Premortem Chronic Traumatic Encephalopathy Diagnoses in Professional Football

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Objective: American-style football (ASF) has gained attention because of possible links between repetitive head injury and neurodegenerative diseases. Although postmortem pathologic changes consistent with chronic traumatic encephalopathy (CTE) have been reported in ASF players, there are currently no established premortem diagnostic criteria for CTE. Nevertheless, presented with symptoms of cognitive impairment, clinicians treating former players may be inclined to suggest CTE without a thorough exploration of comorbid factors that demonstrate similar clinical phenotypes to putative CTE.
Methods: A survey of 3,913 former ASF players aged 24 to 89 was conducted for those who responded by March 2019.
Results: Despite being a postmortem diagnosis, 108 players (2.8%) self-reported clinician-diagnosed CTE. The percentage of players under age 60 years reporting a CTE diagnosis was 2.3% versus 3.7% in participants age 60 or older. Comorbidities in participants self-reporting CTE were significantly more common, including sleep apnea, hypercholesterolemia, obesity, indicators of past or current depression, hypertension, prescription pain medication use, heart conditions, and low testosterone when compared to non-CTE respondents. Patterns of reporting for obesity, hypertension, heart conditions, or hypercholesterolemia differed between older and younger participants. Cognitive impairment symptoms were significantly higher in participants self-reporting CTE.
Interpretation: Some former professional football players have been clinically diagnosed with CTE, a postmortem condition. Comorbidities that can affect cognition were associated with CTE diagnoses in both older and younger players. Although underlying neuropathology cannot be ruled out, treatable conditions should be explored in former athletes demonstrating CTE-linked clinical phenotypes or symptoms as a means of improving cognitive health in these patients.

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Scientific and news media have paid considerable attention to the idea that cognitive impairment in American-style football (ASF) players may be a consequence of repeated head trauma.[1] First reported by Martland in 1928 as punch drunk syndrome,[2] chronic traumatic encephalopathy (CTE) is a neurodegenerative disease pathologically defined at autopsy by deposition of phosphorylated tau (P-tau) in neurons, astrocytes, and cell processes around perivascular structures at the

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depths of the cortical sulci.[3] Recent work has noted postmortem pathologic changes consistent with CTE in 177 of 202 ASF players.[4,5] The 177 affected ASF players had a median age at death of 67 years and retrospective analysis found that the majority had shown cognitive, emotional, and behavioral symptoms for over a decade prior to autopsy.

However, the relationship between CTE pathology and clinical phenotypes among former ASF athletes remain incompletely understood.[6,7] A series of clinical diagnostic criteria have been proposed that include behavioral, cognitive, and motoric features.[8–10] Yet, the agreement between the clinical features of these proposed criteria is modest.[11] in vivo flortaucipir positron emission tomography (PET) imaging has revealed higher tracer retention in former professional ASF players with cognitive and neuropsychiatric symptoms in brain regions affected by CTE.[12] Nonetheless, there was no association between tau deposition as registered on imaging and scores on cognitive and neuropsychiatric tests.

The specificity[13] and progressive nature of CTE[5] have not been fully elucidated, and some evidence suggests that CTE may not be solely unique to repeated head trauma.[13,14] Additionally, in former ASF players with cognitive symptoms, CTE pathology—even when present—might not be the sole contributor of cognitive decline.[6,15] Thus, while National Institute of Neurological Disorders and Stroke (NINDS) pathologic criteria exist,[3] continued refinement of these criteria is needed to better differentiate CTE from other neurodegenerative diseases, such as aging-related tau astrogliopathy. The limitations of in vivo diagnostic tests, absence of clear links between neuropathology, and cognitive symptoms,[6,7] the multifactorial nature of cognitive decline in older age groups, and the impact of possible comorbidities on clinical presentations often impede the identification of definite etiological factors in CTE. As a result, the clinical criteria for antemortem CTE or traumatic encephalopathy syndrome remain proposed[16,17] but not yet established.[6,7,11]

While clinical criteria for CTE or traumatic encephalopathy syndrome remain in debate, few studies have addressed the potential comorbid factors that can impact cognitive function.[11] In the Football Players Health Study (FPHS), we investigated the self-reporting of CTE diagnoses by former players, as well as comorbidities relevant to cognition.[6,7]

Methods

Study Population

Starting in 2014, the FPHS[18] recruited former football players who had received compensation from any National Football League (NFL) team starting in 1960, when the league transitioned from soft leather to hard plastic helmets.[19] We explicitly considered active players ineligible. We obtained email and residential information for 16,089 eligible former players from the NFL Players Association. Of these, return-to-sender address errors or unopened email messages were documented for 1,675 unique former players. Of the remaining 14,414 former players, 3,913 (27.1%) had enrolled as of March 2019. This study was approved by the Institutional Review Board of the Beth Israel Deaconess Medical Center and the Harvard T.H. Chan School of Public Health, and participants provided informed consent prior to participation.

Outcome and Other Data

Participants completed either a paper or online questionnaire about demographics, football careers, and health conditions. Body mass index (BMI) was calculated from self-reported weight (lbs) and height (inches) as (lbs*0.45/(inches*0.025).[2] Players on the offensive or defensive line were categorized as linemen, and all others were categorized as non-linemen. Participants were asked to select categories that described their racial identity: black/African American; white; American Indian/Alaskan Native; Native Hawaiian/Pacific Islander; Asian and other. Black was defined as players who self-identified as black or African American. Former players who self-selected "black" in addition to another race were categorized as black, based on lived experience studies that have shown that perceivers strongly tend to characterize multiracial individuals as belonging to a minority status.[20] White was defined as players who self-identified only as white. Participants who declined to answer this question were categorized as "missing." All remaining participants were categorized as "other." Number of seasons of professional NFL play was divided into 1 to 4 seasons, 5 to 9 seasons, and 10+ seasons.

We considered several different health conditions as reported by the former players. Heart attack, sleep apnea, stroke, dementia, and CTE was based on a yes/no response to the question for the given condition phrased as "Has a Health care provider ever told you that you have had any of the following diagnoses or health outcomes?" followed by options that included: heart attack; sleep apnea; stroke; dementia (Alzheimer's disease); and CTE. Further definitions for these conditions were not provided. We considered a yes response to the question phrased as "Has a medical provider ever recommended or prescribed medication for any of the following conditions?" for "high blood pressure," "diabetes or high blood sugar," "high cholesterol," "low testosterone," "erectile dysfunction (ED)," and "pain" as an indicator of hypertension, diabetes, hypercholesterolemia, low testosterone, erectile dysfunction, and chronic pain, respectively. We

defined having a heart condition as reporting any of the following: (1) diagnosis of "heart attack," (2) medication recommendations or prescriptions for "heart failure" or "heart rhythm problems (atrial fibrillation, supraventricular tachycardia [SVT], or other)," or (3) positive responses to the question "Since leaving active professional play have you had any of the following surgical procedures?" specifically for heart bypass, angioplasty, or stent replacement?

We defined indicators of past or current depression as having (1) a current prescription or prescription recommendation for an antidepressant, or (2) a score >3 on the depression-related Patient Health Questionnaire (PHQ-4).[21] The Quality of Life in Neurological Disorders (NQOL) instrument for Applied Cognition-General Concerns[22] was used to measure cognitive symptoms. The frequencies of 8 symptoms over the previous week were summed and T-scored according to a standardized US sample. Participants who scored 2 or more SDs below the mean were considered to have cognitive impairment.

Statistical Analysis

We used chi-square tests to determine statistically significant differences in health conditions between former players who did and did not report diagnoses of CTE. Statistical significance was considered at a 95% level of confidence and evaluated using R Statistical Software.[23]

Results

The mean age was 52.4 (SD = 14.3; range: 24–89) in the 3,913 former ASF players who responded to the questionnaire. The frequency of self-reported CTE diagnoses was 108 (2.8%) among all players, and 59 (2.3%) in players under age 60 versus 49 (3.7%) in players age 60 or older (Table 1). Black former players reported a higher percentage of CTE than white or other categories. In both age groups, the percentage of linemen self-reporting CTE was higher than in non-linemen. The percentage of CTE reporting did not increase monotonically with more playing seasons: CTE reporting was highest in the 5 to 9 season category, but not with 10+ seasons (see Table 1).

TABLE 1. Demographic and Football-related Characteristics in Former ASF Players by Age and Self-reported CTE Status (N = 3,913)

	Ages 24–89		Ages 24–59		Ages 60–89	
	No CTE N = 3805	CTE N = 108	No CTE N = 2,518	CTE N = 59	No CTE N = 1287	CTE N = 49
Characteristic	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Age						
<60	2,518 (97.7)	59 (2.3)	-	-	-	-
60+	1,287 (96.3)	49 (3.7)	-	-	-	-
Race[a]						
Black	1,413 (96.6)	50 (3.4)	1,116 (97.1)	33 (2.9)	297 (94.6)	17 (5.4)
White	2,234 (97.6)	56 (2.4)	1,299 (98.1)	25 (1.9)	935 (96.8)	31 (3.2)
Other	110 (98.2)	2 (1.8)	83 (98.8)	1 (2.9)	27 (96.4)	1 (3.6)
Position						
Non-linemen	2,492 (97.4)	66 (2.6)	1,640 (98.0)	34 (2.0)	852 (96.4)	32 (3.6)
Linemen	1,313 (96.9)	42 (3.1)	878 (97.2)	25 (2.8)	435 (96.2)	17 (3.8)
Seasons played in NFL[b]						
1–4 Seasons	1,258 (97.7)	29 (2.3)	914 (97.9)	20 (2.1)	344 (97.5)	9 (2.5)
5–9 Seasons	1,633 (96.8)	54 (3.2)	1047 (97.6)	26 (2.4)	586 (95.4)	28 (4.6)
10+ Seasons	914 (97.3)	24 (2.7)	557 (97.7)	13 (2.3)	357 (96.7)	12 (3.3)

[a]Racial identity was not reported for 48 players, none of whom reported CTE. [b]Years played for one player could not be ascertained.
ASF = American-style football; CTE = chronic traumatic encephalopathy; NFL = National Football League.

TABLE 2. Current Health Conditions and Neurological Quality of Life Impairment Status in Former ASF Players by Age and selS-reported CTE Status (N = 3,913)

	All ages (24–89)		Ages 24–59		Ages 60–89	
	No CTE N = 3,805	CTE N = 108	No CTE N = 2,518	CTE N = 59	No CTE N = 1,287	CTE N = 49
Characteristic	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Obese (>30.0 kg/m^2)[a]	1,976 (51.9)	71 (65.7)**	1,373 (54.5)	38 (64.4)	603 (46.9)	33 (67.3)**
Sleep apnea	817 (21.5)	52 (48.1)***	468 (18.6)	25 (42.4)***	349 (27.1)	27 (55.1)***
Indicators of past or current depression	631 (16.6)	73 (67.6)***	426 (16.9)	42 (71.2)***	205 (15.9)	31 (63.3)***
Diabetes	336 (9.1)	14 (14.0)	156 (6.3)	4 (7.4)	180 (14.7)	10 (21.7)
Hypertension[b]	1,414 (37.5)	54 (50.5)**	685 (27.4)	24 (41.4)*	729 (57.4)	30 (61.2)
Low testosterone[c]	654 (17.7)	40 (37.4)***	373 (15.1)	25 (43.1)***	281 (22.9)	15 (30.6)
Stroke	101 (2.7)	7 (6.5)*	34 (1.4)	2 (3.4)	67 (5.2)	5 (10.2)
Rx pain medication	1,016 (26.7)	62 (57.4)***	591 (23.5)	35 (59.3)***	425 (33.0)	27 (55.1)***
Heart condition[d]	696 (18.3)	26 (24.1)	233 (9.3)	11 (18.6)*	463 (36.0)	15 (30.6)
High cholesterol[e]	1,284 (34.3)	50 (48.1)**	598 (24.1)	26 (45.6)***	686 (54.7)	24 (51.1)
Dementia	97 (2.5)	41 (38.0)***	30 (1.2)	20 (33.9)***	67 (5.2)	21 (42.9)***
Cognitive impairment[f]	434 (11.4)	60 (56.1)***	311 (12.4)	34 (57.6)***	123 (9.6)	26 (54.2)***

[a]Twenty-eight players were missing body mass index data.
[b]Thirty-five players were missing hypertension data.
[c]Ninety-two players were missing low testosterone data.
[d]Heart condition includes self-reported heart rhythm issues, myocardial infarction, heart failure, or cardiac surgery.
[e]Seventy-four players were missing cholesterol data.
[f]Ten players were missing neurological quality of life scores.
*$p < 0.05$;
**$p < 0.01$,
***$p < 0.001$ on chi-square test.
ASF = American-style football; CTE = chronic traumatic encephalopathy.

Men of all ages self-reporting a CTE diagnosis were significantly more likely to also report obesity, sleep apnea, indicators of past or current depression, stroke, hypertension, use of prescription pain medication, low testosterone, hypercholesterolemia, dementia, and cognitive impairment (Table 2). Obesity was associated with CTE reporting in older but not younger participants, whereas hypertension, any heart condition, and hypercholesterolemia were significantly more common in younger but not older former players (see Table 2).

Discussion

We found that a number of former ASF players reported clinician-diagnosed CTE. Participants reporting CTE also frequently disclosed other comorbidities with well-established independent adverse cognitive effects. There is currently no validated way to clinically diagnosis CTE,[6] and concerns have been raised regarding the specificity of many symptoms attributed to CTE.[13] Thus, it is disconcerting that a percentage of former players report being told they have a condition that can only be diagnosed postmortem.

Participants may have reported CTE because clinicians told them they have CTE. This is concerning in the absence of validated diagnostic methods, and may imply that exposure to professional football is driving the suggestion of CTE rather than differential diagnoses based on systematic evaluation. Previous research has linked elements of professional ASF exposure to mood disorders,[24] aggression,[25] and hormonal and sexual dysfunction.[26,27] Recently, years of professional play, concussion history, and position were significantly associated with neuropsychiatric symptoms in the largest study of living ASF football players to date.[28] These results align with prior work in nonprofessional football cohorts suggesting a link between cumulative head impacts and neurobehavioral symptoms.[29] Using either exposure to

football as a proxy for repetitive head injury, or using mood and behavioral changes as a phenotypic marker of brain degeneration, clinicians familiar with this literature may be inclined to suggest CTE before considering other contributors to cognitive symptoms.

Alternatively, former players may infer the presence of CTE when other explanations for cognitive impairment are not provided.[30] The common reporting of comorbidities that can affect cognition among players disclosing a CTE diagnosis raises the concern that treatable conditions are going untreated or undertreated. For example, players younger than age 60 reporting CTE also reported significantly more sleep apnea, indicators of past or current depression, hypertension, chronic pain, low testosterone, heart conditions, and hypercholesterolemia. Participants reporting prior depression or current symptoms of depression were more likely to report CTE diagnoses. We note that our definition combines medical history of diagnosis or treatment for depression and current symptoms. Therefore, the percentage of those meeting our criteria is likely greater than that of either of those two considered alone. Given that there are no established premortem clinical criteria for CTE,[11] it is possible that the self-reported diagnosis of CTE was a misinterpretation by former players of what they had been told by their clinicians, or assumed even when CTE was not explicitly mentioned. It seems unlikely, however, that this would occur in the absence of cognitive symptoms.

Former player participants reporting CTE were more likely to self-identify as black than white or other. This may be because some comorbidities known to cause cognitive problems are more prevalent in black men (eg, hypertension[31] and diabetes[32]). Additionally, because black players are more likely to play high-impact positions,[33] presumed exposure may be driving the suggestion of CTE in clinical contexts. A recent study of symptomatic former professional football players has noted that black players had significantly higher indices of head injury, higher blood pressure, higher BMI, and lower right hippocampal volume than white participants.[34] In our study, participants who played between 5 and 9 seasons showed a higher percentage of self-reported CTE than those who played both fewer and more seasons. Although we cannot say for certain why this is, it is possible that healthy worker bias may be at play where the most injured players aren't represented in populations of players with longer careers.[35]

A limitation of our study is that the overall response rate was relatively low (27.1%). If none of the nonparticipants would have reported clinician-diagnosed CTE, then the overall percentage of reported CTE would be only 0.76%, instead of the 2.8% among those players who participated in our study. Thus, 0.76% should be viewed as a lower bound of clinician-diagnosed CTE reporting in former football players. Nevertheless, it is important to note that no player should have received a clinical diagnosis of CTE. It is possible that cognitive status could have affected the likelihood that a former football player joined our study; participation among those with a disease or more severe disease may be higher than among those without because they have an interest in understanding their condition.[36] On the other hand, it is known that cognitive impairment tends to inhibit study participation.[37] Importantly, though, if that participation is not also related to other factors (eg, linemen who report CTE participate at a different rate than non-linemen who report CTE) then the differences by CTE that we see in this study should still be reflective of the whole player population. For example, the higher prevalence of low testosterone among former players with CTE would not be caused by former players who report CTE participating more (or less) than players not reporting CTE. This would only be erroneously caused if participation was based on *both* CTE reporting *and* low testosterone (ie, if players who both report CTE and have low testosterone were more likely to participate than former players who report CTE and do *not* have low testosterone). If such jointly based participation did occur, then the differences we report and their associated p values would not reflect the true differences in the larger population of former players, including those who did not enroll in our study.

The use of self-report represents another limitation of this study: medical records were not obtained, and there was limited survey space for defining procedures, illnesses, and condition severity. Furthermore, data were not collected on clinician and medical facility types (eg, academic hospital specialists vs community providers), which introduces additional variability into the meaning of reported diagnoses. Because we do not know the clinical setting and level of diagnostic workup that were used to support the suggestion of CTE, it is challenging to understand the clinical criteria used for such a diagnosis.

Comorbidity data based on self-report could even represent an under-reporting in some instances; for example, sleep apnea, often goes unrecognized.[38] Other factors, such as number of anesthesia exposures, have been posited as potential risks for dementia and should also be considered in this population[39] as many players often have undergone a number of surgical procedures to address sports-related orthopedic injuries. It must also be kept in mind that many of the comorbidities that could increase risk of cognitive impairment may begin early in life[40,41] and may ultimately not be consequences of exposure to professional ASF.

The data presented in this study were observational, cross-sectional, and based on self-report and it is,

therefore, not possible to make true inferences on the role of comorbidities in CTE or cognitive decline for these participants. Further research using longitudinal data, medical records, and in-person neuropsychological testing is necessary to better elucidate the relationships between perceived CTE diagnoses and comorbid conditions. However, until those data become available, it is important to draw attention to treatable conditions that may have been overlooked or eclipsed by the suggestion of CTE.

We cannot tell whether self-reported CTE diagnoses represent an actual diagnosis given or recorded in a medical chart, or just an articulated suspicion on the part of the medical provider. We also cannot rule out that some of the participants may demonstrate neuropathological changes associated with postmortem CTE. Furthermore, such pathology may or may not be directly linked to their reported symptoms. Nevertheless, the possibility of incorrect reporting of diagnosis or just an impression left with the player that he has CTE is of great concern. Such nebulous diagnoses could produce a nocebo effect and trigger mental health challenges, discourage further diagnostic efforts for potentially treatable conditions, and lead to tragic consequences. In the context of this cohort,[30] the role of nocebo-based effects on symptoms and disability[42] should not be overlooked.[43]

Our findings emphasize the importance of careful clinical assessment of comorbidities and other causes of cognitive decline in former athletes with neurocognitive symptomatology before assuming that CTE is the responsible etiology. The evaluation of former contact and combative sport athletes with cognitive problems should emphasize diagnostic assessment through which treatable conditions are prioritized and addressed, as well as a specialized and careful evaluation of all possible causes of cognitive dysfunction and dementia. The results presented here underscore the need for longitudinal studies, research criteria for CTE phenotyping, more effective patient education regarding clinical uncertainty in this era of intense public discourse, and greater awareness in the public and the medical community of relevant comorbidities.

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Author Contributions

A.P.L., R.Z., R.G., M.W., A.B., L.N., and H.T. contributed to the conception and design of the study. R.G., A.C., A.B., H.T., R.Z., M.W., R.K., and F.S. contributed to the acquisition and analysis of data. A.P.L., R.G., R.Z., M.W., F.S., A.W., H.T., and A.B. contributed to the drafting the text and preparing the tables.

Potential Conflicts of Interest

The authors report no other potential or actual conflicts of interest.

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