (concussions) are more important than asymptomatic hits resulting in subconcussive injury. As with other neurodegenerative diseases, age may be related to risk and pathological severity in CTE. It will be important for future studies to resolve how different measures of exposure to football and age influence the outcome.

In cases with severe CTE pathology, accumulations of amyloid-β, α-synuclein, and TDP-43 were common. These findings are consistent with previous studies that show deposition of multiple neurodegenerative proteins after exposure to TBI[32] and with work showing that neuritic amyloid-β plaques are associated with increased CTE neuropathological stage.[33] Diagnoses of comorbid neurodegenerative diseases, including AD, Lewy body disease, motor neuron disease, and frontotemporal lobar degeneration, were also common in cases with severe CTE pathology. Overall, 19% of participants with CTE had comorbid Lewy body disease, which aligns with a recent observation by Crane et al[34] regarding the increased prevalence of Lewy body pathology after single TBI. Chronic traumatic encephalopathy was not assessed in the analysis by Crane et al; to investigate the possibility of CTE after single TBI would require more extensive sampling of the depths of the cortical sulci with ptau immunostaining, as silver stains typically do not detect CTE pathology.

Table 2. Neuropathological Findings in 177 American Football Players, Stratified by Severity of Phosphorylated Tau Pathology (CTE Stage)[a]

CTE Stage	No. of Brain Donors	Age at Death, Median (IQR), y	Neuropathological Features, No. (%)						Other Neuropathological Diagnoses, No. (%)					Pure CTE, No. (%)
			Aß	DP	NP	AA	TDP-43	αs	AD	LBD	FTLD TDP-43	FTLD-Tau	MND	
1	11	36 (25-56)	2 (18)	2 (18)	1 (9)	1 (9)	2 (18)	1 (9)	0	1 (9)	1 (9)	0	0	8 (73)
2	33	49 (29-65)	8 (24)	8 (24)	5 (15)	7 (21)	10 (30)	3 (9)	1 (3)	2 (6)	1 (3)	1 (3)	4 (12)	21 (64)
3	76	67 (57-78)	45 (59)	41 (54)	25 (33)	29 (38)	26 (34)	16 (21)	4 (5)	15 (20)	1 (1)	3 (4)	6 (8)	42 (55)
4	57	76 (69-82)	52 (91)	52 (91)	42 (74)	32 (56)	47 (83)	23 (40)	18 (32)	16 (28)	5 (9)	2 (4)	1 (2)	27 (47)
Total	177	67 (53-78)	107 (61)	103 (58)	73 (41)	69 (39)	85 (48)	43 (24)	23 (13)	34 (19)	8 (5)	6 (3)	11 (6)	98 (55)

Abbreviations: AA, amyloid angiopathy; Aß, amyloid-β; AD, Alzheimer disease; αs, α-synuclein immunopositive Lewy bodies; CTE, chronic traumatic encephalopathy diagnosed neuropathologically; DP, diffuse Aß plaques; FTLD-tau, frontotemporal lobar degeneration-tau; FTLD TDP-43, frontotemporal lobar degeneration TDP-43; IQR, interquartile range; LBD, Lewy body disease; MND, motor neuron disease; NP, neuritic Aß plaques; TDP-43, TDP-43 immunopositive neurites or inclusions.

[a] Pure CTE is defined as CTE with no neuropathological evidence of other comorbid neurodegenerative disease. Stage I CTE is characterized by 1 or 2 perivascular CTE lesions at the depths of the cerebral sulci in the cerebral cortex. In stage II, 3 or more CTE lesions are found in multiple cortical regions. In stage III CTE, many CTE lesions, superficial cortical neurofibrillary tangles, and diffuse neurofibrillary degeneration of the entorhinal and perirhinal cortices, amygdala, and hippocampus are found. In stage IV CTE, CTE lesions and neurofibrillary tangles are densely distributed throughout the cerebral cortex, diencephalon, and brain stem with neuronal loss, gliosis, and astrocytic phosphorylated tau pathology.

Behavioral, mood, and cognitive symptoms were common among participants with either mild or severe CTE pathology. In participants with severe CTE pathology, there was marked ptau pathology in brain regions that have been associated with symptoms frequently reported: impulsivity, depressive symptoms, apathy, anxiety, and explosivity (prefrontal cortex, amygdala, locus coeruleus); episodic memory symptoms (hippocampus and entorhinal and perirhinal cortices); and attention and executive function symptoms (prefrontal cortex). Participants with mild CTE pathology often had these symptoms despite having relatively circumscribed cortical pathology and absence of ptau pathology in the hippocampus, entorhinal cortex, or amygdala. This may suggest that other pathologies not captured by the pathological data set, such as neuroinflammation, axonal injury, or astrocytosis, or pathologies in neuroanatomical regions not evaluated contribute to these clinical symptoms. Microglial neuroinflammation appears to precede tau accumulation in CTE,[35] suggesting it may play a role in early symptoms.

Informants reported that 43% of participants had behavior or mood symptoms as their initial presentation. Many of these participants had a substance use disorder, demonstrated suicidality, or had a family history of psychiatric illness. Behavior or mood symptoms may be the initial presentation for a subset of individuals with CTE, or alternatively, CTE ptau pathology may lower the threshold for psychiatric manifestations in susceptible individuals. These clinical observations confirm and expand on previous reports of 2 primary clinical presentations of CTE.[9]

There is substantial evidence that CTE is a progressive, neurodegenerative disease. In this study, 107 participants (96%) had a progressive clinical course based on informant report. In addition, pathological severity of CTE was correlated with age at death (Table 3). However, a postmortem study evaluates brain pathology at only 1 time point and is by definition cross-sectional. In addition, the participants were not observed longitudinally during life. Although associations with age in cross-sectional samples can result from age-related progression within individuals, they can also arise from birth cohort effects, differential survival, or age-related differences in how individuals were selected into the study. Population-based prospective studies are needed to address the issue of progression of CTE pathology and age at symptom onset.

The strengths of this study are that this is the largest CTE case series ever described to our knowledge, more than doubling the size of the 2013 report,[6] and that all participants were exposed to a relatively similar type of repetitive head trauma while playing the same sport. In addition, the comprehensive neuropathological evaluation and retrospective clinical data collection were independently performed while blinded to the findings of the other investigators.

This study had several limitations. First, a major limitation is ascertainment bias associated with participation in this brain donation program. Although the criteria for participation were based on exposure to repetitive head trauma rather than on clinical signs of brain trauma, public awareness of a possible link between repetitive head trauma and

Table 3. Clinical Features Reported in 111 American Football Players Diagnosed as Having CTE, Stratified by Neuropathological Severity[a]

Clinical Features	No. (%) of Brain Donors		
	Mild CTE	Severe CTE	Total
Progressive course	23 (85)	84 (100)	107 (96)
Cognitive symptoms[b]	23 (85)	80 (95)	103 (93)
Memory	19 (73)	76 (92)	95 (86)
Executive function	19 (73)	67 (81)	86 (79)
Attention	18 (69)	67 (81)	85 (78)
Language	10 (39)	54 (66)	64 (59)
Visuospatial	7 (27)	44 (54)	51 (47)
Fluctuating cognition	2 (8)	17 (21)	19 (18)
Dementia[b]	9 (33)	71 (85)	80 (72)
Behavioral or mood symptoms[b]	26 (96)	75 (89)	101 (91)
Impulsivity	23 (89)	65 (80)	88 (82)
Depressive symptoms	18 (67)	46 (56)	64 (59)
Explosivity	18 (67)	38 (45)	56 (51)
Apathy	13 (50)	43 (52)	56 (51)
Anxiety	14 (52)	41 (50)	55 (51)
Hopelessness	18 (69)	36 (46)	54 (52)
Verbal violence	17 (63)	28 (34)	45 (41)
Social inappropriateness	13 (48)	26 (32)	39 (36)
Physical violence	14 (52)	23 (28)	37 (34)
Paranoia	11 (41)	26 (31)	37 (34)
Suicidality (ideation, attempts, or completions)	15 (56)	21 (25)	36 (33)
Visual hallucinations	6 (23)	22 (27)	28 (26)
Mania	6 (22)	3 (4)	9 (8)
Posttraumatic stress disorder (exposure and symptoms consistent with)	3 (11)	9 (11)	12 (11)
Substance use disorder	18 (67)	41 (49)	59 (53)
Alcohol	13 (50)	31 (37)	44 (41)
Anabolic steroid	0	4 (5)	4 (4)
Other	14 (54)	23 (28)	37 (34)
Motor symptoms[b]	13 (48)	63 (75)	76 (68)
Gait instability	7 (26)	55 (66)	62 (56)
Slowness	5 (19)	42 (50)	47 (42)
Coordination difficulties	7 (26)	38 (45)	45 (41)
Falls	4 (15)	39 (46)	43 (39)
Tremor	5 (19)	33 (39)	38 (34)
Dysphagia	3 (11)	14 (18)	17 (16)
Dysarthria	5 (19)	10 (13)	15 (14)
Headache	8 (30)	11 (14)	19 (18)
Diagnoses in life			
Motor neuron disease	1 (4)	3 (4)	4 (4)
Parkinson disease	1 (4)	5 (6)	6 (6)
Alzheimer disease	1 (4)	21 (25)	22 (20)
Obstructive sleep apnea (diagnosis or symptoms)	7 (27)	36 (46)	43 (41)
Rapid eye movement sleep behavior disorder (diagnosis or symptoms)	7 (27)	23 (29)	30 (29)

Abbreviation: CTE, chronic traumatic encephalopathy.

[a] There were 111 participants with standardized informant reports, including 27 participants with mild CTE and 84 participants with severe CTE. Sample sizes differed across clinical features because features marked as unknown by the clinician were excluded. For participants with mild CTE, sample sizes ranged from 25 to 27 and for participants with severe CTE, sample sizes ranged from 78 to 84. Mild CTE (CTE neuropathological stages I and II) is characterized by sparse to frequent perivascular CTE lesions at the sulcal depths of the cerebral cortex. Severe CTE (CTE neuropathological stages III and IV) consists of multiple CTE lesions in the cerebral cortex and moderate to severe neurofibrillary degeneration of medial temporal lobe, diencephalon, and brain stem.

[b] Symptoms were present in the last year of life.

CTE may have motivated players and their families with symptoms and signs of brain injury to participate in this research. Therefore, caution must be used in interpreting the high frequency of CTE in this sample, and estimates of prevalence cannot be concluded or implied from this sample. Second, the VA-BU-CLF brain bank is not representative of the overall population of former players of American football; most players of American football have played only on youth or high school teams, but the majority of the brain bank donors in this study played at the college or

professional level. Additionally, selection into brain banks is associated with dementia status, depression status, marital status, age, sex, race, and education.[36] Third, this study lacked a comparison group that is representative of all individuals exposed to American football at the college or professional level, precluding estimation of the risk of participation in football and neuropathological outcomes.

Conclusions

In a convenience sample of deceased football players who donated their brains for research, a high proportion had neuropathological evidence of CTE, suggesting that CTE may be related to prior participation in football.

ARTICLE INFORMATION

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Neurodegenerative causes of death among retired National Football League players

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ABSTRACT

Objective: To analyze neurodegenerative causes of death, specifically Alzheimer disease (AD), Parkinson disease, and amyotrophic lateral sclerosis (ALS), among a cohort of professional football players.

Methods: This was a cohort mortality study of 3,439 National Football League players with at least 5 pension-credited playing seasons from 1959 to 1988. Vital status was ascertained through 2007. For analysis purposes, players were placed into 2 strata based on characteristics of position played: nonspeed players (linemen) and speed players (all other positions except punter/kicker). External comparisons with the US population used standardized mortality ratios (SMRs); internal comparisons between speed and nonspeed player positions used standardized rate ratios (SRRs).

Results: Overall player mortality compared with that of the US population was reduced (SMR 0.53, 95% confidence interval [CI] 0.48–0.59). Neurodegenerative mortality was increased using both underlying cause of death rate files (SMR 2.83, 95% CI 1.36–5.21) and multiple cause of death (MCOD) rate files (SMR 3.26, 95% CI 1.90–5.22). Of the neurodegenerative causes, results were elevated (using MCOD rates) for both ALS (SMR 4.31, 95% CI 1.73–8.87) and AD (SMR 3.86, 95% CI 1.55–7.95). In internal analysis (using MCOD rates), higher neurodegenerative mortality was observed among players in speed positions compared with players in nonspeed positions (SRR 3.29, 95% CI 0.92–11.7).

Conclusions: The neurodegenerative mortality of this cohort is 3 times higher than that of the general US population; that for 2 of the major neurodegenerative subcategories, AD and ALS, is 4 times higher. These results are consistent with recent studies that suggest an increased risk of neurodegenerative disease among football players. *Neurology*® 2012;79:1970–1974

GLOSSARY

AD = Alzheimer disease; **ALS** = amyotrophic lateral sclerosis; **CI** = confidence interval; **CTE** = chronic traumatic encephalopathy; **ICD** = International Classification of Diseases; **MCOD** = multiple cause of death; **NDI** = National Death Index; **NFL** = National Football League; **NIOSH** = National Institute for Occupational Safety and Health; **PD** = Parkinson disease; **SMR** = standardized mortality ratio; **SSR** = standardized rate ratio.

In 1994, the National Institute for Occupational Safety and Health (NIOSH) conducted a mortality study of National Football League (NFL) players.[1] One notable result was an increase in "nervous system" deaths due to 4 cases of amyotrophic lateral sclerosis (ALS). Little additional study on neurologic disorders in football players was conducted until several prominent NFL players retired from the game with lingering and unresolved neurologic sequelae from recurrent mild traumatic brain injuries (concussions).[2] Since then multiple studies have raised concerns about the longer-term health effects of recurrent concussions.[3,4] Research based on autopsy data has identified chronic traumatic encephalopathy (CTE) as a pathologically distinct neurodegenerative condition affecting a wide range of individuals, including football players, who have experienced multiple concussions.[5–7] CTE results from the progressive decline in neuron functioning occurring years or

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Go to Neurology.org for full disclosures. Disclosures deemed relevant by the authors, if any, are provided at the end of this article.

decades after exposure to repetitive concussive injuries and presents clinically as progressive neurologic dysfunction affecting mental status, balance, and movement.[8]

The purpose of this article is to report the results of an analysis of NFL player mortality from neurodegenerative disorders including Alzheimer disease (AD), Parkinson disease (PD), and ALS. It is not possible to directly examine mortality from CTE because the pathologic refinement of the CTE diagnosis has only occurred within the last few years, and CTE is not listed as a cause of death in any revision of the International Classification of Diseases (ICD). As an alternative, because it is now known that neurologic conditions previously attributed to AD, PD, and ALS may actually have been related to CTE,[4,9] an analysis that combined all neurodegenerative causes of death was conducted; this analysis included deaths that may be related to CTE even if not reported as such on death certificates.

METHODS Full details of the cohort have been described previously.[1,10] In brief, the cohort includes 3,439 NFL players identified by a pension fund database of vested players with at least 5 credited playing seasons between 1959 and 1988. Vital status was ascertained from pension fund records, the Social Security Administration, and the Internal Revenue Service. Players were matched to the National Death Index (NDI) beginning in 1979 (when the NDI began) with follow-up through 2007. The NDI provided underlying and contributing causes of death, coded to the ICD revision in effect at the time of death. Death certificates were obtained from state vital statistics offices and were coded by a certified nosologist when death information was not provided by the NDI.

Mortality was analyzed using the NIOSH life table analysis system (LTAS.NET).[11] Analyses used US male mortality rates (1960–2007) for 119 cause of death categories.[12] Mortality for 3 neurodegenerative causes of death was evaluated using updated custom rate files.[13] Standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) were adjusted for race, age (in 5-year categories), and calendar year (in 5-year categories). Because AD and PD are more likely to be listed as a contributing cause than as the underlying cause, additional analyses used multiple cause of death (MCOD) rate files to examine all causes listed on the death certificates. Good candidates for MCOD analyses are diseases of long duration, not necessarily fatal, that are serious enough to be noted on the death certificate.[14]

Recent studies suggested that football players who play certain positions are at higher risk of concussion because of the high acceleration, rotational acceleration, and multiple impacts they experience during games.[15,16] Data collected using exposure assessment methods including video analysis, simulation and reconstruction techniques, and helmet-mounted accelerometers suggest that although linemen experience the highest number of head impacts, other positions experience higher acceleration impacts that result in concussions.[16–18] To examine possible neurologic mortality differences from the high acceleration head impacts, we stratified the players into 2 categories based on position played[10] (identified using annual data compiled in commercial publications): speed (quarterback, running back, halfback, fullback, wide receiver, tight end, defensive back, safety, and linebacker) and nonspeed (all defensive and offensive linemen); punters and kickers were excluded from the stratified analysis. LTAS.NET was used to calculate directly standardized rate ratios (SRRs) and 95% CIs for the neurodegenerative causes using the nonspeed players as an internal referent; 95% CIs that excluded unity were considered to be statistically significant.

Standard protocol approvals, registrations, and patient consents. The protocol for this study was approved by the NIOSH Institutional Review Board and has been assigned approval number HSRB 06-DSHEFS-04XP.

RESULTS Approximately 39% of the cohort is African American, and 62% played speed positions (table 1). African American players comprise almost half (48%) of the speed stratum but only 28% of the nonspeed stratum. There were minimal differences between the strata for all other cohort characteristics. The cohort is relatively young (median age of 57 at date last observed), and only 10% are deceased.

Compared with that of US men, the overall mortality in the cohort was significantly reduced (table 2); however, mortality was significantly elevated for all neurodegenerative causes combined and for the subclassifications of AD (when all causes on death certificates were considered) and ALS. Mortality from PD was elevated but did not reach statistical significance. Overall, results based on all contributing causes were similar to results based on underlying causes with the exception of AD, which was more likely to be listed as a contributing cause rather than the underlying cause on death certificates. Neurodegenerative mortality stratified by speed position considered all death certificate causes (table 3). Compared with those for US men, SMRs for the speed positions were significantly elevated for all neurodegenerative causes combined, AD, and ALS, but not for PD. Neurodegenerative mortality was not elevated for the nonspeed positions. Compared with the nonspeed positions, mortality was nonsignificantly elevated for the speed positions for all neurodegenerative causes combined, AD, and ALS, but not for PD. These results were highly imprecise because of the small numbers.

DISCUSSION Although the overall mortality of this cohort is significantly lower than expected (SMR 0.53), the neurodegenerative mortality is 3 times higher than that of the general US population; that for 2 of the major neurodegenerative subcategories, AD and ALS, is 4 times higher. These results are consistent with recent studies that suggest an in-

Table 1 Characteristics of the National Football League Players Cohort, overall and by position category (1960–2007)[a]

Characteristic	Overall (n = 3,439)	Speed (n = 2,145)	Nonspeed (n = 1,166)
Race, n (%)			
White	2,070 (60)[b]	1,111 (52)	835 (72)
African American	1,355 (39)	1,029 (48)	323 (28)
Other	14 (<1)	5 (<1)	8 (1)
Vital status as of December 31, 2007, n (%)			
Alive	3,105 (90)	1,972 (92)	1,014 (87)
Dead	334 (10)	173 (8)	152 (13)
First credited season			
Median (range)	1973 (1950-1984)	1974 (1950-1984)	1972 (1950-1984)
<1980, n (%)	2,685 (78)	1,654 (77)	930 (80)
≥1980, n (%)	754 (22)	491 (23)	236 (20)
No. credited seasons (as of 1988/1989 season), median (range)[c]	8 (5-25)	7 (5-21)	8 (5-20)
Age at death, y, median (range)	54 (27-81)	54 (27-80)	53 (29-81)
Age at date last observed, alive			
Median (range)	57 (45-88)	56 (45-82)	57 (45-83)
<50 y, n (%)	633 (20)	409 (21)	203 (20)
50–54 y, n (%)	738 (24)	502 (25)	208 (21)
55–59 y, n (%)	565 (18)	338 (17)	206 (20)
60–69 y, n (%)	890 (29)	552 (28)	300 (30)
≥70 y, n (%)	279 (9)	171 (9)	97 (10)

[a] Player position was collapsed into 2 strata for analysis purposes: speed positions (fullback, halfback, defensive back, quarterback, wide receiver, running back, linebacker, and tight end) and nonspeed positions (defensive end/lineman/tackle, guard, nose guard, tackle, center, and offensive end/guard/lineman/tackle). Punters and kickers are included in the overall results only.
[b] Percentages may not sum to 100% due to rounding.
[c] Number of credited seasons does not necessarily equal the number of seasons played.

creased risk of neurodegenerative disease among football players.

It is not possible to determine from our study what has caused this increased risk. Research suggests that football players who have experienced one or more concussive blows to the head are at increased risk of neurologic disorders. In retired professional players, one study observed a 5-fold prevalence of mild cognitive disorders and a 3-fold prevalence of significant memory problems for players who experienced 3 or more concussions compared with players with fewer than 3 concussions.[3] Excess neurologic mortality and morbidity has also been reported in players of other sports for which head impacts and concussion are common: soccer, boxing, horse racing, and hockey.[19]

Studies that examined the incidence of concussion in football players found that players in speed positions experienced concussions more commonly than players in nonspeed positions. Speed players are those who are able to build up considerable momentum before the point of being tackled or tackling another player.[15,17,20] Offensive and defensive linemen (nonspeed players) usually engage other players soon after the football is snapped, thus mitigating the potential to build up momentum before a tackle or a block.[15,16]

Although our study used causes of death from AD, PD, and ALS as reported on death certificates, recent research now suggests that CTE may have been the true primary or secondary factor in some of these deaths. Whereas CTE is a clinically distinct neurologic diagnosis, CTE symptoms are often similar to those found in patients with AD, PD, and ALS.[6,21] In addition, CTE is not listed as a distinct cause of death recognized in current or previous ICD revisions, precluding the calculation of CTE-specific results. To account for possible misclassification, we reported combined results for all neurodegenerative causes.

Our study had several limitations. Our analysis is based on a few neurodegenerative deaths; therefore, the confidence intervals surrounding our SMR and SRR values are relatively broad. The few deaths also limited our ability to stratify players into more than 2 broad position categories; therefore, we were not able to identify potentially important differences in neu-

Table 2 Overall mortality, selected causes, National Football League Players Cohort (1960–2007)

	Underlying[a]		Contributing[b]	
Cause of death	No.	SMR (95% CI)	No.	SMR (95% CI)
All deaths	334	0.53 (0.48–0.59)	782	0.54 (0.51–0.58)
All cancers	85	0.58 (0.46–0.72)	122	0.63 (0.53–0.76)
All cardiovascular diseases	126	0.68 (0.56–0.81)	340	0.71 (0.64–0.79)
All neurodegenerative causes	10	2.83 (1.36–5.21)	17	3.26 (1.90–5.22)
Dementia/Alzheimer disease[c]	2	1.80 (0.22–6.50)	7	3.86 (1.55–7.95)
Amyotrophic lateral sclerosis[d]	6	4.04 (1.48–8.79)	7	4.31 (1.73–8.87)
Parkinson disease[e]	2	2.14 (0.26–7.75)	3	1.69 (0.35–4.94)
All injuries	41	0.63 (0.45–0.86)	57	0.69 (0.52–0.89)
Violence	13	0.27 (0.14–0.46)	13	0.26 (0.14–0.45)
All other causes	59	0.34 (0.26–0.43)	233	0.37 (0.33–0.42)

Abbreviations: CI = confidence interval; ICD = International Classification of Diseases; SMR = standardized mortality ratio (US referent rates).
[a] Underlying indicates the number of deaths for which the cause was selected as the underlying cause of death on the death certificate.
[b] Contributing indicates the number of times the cause appeared on the death certificate (i.e., underlying and contributing).
[c] ICD-7 codes 304–305, ICD-8 codes 290.0–290.1, ICD-9 codes 290.0–290.3 and 331.0, and ICD-10 code G30; includes senile and presenile dementia but excludes cerebrovascular dementia because it is probably due to underlying cerebral vascular disease.
[d] ICD-7 code 356.1, ICD-8 code 348.0, ICD-9 code 335.2, and ICD-10 code G12.2.
[e] ICD-7 code 350, ICD-8 code 342, ICD-9 code 332, and ICD-10 codes G20–G21.

rodegenerative mortality risk across the various positions included within the speed position group.

Because our cohort was limited to longer-term professional players, our findings may not be applicable to other professional or nonprofessional football players. However, recent autopsy studies have reported pathologic findings of CTE in college-age and professional football players with relatively short playing careers.[22] We did not have data on player injuries or concussions. If chronic mild to moderate concussion is an actual risk factor for neurodegenerative mortality, the magnitude of the risk may depend on the intensity and frequency of brain injuries incurred over a number of years. A few studies have attempted to measure these injuries for a limited number of players over a limited period of time but such measurements have proven to be difficult and underreporting is a problem.[23,24] Finally, we did not have information on environmental, genetic, or other risk factors for neurologic disorders.

Although the results of our study do not establish a cause-effect relationship between football-related concussion and death from neurodegenerative disorders, they do provide additional support for the find-

Table 3 Mortality for neurodegenerative causes of death (considering all causes of death reported on the death certificate) stratified by position category, National Football League Players Cohort (1960–2007)

	Nonspeed[a]		Speed		
Cause of death	No.[b]	SMR (95% CI)	No.	SMR (95% CI)	Speed vs nonspeed: SRR (95% CI)
All neurodegenerative causes	3	1.58 (0.33–4.61)	14	4.74 (2.59–7.95)	3.29 (0.92–11.7)
Dementia/Alzheimer disease[c]	1	1.51 (0.04–8.41)	6	6.02 (2.21–13.1)	5.96 (0.72–49.6)
Amyotrophic lateral sclerosis	1	1.71 (0.04–9.50)	6	6.24 (2.29–13.6)	3.88 (0.47–32.2)
Parkinson disease	1	1.53 (0.04–8.53)	2	2.01 (0.24–7.25)	1.19 (0.11–13.2)

Abbreviations: CI = confidence interval; SMR = standardized mortality ratio (US multiple cause of death referent rates); SRR = directly standardized rate ratio (internal analysis).
[a] Punters and kickers were excluded, and remaining player positions were collapsed into 2 strata for analysis purposes: speed positions (fullback, halfback, defensive back, quarterback, wide receiver, running back, linebacker, and tight end) and nonspeed positions (defensive and offensive linemen).
[b] Number indicates the number of times the cause appeared on the death certificate (i.e., underlying and contributing causes).
[c] Includes senile and presenile dementia but excludes cerebrovascular dementia.

ing that professional football players are at an increased risk of death from neurodegenerative causes. Additional studies to quantify the cumulative effects of brain injuries, in particular the relative effects of concussive-level injuries, will be of particular importance in understanding the underlying disease mechanisms.

AUTHOR CONTRIBUTIONS

Study concept and design: E.J. Lehman, M.J. Hein. Acquisition of data: S.L. Baron, C.M. Gersic. Study coordination: C.M. Gersic. Analysis and interpretation of data: E.J. Lehman, M.J. Hein, S.L. Baron. Drafting/revising manuscript: E.J. Lehman, M.J. Hein, S.L. Baron, C.M. Gersic. Critical revision of the manuscript for important intellectual content: E.J. Lehman, M.J. Hein, S.L. Baron. Statistical analysis: E.J. Lehman, M.J. Hein. Obtain funding: E.J. Lehman. Administrative, technical, or material support: E.J. Lehman, C.M. Gersic. Study supervision: E.J. Lehman, S.L. Baron.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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