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RESEARCH ARTICLE

Plasma P-tau181 and P-tau217 in Patients With Traumatic Encephalopathy Syndrome With and Without Evidence of Alzheimer Disease Pathology

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Abstract

Background and Objectives

Traumatic encephalopathy syndrome (TES) has overlapping clinical symptoms with Alzheimer disease (AD). AD pathology commonly co-occurs with chronic traumatic encephalopathy (CTE) pathology. There are currently no validated CTE biomarkers. AD-specific biomarkers such as plasma P-tau181 and P-tau217 may help to identify patients with TES who have AD pathology.

Methods

We measured plasma P-tau181 and P-tau217 (Meso Scale Discovery electrochemiluminescence) in patients with TES, mild cognitive impairment/dementia with biomarker-confirmed AD ("AD"), and healthy controls ("HC"). Patients underwent amyloid-beta (Aβ)-PET and a subset underwent tau-PET using [18F]Flortaucipir. We compared plasma P-tau levels controlling for age and sex and also performed AUC analyses to evaluate the accuracy of group differentiation. In patients with TES, we evaluated associations between plasma P-tau, years of repetitive head impact exposure, and tau-PET. Four TES patients with autopsy-confirmed CTE were described qualitatively.

Results

The sample included 131 participants (TES, N = 18; AD, N = 65; HC, N = 48). Aβ(+) patients with TES (N = 10), but not Aβ(−) TES, had significantly higher plasma P-tau levels than HC (P-tau181: $p < 0.001$, $d = 1.34$; P-tau217: $p < 0.001$, $d = 1.59$). There was a trend for Aβ(+) TES having higher plasma P-tau than Aβ(−) TES (P-tau181: $p = 0.06$, $d = 1.06$; P-tau217: $p = 0.09$, $d = 0.93$). AUC analyses showed good classification of Aβ(+) TES from HC for P-tau181 (AUC = 0.87 [0.71–1.00]) and P-tau217 (AUC = 0.93 [0.86–1.00]). Plasma P-tau217 showed fair differentiation of Aβ(+) TES from Aβ(−) TES (AUC = 0.79 [0.54–1.00], $p = 0.04$), whereas classification accuracy of P-tau181 was slightly lower and not statistically significant (AUC = 0.71 [0.46–0.96], $p = 0.13$). Patients with AD had higher tau-PET tracer uptake than Aβ(+) TES and were well differentiated using P-tau181 (AUC = 0.81 [0.68–0.94]) and P-tau217 (AUC = 0.86 [0.73–0.98]). Plasma P-tau correlated with the tau-PET signal in Aβ(+) TES but not in Aβ(−) TES, and there was no association between plasma P-tau and years of repetitive head impact exposure. TES patients with severe CTE and no AD at autopsy had low P-tau181 and P-tau217 levels.

Discussion

Measuring P-tau181 and P-tau217 in plasma may be a feasible and scalable fluid biomarker for identifying AD pathology in TES. Low plasma P-tau levels may be used to increase clinical suspicion of CTE over AD as a primary pathology in TES. Currently, there is no support for P-tau181 or P-tau217 as in vivo biomarkers of CTE tau. Larger studies of patients with pathologically confirmed CTE are needed.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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From the Memory and Aging Center (B.M.A.T.C., J.A.T., L.V., W.G.M., K.B.C., A.M.S., R.L.J., L.I., D.S.-M., J.C.R., R.C.G., B.L.M., L.T.G., A.L.B., J.H.K., G.D.R.), Department of Neurology, Weill Institute for Neurosciences, University of California San Francisco; Department of Neurology (W.G.M.), University of Minnesota, Minneapolis; San Francisco Veterans Affairs Medical Center (R.C.G.); and Department of Radiology & Biomedical Imaging, University of California (G.D.R.), San Francisco.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AD = Alzheimer disease; **ADNC** = AD neuropathologic change; **AUC/ROC** = area under the receiver operating characteristic curve; **Aβ** = amyloid-beta; **CDR** = Clinical Dementia Rating; **CTE** = chronic traumatic encephalopathy; **CV** = coefficient of variation; **FTP** = flortaucipir; **HC** = healthy control; **LLOQ** = lower limit of quantification; **MCI** = mild cognitive impairment; **PIB** = Pittsburgh compound B; **SUVR** = standardized uptake value ratio; **TES** = traumatic encephalopathy syndrome; **UCSF** = University of California, San Francisco.

Classification of Evidence

This study provides Class III evidence that (1) among patients with TES and abnormal Aβ-PET scans, elevated plasma P-tau can differentiate between affected individuals and HCs; (2) low plasma P-tau may help identify patients with TES who do not have Alzheimer; and (3) plasma P-tau181 and P-tau217 are not useful biomarkers of patients with TES who do not have AD.

Traumatic encephalopathy syndrome (TES) is a proposed framework for characterizing symptoms predictive of underlying chronic traumatic encephalopathy (CTE) pathology.[1] CTE is a neurodegenerative tauopathy closely tied to repetitive head impact exposure.[2] Initial TES criteria had high sensitivity (97%) but low specificity (20%) to CTE, and the criteria have recently been revised.[1,3] Currently, there are no biomarkers for accurately identifying CTE during life. However, leveraging advancements in well-validated biomarkers of common CTE copathologies, such as Alzheimer disease (AD), could significantly improve diagnostic differential and management of repetitive head trauma patients with cognitive and neurobehavioral symptoms. Recently, plasma-based markers of AD pathology (P-tau181 and P-tau217) have garnered significant attention given their potential scalability, noninvasiveness, and low cost.[4–7]

Neuropathologic features of AD such as amyloid-beta (Aβ) neuritic plaques have been identified as copathology in up to 74% of severe CTE cases on autopsy and are associated with older age at death.[8,9] AD and CTE copathology complicates the ability to link clinical symptoms to a single underlying pathology. Amnestic, dysexecutive, and neurobehavioral symptoms are core features of TES that also commonly occur in patients with AD.[10–12] Dysexecutive and neurobehavioral features are especially prominent in patients with AD with symptom onset before age 65 years,[11,13] which provides further challenges in differentiating early-onset AD vs CTE in patients with TES who frequently present with symptoms in their 50s and 60s. In addition, head trauma is a recognized independent risk factor for AD.[14] These considerations highlight the need for tools to help identify TES patients with AD pathology.

In addition to overlapping clinical symptoms, the hyperphosphorylated tau aggregates seen in CTE and AD share several features.[2] Both CTE and AD tau are mixed 3R/4R tauopathies with paired helical filament structures, although recent work has highlighted subtle differences in folding patterns and a unique hydrophobic molecule enclosed within the CTE tau fold.[15] Elevated levels of plasma P-tau181 and P-tau217 seem to reflect Aβ-mediated changes in tau phosphorylation and secretion in AD and are not elevated in frontotemporal lobar degeneration associated with tau pathology (e.g., corticobasal degeneration, progressive supranuclear palsy, Pick disease, and pathogenic microtubule-associated protein tau variants).[5–7] Plasma P-tau181 and P-tau217 have not yet been well characterized in TES or CTE.

Accurately determining whether AD pathology is contributing to TES symptoms has important implications for patients including clinical management, appropriateness for disease-specific therapies, eligibility for clinical trials targeting TES/CTE, and prognostication. This study primarily investigated whether plasma P-tau181 and P-tau217 were elevated in patients with TES with and without evidence of AD pathology. We evaluated plasma P-tau181 and P-tau217 concentrations in TES patients with and without Aβ-PET positivity, AD patients (Aβ-PET and tau-PET positive) without a history of head trauma, and healthy controls (HCs). The presence of Aβ pathology was determined by Aβ-PET imaging for all participants, and a subset also underwent tau-PET. Four patients with TES had autopsy confirmation of underlying CTE and/or AD neuropathology. Associations between duration of repetitive head impact exposure, plasma P-tau markers, and cortical tau burden were also evaluated in the patients with TES.

Methods

Participants

This study included research participants from the University of California, San Francisco (UCSF) Memory and Aging Center enrolled through either the UCSF Alzheimer's Disease Research Center or Longitudinal Brain Aging Program (HCs). Self-reported sociodemographic variables collected included age, sex, years of education, and race. Race categories (e.g., White or Black) were defined based on the US Office of Management and Budget's Revisions to the standards for the Classification of Federal Data on Race and Ethnicity. Race reporting was consistent with the US National Institutes of Health policies. Race data were collected because adverse outcomes associated with social determinants of poor health may disproportionately affect underserved race groups.

All participants underwent standard clinical evaluation including comprehensive history, neurologic examination, neuropsychological testing, caregiver interview and functional assessment (Clinical Dementia Rating scale; CDR[16]), and brain structural MRI. A consensus clinical diagnosis of TES, mild cognitive impairment (MCI) or dementia due to AD ("AD"), or HC was provided by a multidisciplinary team.

All participants with TES met 2014 research criteria[17] and were characterized retrospectively using the updated 2021 criteria.[1] The updated criteria include classification of the likelihood of underlying CTE pathology in living individuals ("Suggestive of CTE," "Possible CTE," or "Probable CTE") based on the degree of lifetime head trauma exposure, core clinical features, severity of functional impairment, and number of additional supportive features. Two investigators (B.A. and J.T.) independently classified each participant with TES using revised TES criteria and then adjudicated discrepancies to reach consensus. Participants with TES in our cohort were all male and almost exclusively former American football players except for 1 former rugby player.

Participants with AD met clinical research criteria for probable AD dementia[10] or MCI.[18] To maximize specificity of underlying AD pathology, all participants with AD had *both* Aβ-PET and tau-PET imaging consistent with AD. To minimize the likelihood of CTE copathology, we only included AD participants without evidence of prior traumatic brain injury or collision sport exposure. Prior head trauma exposure was determined through a review of medical history data collected through research on standardized forms including the National Alzheimer's Coordinating Center Uniform Data Set Health History.[19] We additionally reviewed all medical history documented through neurologic examinations in clinical and research settings.

HC participants were clinically normal, functionally independent (CDR Global = 0), community-dwelling older adults participating in the UCSF Longitudinal Brain Aging Program. All participants were Aβ-PET negative and lacked cognitive symptoms or a history of neurologic, psychiatric, or other notable medical history including prior traumatic brain injury or sleep apnea.

Plasma P-tau181 and P-tau217 Analyses

Blood samples were obtained by venipuncture in EDTA tubes for plasma following the Alzheimer's Disease Neuroimaging Initiative protocol and analyzed in duplicate with a chemiluminescence-based immunoassay using the Meso Scale Discovery platform. This platform has demonstrated superiority for quantifying P-tau species.[20] Within 60 minutes of collection, the samples were centrifuged at 3,000 rpm at room temperature, aliquoted, and stored at −80°C. The P-tau assays were designed to measure P-tau in plasma (either P-tau217 or P-tau181) and optimized to measure disease-related differences through the selection of monoclonal antibodies used in the assays. Additional assay methodology and procedures for optimizing coanalysis of P-tau181 and P-tau217 simultaneously are provided elsewhere[7] and in eMethods (links.lww.com/WNL/C36).

Based on quality control data obtained from a larger participant sample including those in this study,[7] the average coefficient of variation (%CV) was 3.9% for P-tau181 and 5.2% for P-tau217. All samples had a %CV below 20%. The lower limit of quantification (LLOQ) was 0.28 pg/mL for P-tau181 and 0.08 pg/mL for P-tau217. Samples below the LLOQ (P-tau181: 1 HC; P-tau217: 8 HC, 1 TES) were included in analyses using the provided concentrations since the %CV remained <20%.

AD Pathology Status (PET Neuroimaging)

Aβ status was available for study participants based on PET acquired with 11C-Pittsburgh compound B (PIB; N = 100) or 18F-Florbetapir (N = 30) at an average of 208 ± 398 days from the plasma sample. One participant in the TES group did not undergo Aβ-PET but was found to have no diffuse or neuritic Aβ plaques at autopsy (Thal phase 0) and was therefore classified as Aβ(−). Aβ-PET positivity for all scans was based on expert visual read as previously validated against neuropathologic standards.[21,22] To characterize Aβ burden, standardized uptake value ratios (SUVRs) were calculated independently for 129 of 130 participants with Aβ-PET scans using an MRI-based pipeline as previously described[23,24] with the cerebellar grey matter reference region for PIB and whole cerebellum for florbetapir. SUVR could not be calculated for 1 participant because of lack of corresponding structural MRI. SUVRs were then converted to Centiloids (CLs) scale to harmonize data across the 2 tracers. A value of 100 CLs corresponds to the average degree of amyloid deposition observed in patients diagnosed with mild-moderate AD dementia.[25]

In a subset of study participants, tau-PET with 18F-flortaucipir (FTP-PET) was acquired an average of 80 ± 108 days from the plasma sample. Tau burden was measured by calculating SUVRs using average whole cortical SUVR. Tau-PET positivity was defined as SUVR > 1.22.[26] We secondarily evaluated a separate temporal meta-region of interest (ROI) vulnerable to AD pathology (entorhinal, amygdala, parahippocampal, fusiform, inferior temporal, and middle temporal regions),[27] but the whole cortical SUVR was evaluated in our study, given the possibility that TES participants with CTE neuropathology may exhibit abnormal FTP uptake in frontal cortices with or without uptake in putative AD regions.[28–30] Additional PET acquisition and processing methods are provided in eMethods (links.lww.com/WNL/C36).

Neuropathologic Assessment

Four participants with TES underwent autopsy (mean 2.8 ± 0.9 years after blood draw; range 2.2–4.1 years) with standardized sampling and staining protocols in the UCSF Neurodegenerative Disease Brain Bank described elsewhere.[31] For identifying tauopathy, immunohistochemistry was performed using

Table 1 Sample Characteristics Stratified by Traumatic Encephalopathy Syndrome (TES), Healthy Control (HC), and Mild Cognitive Impairment (MCI) or Dementia due to Alzheimer Disease (AD) Groups

	Traumatic encephalopathy syndrome				
	Aβ(−)	Aβ(+)	All TES	HCs	MCI/dementia due to AD
N	8	10	18	48	65
Age, y	57.2 (13.4)	69.7 (6.5)	64.1 (11.7)	70.0 (9.1)	66.4 (9.7)
Sex, N (%) female	0 (0)	0 (0)	0 (0)	21 (44)	38 (58)
Education, y	16.1 (1.1)	16.4 (2.1)	16.3 (1.7)	17.5 (2.0)	17.0 (2.6)
Race, N (%)					
White	7 (88)	9 (90)	16 (89)	46 (96)	61 (94)
Black	1 (13)	1 (10)	2 (11)	0 (0)	1 (2)
Asian	0 (0)	0 (0)	0 (0)	2 (4)	3 (5)
APOE genotype, N (%) e4	2 (25)	3 (30)	5 (28)	14 (29)	44 (68)
CDR-Sum of Boxes	3.0 (2.0–4.0)	5.0 (3.0–7.0)	3.5 (2.5–6.0)	0.0 (0.0–0.0)	4.0 (3.0–5.0)
MMSE	27 (20–28)	22 (21–26)	24 (21–27)	29 (29–30)	23 (17–26)
RHIE (y)	12 (9–15)	13 (7–18)	12 (9–17)	—	—
Aβ-PET, CLs[a]	−5.1 (7.8)	42.0 (10.3)	24.3 (34.8)	7.8 (17.6)	96.3 (32.7)
Tau-PET (flortaucipir)					
N	6	7	13	—	65
Whole cortical SUVR	1.06 (0.07)	1.40 (0.32)	1.24 (0.29)	—	1.67 (0.41)
P-tau181 (pg/mL)	0.75 (0.52–1.13)	1.44 (0.83–1.89)	0.99 (0.65–1.79)	0.58 (0.46–0.77)	2.17 (1.65–2.80)
P-tau217 (pg/mL)	0.15 (0.09–0.22)	0.29 (0.19–0.48)	0.20 (0.14–0.39)	0.11 (0.08–0.14)	0.64 (0.50–0.93)

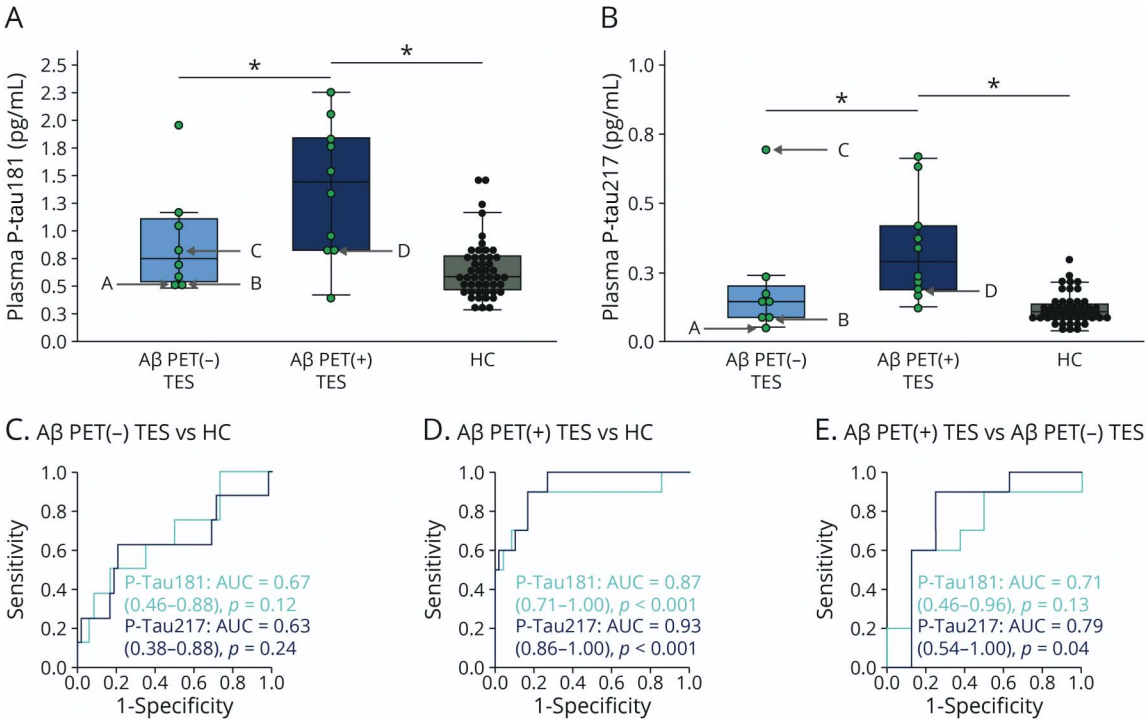
Abbreviations: Aβ = amyloid-beta; AD = Alzheimer disease; CDR = Clinical Dementia Rating scale; CL = Centiloid; HC = healthy control; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; RHIE = repetitive head impact exposure; SUVR = standardized uptake value ratio; TES = traumatic encephalopathy syndrome.
Data are also shown stratified by Aβ status within the TES cohort. Descriptive data are presented as either mean (SD) or median (lower quartile − upper quartile). All HC participants had negative Aβ-PET scans (visual read). All participants with MCI/dementia-AD had a positive Aβ-PET (visual read), while 58 of 65 (89%) exceeded the quantitative threshold for a positive tau-PET based on average whole cortical SUVR > 1.22. When using a positivity threshold from a separate temporal metaregion of interest encompassing AD vulnerable regions, 65 of 65 (100%) participants with MCI/dementia-AD had a positive tau-PET scan (data not shown). Specific duration of RHIE was unknown for 2 participants with TES (1 Aβ(−) and 1 Aβ(+)).
[a] Aβ-PET was available for all but one patient with TES, whose Aβ status was determined to be negative based on the absence of diffuse or neuritic Aβ plaques at autopsy (Thal phase 0). CL values could be calculated for 16 of the 17 patients with TES and an Aβ-PET scan due to the lack of corresponding structural MRI in 1 participant (Aβ negative based on visual read).

antibodies against hyperphosphorylated tau (CP-13, S202/T205, mouse, 1:250, courtesy of P. Davies) with sampling procedures following the recommended guidelines for CTE diagnosis.[32] All 4 TES cases had evidence of CTE. CTE severity was defined qualitatively using McKee staging[33] and "High" (N = 2) or "Low" (N = 2) based on recently proposed classification methods that account for the number of brain regions with CTE tau deposition (regardless of burden/density).[32] AD burden (Aβ plaques and AD tau tangles) was defined as "None," "Low," "Moderate," or "High" AD neuropathologic changes (ADNC) based on current National Institute on Aging and Alzheimer's Association criteria.[34]

Statistical Analyses

Demographic and clinical characteristics of study cohorts were compared using analysis of variance or χ^2 tests. Plasma P-tau181 and P-tau217 values were log transformed before analyses to better approximate a normal distribution. We first compared P-tau181 and P-tau217 concentrations between TES and HC participants using analysis of covariance adjusting for age and sex. Accuracy of cohort differentiation was assessed with area under the receiver operating characteristic curve (AUC/ROC) analysis. AUC/ROC analyses were also performed to determine classification accuracy of participants with TES vs AD , irrespective of age or sex. All analyses were then performed after stratifying participants with TES based on Aβ(+) and Aβ(−) status to evaluate the role of comorbid Alzheimer spectrum neuropathology within participants with TES. Given the relatively small N of the Aβ-stratified TES groups, interpretation of findings was weighted toward effect size estimates. For group-wise comparisons, Cohen *d* effect sizes were interpreted as small, medium, and large based on cutoffs of 0.2, 0.5, and 0.8,

Figure 1 Plasma P-tau Levels in TES Vs HC



Plasma P-tau181 (A) and P-tau217 (B) levels in patients with TES (stratified by Aβ status) vs Aβ-PET negative HCs. A subset of participants with autopsy confirmation of neuropathologic diagnoses (arrows) include (A) High CTE (No ADNC), (B) High CTE + TDP-43 type B with motor neuron disease (No ADNC), (C) Low CTE + Lewy body disease (Low ADNC), and (D) Low CTE (High ADNC). ROC curves depict classification accuracy of plasma P-tau181 (teal) and P-tau217 (dark blue) for differentiating Aβ-PET negative (C) and Aβ-PET positive (D) participants with TES from HCs and differentiating Aβ-PET positive TES from Aβ-PET negative TES (E). *Large effect size (Cohen d > 1.0). ADNC = AD neuropathologic change; HC = healthy control; ROC = receiver operating characteristic; TES = traumatic encephalopathy syndrome.

respectively.[35] For classification accuracy, AUC values were interpreted as "poor" (0.60–0.69), "fair" (0.70–0.79), "good" (0.80–0.89), and "excellent" (0.90–1.00).[36]

Finally, we performed a series of exploratory analyses to further characterize potential associations between repetitive head trauma, plasma P-tau levels, and CTE vs AD neuropathology. First, in the subset of 4 TES participants with autopsy-confirmation of neurodegenerative disease(s), we qualitatively describe associations between plasma P-tau181 and P-tau217 levels relative to documented CTE and/or AD pathology. Second, we analyzed the correlation between plasma P-tau181 and P-tau217 levels with the total number of years of American football participation (Spearman rho) given evidence of increased risk and burden of CTE pathology with more years of play.[37] Finally, we assessed the correlation between plasma P-tau concentrations and FTP SUVR in participants with TES and AD (Spearman rho).

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the institutional review board at UCSF (IRBs #10-02076 and #10-00619). All participants provided written informed consent at the time of study recruitment.

Data Availability

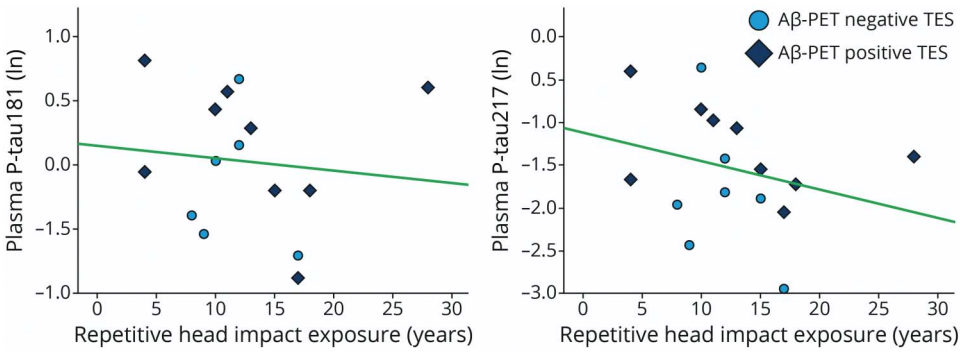
Qualified researchers from academic, not-for-profit institutions can request deidentified data associated with this study through the UCSF Memory and Aging Center after obtaining IRB approval from the UCSF Human Research Protection Program and completing a resource request (memory.ucsf.edu/research-trials/professional/open-science).

Results

Sample Characteristics

The study sample included 131 participants (TES, N = 18; AD, N = 65; HC, N = 48; Table 1). Participants with TES were younger than HC (mean 5.8 years younger; $p = 0.08$, $d = 0.60$). All participants with TES were male compared with 56% of the HC and 42% of the participants with AD. Self-identified race of the sample was 94% White (N = 123), 4% Asian (N = 5), and 2% Black (N = 2). Within the HC group, men and women did not significantly differ in levels of plasma P-tau181 ($p = 0.70$, $d = 0.11$) or P-tau217 ($p = 0.34$, $d = 0.28$) and neither P-tau marker was significantly associated with age (P-tau181: r = −0.16, $p = 0.29$; P-tau217: r = 0.02, $p = 0.90$). Participants with TES did not significantly differ from participants with AD in age (mean 2.3 years younger, $p = 0.66$, $d = 0.23$), global cognition (Mini-Mental State Examination;

Figure 2 Cumulative Years of Repetitive Head Trauma Exposure and Plasma P-tau Levels



There was no statistically significant association for P-tau181 (rho = −0.23, p = 0.39) or P-tau217 (rho = −0.28, p = 0.30).

p = 0.37, d = 0.25), or clinical disease severity (CDR Sum of Boxes; p = 0.98, d = 0.04). Participants in the AD group classified as early-onset (N = 37) vs late-onset AD (N = 28) did not have significantly different concentrations of plasma P-tau181 (p = 0.97, d = 0.01), plasma P-tau217 (p = 0.14, d = 0.38), or CDR Sum of Boxes (p = 0.21, d = 0.32).

Among the TES group, consensus levels of diagnostic certainty included 7 "Probable CTE," 5 "Possible CTE," and 5 "Suggestive of CTE." One participant with TES (former professional American football player) met 2014 criteria but not 2021 criteria. Among the AD group, clinical syndromes were classified as single or multidomain amnestic (N = 54), logopenic variant primary progressive aphasia (N = 6),[38] behavioral/dysexecutive (N = 3),[11] and nonamnestic multidomain (N = 2). Based on age at symptom onset before 65 years, 37 participants (57%) were considered early-onset AD.

The frequency of Aβ positivity across our study cohort was 10 of 18 (56%) for participants with TES, 65 of 65 (100%) for participants with AD, (by design) and 0 of 48 (0%) for HCs (by design). Tau-PET was available in 13 of 18 patients with TES and 65 of 65 patients with AD. The frequency of FTP-PET quantitative positivity based on average cortical SUVR was 3 of 13 (23% of those with FTP-PET) for TES and 58 of 65 (89%) for participants with AD. Of note, quantitative tau-PET positivity rates were higher (6/13 TES, 65/65 AD) when based on a separate temporal meta-ROI vulnerable to AD pathology.

Plasma P-tau181 and P-tau217 in TES vs HCs

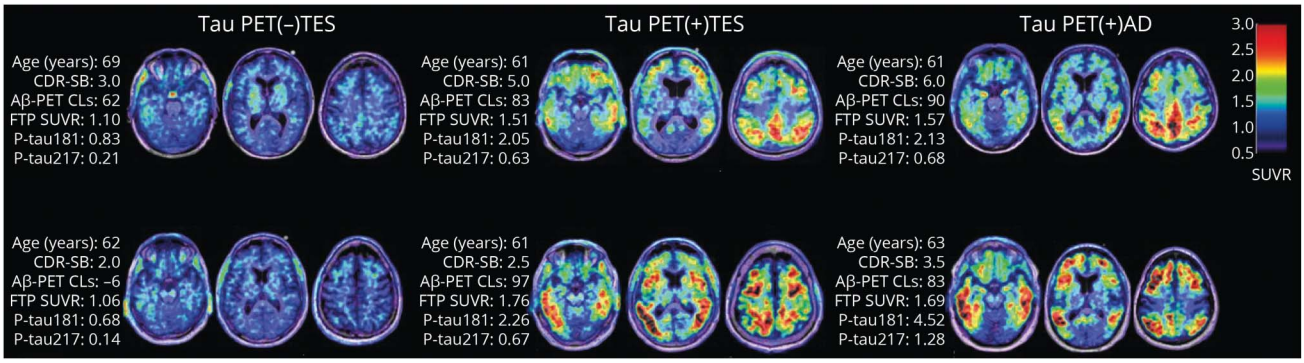
Participants with TES had significantly higher P-tau181 (p < 0.001, d = 0.99) and P-tau217 (p < 0.001, d = 1.10) levels than HC. Differences remained statistically significant when additionally controlling for Aβ burden (CLs), although the effect sizes were attenuated (P-tau181, d = 0.72; P-tau217, d = 0.68). When stratifying Participants with TES by Aβ status, only Aβ(+) participants with TES had significantly higher P-tau181 (p < 0.001; d = 1.34; Figure 1) and P-tau217 (p < 0.001; d = 1.59) than HC. Although there was limited power to detect differences because of the small group sample size, there were statistical trends and large effect sizes for plasma P-tau181 (p = 0.06, d = 1.06) and P-tau217 (p = 0.09, d = 0.93) being higher in Aβ(+) TES compared with Aβ(−) TES. There were no significant differences in plasma P-tau181 or P-tau217 concentrations between patients with TES based on the level of diagnostic certainty (Suggestive of CTE, Possible CTE, Probable CTE; see eTable 1 and eFigure 1 links.lww.com/WNL/C36). The results were similar when matching the HC and TES groups on sex and age instead of including these factors as covariates, as well as after excluding samples below the lower limit of P-tau quantification (data not shown).

Both plasma P-tau181 and P-tau217 showed fair classification accuracy of all participants with TES and HC (P-tau181: AUC = 0.78 [0.64–0.89], p < 0.001; P-tau217: AUC = 0.80 [0.66–0.93], p < 0.001; Figure 1). When stratifying patients with TES by Aβ status, classification accuracy was good to excellent for differentiating Aβ(+) TES from HC (P-tau181: AUC = 0.87 [0.71–1.00], p < 0.001; P-tau217: AUC = 0.93 [0.86–1.0], p < 0.001; Figure 1) and poor for differentiating Aβ(−) TES from HC (P-tau181: AUC = 0.67 [0.46–0.88], p = 0.12; P-tau217: AUC = 0.63 [0.38–0.88], p = 0.24). Plasma P-tau217 showed fair differentiation of Aβ(+) TES from Aβ(−) TES (AUC = 0.79 [0.54–1.00], p = 0.04). Plasma P-tau181 also showed fair differentiation of Aβ(+) TES from Aβ(−) TES (AUC = 0.71 [0.46–0.96]), but this was not statistically significant (p = 0.13). Taken together, higher P-tau181 and P-tau217 levels in TES compared with HC seem to be driven by the subset of TES participants with significant cortical Aβ burden.

Discriminability of TES From MCI/Dementia due to AD

We then evaluated how well plasma P-tau181 and P-tau217 discriminated between participants with TES (stratified by Aβ status) and AD. Both plasma P-tau181 and P-tau217 showed excellent discrimination of AD from Aβ(−) TES (P-tau181: AUC = 0.94 [0.85–1.00], p < 0.001; P-tau217: AUC = 0.92 [0.78–1.00], p < 0.001) and HC (P-tau181: AUC = 0.99

Figure 3 Case Examples of Plasma P-tau and FTP-PET in TES and AD



Four TES participants with negative (N = 2) and positive (N = 2) FTP-PET scans (whole cortex; positivity threshold SUVR > 1.22) are shown with 2 AD participants with positive FTP-PET. Warmer colors represent regions of increased FTP tracer uptake. TES participants with positive FTP-PET exhibited increased tracer uptake in putative AD regions (posterior lateral temporal and parietal cortex), suggesting high likelihood of AD pathology as a primary contributor to clinical symptoms. Dorsal frontal regions, which commonly are associated with early CTE tau deposition, showed elevated FTP tracer uptake in patients both with and without prior repetitive head trauma exposure. All FTP-PET positive participants had positive Aβ-PET scans. These case examples also highlight the higher levels of plasma P-tau181 and P-tau217 (pg/mL) observed in participants with strong evidence of underlying AD pathology based on positive tau and Aβ-PET scans compared with those with no PET evidence of AD tau pathology. This was apparent in participants diagnosed with MCI/dementia due to AD and in participants with extensive prior head trauma diagnosed with TES confirmed to have underlying AD based on PET. Aβ-PET CLs = amyloid-PET Centiloids quantification; AD = Alzheimer disease; CDR-SB = Clinical Dementia Rating Sum of Boxes; CTE = chronic traumatic encephalopathy; FTP = flortaucipir; SUVR = standardized uptake value ratio; TES = traumatic encephalopathy syndrome.

[0.98–1.00], $p < 0.001$; P-tau217: AUC = 0.996 [0.99–1.00], $p < 0.001$). Although not as strong, both plasma P-tau181 (AUC = 0.81 [0.68–0.94], $p = 0.002$) and P-tau217 (AUC = 0.86 [0.73–0.98], $p < 0.001$) showed good discrimination of AD from Aβ(+) TES, with AD having significantly higher plasma P-tau levels than Aβ(+) TES.

Plasma P-tau181 and P-tau217 in Autopsy-Confirmed CTE

Four participants with TES had autopsy confirmation of either High CTE (N = 2) or Low CTE (N = 2; see eTable 2 links.lww.com/WNL/C36). The 2 TES participants with High CTE had no ADNC. Both had among the *lowest* concentrations of plasma P-tau181 (0.48 and 0.50 pg/mL) and P-tau217 (0.09 and 0.05 pg/mL) in the study. The 2 TES participants with Low CTE also had AD neuropathology and showed low-to-intermediate plasma P-tau levels relative to the overall cohort (Low CTE + High ADNC: P-tau181 = 0.82 pg/mL, P-tau217 = 0.18 pg/mL; Low CTE + Low ADNC: P-tau181 = 1.04 pg/mL, P-tau217 = 0.70 pg/mL). Autopsy-confirmed TES participants are highlighted in Figure 1.

Exploratory Analyses of Plasma P-tau181 and P-tau217 With Years of Repetitive Head Impact Exposure and Tau-PET

Details regarding years of American football participation (or rugby in 1 participant) were available for 16 of the 18 participants with TES. There was no significant correlation between total years of participation and plasma P-tau181 or P-tau217 levels. More years of exposure unexpectedly was associated with lower P-tau levels, though not statistically significant (P-tau181: rho = −0.23, $p = 0.39$; P-tau217: rho = −0.28, $p = 0.30$; Figure 2).

Plasma P-tau181 and P-tau217 were plotted against FTP-PET average cortical SUVR (eFigure 2 links.lww.com/WNL/C36). The average tau-PET SUVR for the 7 Aβ(+) participants with TES (1.40 ± 0.32) was less than the AD group average (1.67 ± 0.41). As expected, higher plasma P-tau181 (rho = 0.28, p = 0.02) and P-tau217 (cortical ROI: rho = 0.53, p < 0.001) were associated with higher FTP-PET SUVR in participants with AD. The 7 Aβ(+) participants with TES seemed to have a similar positive association. In Aβ(−) participants with TES (N = 6), there visually seemed to be minimal association between P-tau181 and P-tau217 and FTP-PET SUVR. All Aβ(−) participants with TES had negative FTP-PET scans on quantitative measures. Positive and negative FTP-PET scan case examples for TES (N = 2 negative, N = 2 positive) and AD (N = 2 positive) are shown in Figure 3 along with the corresponding plasma P-tau181 and P-tau217 levels.

Classification of Evidence

This study provides Class III evidence that (1) among patients with TES and abnormal Aβ-PET scans, elevated plasma P-tau can differentiate between affected individuals and HCs; (2) low plasma P-tau may help identify patients with TES who do not have AD; and (3) plasma P-tau181 and P-tau217 are not useful biomarkers of patients with TES who do not have AD.

Discussion

Plasma P-tau181 and P-tau217 have shown promise as biomarkers for detecting AD pathology and differentiating AD from other neurodegenerative diseases.[7] Neither have been carefully characterized in repetitive head trauma patients with

clinical TES despite isoform similarities in tau aggregates in CTE and AD. We therefore evaluated TES patients with and without PET biomarker evidence of Aβ pathology to help determine whether plasma P-tau has utility in identifying AD pathology within TES cohorts. The results suggested that plasma P-tau181 and P-tau217 may be selectively elevated when AD pathology is present and thus a potentially useful biomarker for identifying AD pathology in patients with TES. Preliminary evidence in neuropathologically confirmed patients with TES suggested that P-tau181 and P-tau217 are not elevated in CTE without AD pathology. However, we cannot rule out the possibility that the patients with TES in our study had an insufficient CTE pathology burden to be detected using current methods.

We found that patients with TES overall had significantly higher levels of plasma P-tau181 and P-tau217 compared with HCs, but these effects were driven by TES patients with Aβ pathology. Plasma P-tau showed good to excellent discrimination of Aβ(+) TES, but not Aβ(−) TES, from HCs. These results are consistent with previous work showing accurate differentiation of patients with AD-related clinical syndromes and biomarker evidence of Aβ pathology from clinically impaired patients with presumed non-AD pathology.[5–7] Our study extends these findings to well-characterized patients with TES for whom it can be clinically challenging to differentiate between underlying CTE pathology, AD pathology, or both. Given that plasma P-tau seems sensitive to clinically meaningful AD pathology[5–7,39] and in light of advances in the development of disease-modifying treatments for AD, plasma P-tau markers warrant additional study in the contexts of TES clinical prognosis and eligibility of patients with TES for future AD therapies.

Fluid and PET biomarkers validated for detecting AD tau demonstrate suboptimal detection of CTE tau[28,40] despite sharing many, but not all, structural features with AD tau.[2,15] Plasma P-tau181 and P-tau217 elevation seems to reflect Aβ-mediated changes in tau phosphorylation and secretion seen in AD but not in FTLD tauopathies. We provide preliminary evidence further supporting the specificity of these plasma P-tau biomarkers for AD pathology based on (1) 2 TES patients with widespread CTE and no AD pathology at autopsy having among the lowest plasma P-tau levels in the entire study cohort and (2) lack of positive association between plasma P-tau and years of collision sport exposure, a putative risk factor for the presence and severity of CTE pathology. Higher plasma P-tau was associated with tau-PET signal only in TES patients with a positive Aβ-PET scan. Taken together, it is unlikely that elevated plasma P-tau181 or P-tau217 reflects CTE tau pathology but rather signals the presence of AD pathology. Neither high nor low levels of plasma P-tau can definitively rule in or rule out CTE pathology, but low plasma P-tau levels may heighten suspicion of CTE instead of AD as a primary pathology in clinically impaired patients with TES. These findings must be verified in larger samples of patients found to have severe CTE pathology burden at autopsy without co-occurring AD.

TES research criteria were designed to assist with identifying CTE pathology in vivo. Initial criteria had high sensitivity but low specificity to CTE pathology,[3] and revised criteria are now being studied.[1] AD is among the most common pathologies that co-occurs with CTE[8] and is a key driver of cognitive decline among older adults with mixed neuropathology.[41] Qualifying symptom clusters for TES include cognitive (amnestic or dysexecutive) and neurobehavioral (explosivity, impulsivity, emotional lability) phenotypes.[1] Patients with AD most commonly present with memory concerns but also frequently exhibit dysexecutive and/or behavioral changes, especially in patients with younger onset. Overlapping symptom profiles have posed a major challenge for previous in vivo studies relying on head trauma exposure and symptoms alone as proxies for presumed CTE pathology.[12] Other fluid biomarker studies (e.g., total tau, CSF P-tau181 and $A\beta_{1\text{-}42}$) in former professional American football players considered high-risk for CTE have revealed inconsistent differentiation from controls and variable associations with extent of lifetime head trauma exposure.[42–44] In vivo biomarkers for CTE pathology and common copathologies such as TDP-43 and alpha-synuclein remain elusive. Our data suggest that plasma P-tau181 or P-tau217 may at least help determine when AD pathology is contributing to the TES clinical presentation, which potentially benefits future studies of both AD and CTE.

We note that multiple age-related neurodegenerative pathologies including AD, TDP-43 proteinopathies, and alpha synucleinopathies have been linked to prior repetitive head trauma exposure.[8,45,46] CTE is unique in that, with a few equivocal exceptions,[47,48] it has only been described in individuals with prior head trauma. It is plausible, if not likely, that the extensive repetitive head trauma sustained by some patients with TES directly or indirectly contributes to the pathogenesis of non-CTE neuropathologies. Whether biomarkers ultimately will help differentiate AD or other proteinopathies found in patients with TES from those seen in patients without prior head trauma is an open question. Additional research is needed to determine whether biomarkers validated in AD patients without repetitive head trauma behave similarly in TES patients with AD pathology.

A key strength of our study was the availability of Aβ-PET imaging and/or autopsy data to characterize the presence of Alzheimer spectrum pathology in all study participants, and tau-PET in most of the participants with TES and all participants with AD. In addition, most of our participants with AD (57%) had symptom onset before age 65 years, which more closely approximates typical age at symptom onset in TES and reflects a challenging diagnostic differential facing clinicians (i.e., early-onset AD vs CTE). We also had access to a small subgroup of patients with TES with antemortem plasma collection and autopsy-confirmation of neurodegenerative pathologies. Previous fluid biomarker studies of former collision sport athletes typically have not accounted for the presence of AD pathology,[44] which complicates conclusions

that biomarker changes are due to any one pathology such as CTE.

Our study was limited by a small, cross-sectional sample of TES patients without a replication cohort. The results should be considered preliminary because of the small N, which may especially affect interpretation of statistically nonsignificant results in subgroup analyses, such as AUC/ROC analyses that stratified the patients with TES by their Aβ status. We had few participants with autopsy-based characterization of neurodegenerative disease(s). Our sample overall had limited racial diversity, and the observed relationships may not generalize to traditionally underrepresented race groups at higher risk for suffering the negative effects of social determinants of poor health (e.g., structural and systematic racism). This is particularly relevant for professional American football players who are considered at highest risk for TES or CTE and disproportionately self-identify as Black compared with the general population. However, available data suggest plasma P-tau181 and P-tau217 may perform equally well or slightly better in typically underrepresented racial/ethnic groups.[4] Alternative assays for plasma P-tau181 and P-tau217 exist that may have different sensitivities to lower concentrations. Although largely comparable, continued study in patients with TES is warranted as technologies continue to evolve.[49] The 4 TES patients with autopsy data had variable amounts of time between blood draw and death. Lifetime head trauma exposure in the TES cohort was based on self-report, although we supplemented self-report with a review of publicly available records when possible (e.g., former professional American football players). We relied on medical records and available medical history data from research visits to rule out head trauma in our non-TES cohorts, which may underestimate actual lifetime exposure, especially youth or adolescent collision sport experiences that are unlikely to be documented or ruled out systematically. Epidemiologic data suggest ~30% of older adults have sustained at least 1 mild traumatic brain injury in their lifetime[50] with higher frequencies expected when also considering any collision sport experience. However, we suspect that the TES cohort would have substantially greater exposure than the potentially unaccounted for exposure in the non-TES groups, and if present, collision sport participation in the non-TES groups likely would be less than what is considered high risk for CTE (e.g., >10 years).[1,37]

Measuring P-tau181 and P-tau217 in plasma may be a feasible and scalable method for detecting AD pathology in clinically impaired older adults with prior repetitive head trauma when CTE and AD are on the differential. We found no support for P-tau181 or P-tau217 as in vivo biomarkers of CTE tau, but larger studies of patients with varying severities of pathologically confirmed CTE are required. In the absence of CTE biomarkers, plasma P-tau181 or P-tau217 can help identify TES patients with AD pathology contributing to their symptoms and clinical prognosis. Low levels of plasma P-tau181 or P-tau217 may support increased clinical suspicion of CTE over AD as a primary or contributing pathology.

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Disclosure

A.M. Staffaroni has served as a consultant for Passage Bio and Takeda. J.C. Rojas reports being a site PI for clinical trials sponsored by Eli Lilly. J.H. Kramer has provided consultation to Biogen. G.D. Rabinovici has served as consultant for Eli Lilly, Eisai, Genentech, Roche, Johnson & Johnson, Merck, and Axon Neurosciences. L.T. Grinberg has received grant funding from Eli Lilly and consulted for CuraSen Inc. A.L. Boxer has served as a consultant for Aeton, Abbvie, AGCT, Amgen, Arkuda, Arvinas, Ascenuron, Eisai, Ionis, Lundbeck, Novartis, Passage BIO, Sangamo, Samumed, Third Rock, Toyama, and UCB. All authors deny conflicts of interest directly pertaining to this study. Go to Neurology.org/N for full disclosures.

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Appendix *(continued)*

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