Reduced CSF p-Tau(181) to Tau ratio is a biomarker for FTLD-TDP

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ABSTRACT

Objectives: To validate the ability of candidate CSF biomarkers to distinguish between the 2 main forms of frontotemporal lobar degeneration (FTLD), FTLD with TAR DNA-binding protein 43 (TDP-43) inclusions (FTLD-TDP) and FTLD with Tau inclusions (FTLD-Tau).

Methods: Antemortem CSF samples were collected from 30 patients with FTLD in a single-center validation cohort, and CSF levels of 5 putative FTLD-TDP biomarkers as well as levels of total Tau (t-Tau) and Tau phosphorylated at threonine 181 (p-Tau\textsubscript{181}) were measured using independent assays. Biomarkers most associated with FTLD-TDP were then tested in a separate 2-center validation cohort composed of subjects with FTLD-TDP, FTLD-Tau, Alzheimer disease (AD), and cognitively normal subjects. The sensitivity and specificity of FTLD-TDP biomarkers were determined.

Results: In the first validation cohort, FTLD-TDP cases had decreased levels of p-Tau\textsubscript{181} and interleukin-23, and increased Fas. Reduced ratio of p-Tau\textsubscript{181} to t-Tau (p/t-Tau) was the strongest predictor of FTLD-TDP pathology. Analysis in the second validation cohort showed CSF p/t-Tau ratio <0.37 to distinguish FTLD-TDP from FTLD-Tau, AD, and healthy seniors with 82% sensitivity and 82% specificity.

Conclusion: A reduced CSF p/t-Tau ratio represents a reproducible, validated biomarker for FTLD-TDP with performance approaching well-established CSF AD biomarkers. Introducing this biomarker into research and the clinical arena can significantly increase the power of clinical trials targeting abnormal accumulations of TDP-43 or Tau, and select the appropriate patients for target-specific therapies.

Classification of evidence: This study provides Class II evidence that the CSF p/t-Tau ratio distinguishes FTLD-TDP from FTLD-Tau. 

GLOSSARY

\textit{Ap42} = \textit{\textalpha}-amyloid 1–42; \textit{AD} = Alzheimer disease; \textit{ALS} = amyotrophic lateral sclerosis; AUC = area under the curve; CI = confidence interval; \textit{FTD} = frontotemporal degeneration; \textit{FTLD} = frontotemporal lobar degeneration; \textit{FTLD-Tau} = frontotemporal lobar degeneration with Tau inclusions; \textit{FTLD-TDP} = frontotemporal lobar degeneration with TAR DNA-binding protein 43 (TDP-43) inclusions; \textit{IL} = interleukin; \textit{Penn} = University of Pennsylvania; \textit{PN} = peripheral neuropathy; \textit{PSP} = progressive supranuclear palsy; p-Tau\textsubscript{181} = Tau phosphorylated at threonine 181; ROC = receiver operating characteristic; t-Tau = total Tau.

Frontotemporal lobar degeneration (FTLD) is distinct from Alzheimer disease (AD) and Parkinson disease in that there is poor correlation between the clinical syndromes (such as behavioral variant frontotemporal degeneration [FTD]) and the specific underlying pathology.\textsuperscript{1,2} While some syndromes have better association with FTLD-TDP (FTLD with TAR DNA-binding protein 43 [TDP-43] inclusions) or FTLD-Tau (FTLD with Tau inclusions), it is difficult to use group-level associations to predict each individual’s exact pathology. A reliable biomarker that accurately predicts the underlying FTLD pathology at the patient level is desperately needed for successful implementation of substrate-specific therapeutic trials targeting abnormal TDP-43 or Tau accumulations. We previously selected patients with known FTLD-TDP pathology (autopsy, mutations associated with FTLD-TDP, and FTDL with amyotrophic lateral sclerosis [ALS] or FTD-ALS) and FTLD-Tau pathology (autopsy, mutations associated with FTLD-Tau,
CSF levels of all biomarkers were measured at Emory. CSF levels of Aβ42, t-Tau, and p-Tau_{181} were measured with commercially available kits (AlzBio3; Innogenetics, Ghent, Belgium) in a Luminex 200 platform by a single experienced technician (K.W.) blinded to the FTLD grouping. Specifically, frozen aliquots were allowed to thaw at room temperature for 30 minutes, and each aliquot was then vortexed vigorously for 15 seconds. Once the necessary reagents were loaded into the assay plate, each aliquot was then revortexed for 15 seconds. Once the necessary reagents were loaded into the corresponding wells, 24-gauge spinal needles were used to collect CSF samples into polypropylene tubes. Aliquots (0.5 mL) were immediately prepared, bar-coded, frozen, and stored at −80°C until analysis. Samples from Emory and Penn were shipped overnight on dry ice to Emory and handled in a manner that avoided changes in pH due to exposure of frozen samples to CO₂ and carboxylic acid. No complications from CSF sampling were observed in the current study.

CSF sampling and analysis. Baseline CSF samples were obtained prospectively before measurement of CSF biomarkers according to protocols similar to the AD Neuroimaging Initiative. 

METHODS Standard protocol approvals, registrations, and patient consents. Studies conducted at Emory were approved by the Emory Institutional Review Board, and studies conducted at Penn were approved by the Penn Institutional Review Board. We obtained informed consents from each subject or his/her legal representative. W.H. has full access to all the data and final responsibility for the decision to submit for publication.

Subjects. We prospectively recruited volunteers to undergo ante-mortem CSF collection (figure 1). Emory samples included those prospectively collected from 2010 to 2013, and Penn samples included samples collected from 1997 to 2013. Because the exact FTLD pathology is unknown in most clinically diagnosed patients, we included patients who followed to autopsy with neuropathologically confirmed diagnosis of FTLD-TDP or FTLD-Tau (n = 25), and patients carrying mutations predictive of FTLD-TDP (C9ORF72 and PGRN, n = 14) or FTLD-Tau (MAPT, n = 7). Genetic testing for mutations in C9ORF72, PGRN, and MAPT was performed at Penn for Penn samples, and at Athena Diagnostics (Worcester, MA) or at Penn for Emory samples. We further enriched the cohorts with subjects with FTD-Plus syndromes in which the additional clinical diagnosis accurately predicts the pathology, including FTD-ALS (with ALS characterized by inclusions immunoreactive to TDP-43, n = 16) and FTD-PSP (with PSP characterized by inclusions immunoreactive to Tau, n = 14). Finally, patients with semantic dementia and normal CSF Tau and β-amyloid 1–42 (Aβ42) levels (i.e., inconsistent with a diagnosis of AD), a primary progressive aphasia syndrome highly associated with FTLD-TDP after exclusion of AD cases, were also included (n = 7). Consecutive patients were recruited if they fulfilled the inclusion criteria. Each patient underwent detailed neurologic and laboratory examination to ensure the accuracy of clinical diagnosis according to established criteria for AD, behavioral variant FTLD, semantic dementia, FTD-ALS, and FTD-PSP. We did not include subjects with ALS only or PSP only because discovery work using populations preferentially biased toward these 2 groups may reveal CSF changes associated with the particular disease rather than the general FTLD pathologic subtype. In addition, we also recruited subjects with AD, normal cognition with and without peripheral neuropathy (PN) from Emory for this study to determine whether biomarker changes were specific to FTLD-TDP or nonspecifically associated with brain or peripheral nerve disease. APOE genotyping was performed at each center.

CSF levels of all biomarkers were measured at Emory. CSF levels of Aβ42, t-Tau, and p-Tau_{181} were measured with commercially available kits (AlzBio3; Innogenetics, Ghent, Belgium) in a Luminex 200 platform by a single experienced technician (K.W.) blinded to the FTLD grouping. Specifically, frozen aliquots were allowed to thaw at room temperature for 30 minutes, and each aliquot was then vortexed vigorously for 15 seconds. Once the necessary reagents were loaded into the assay plate, each aliquot was then revortexed for 15 seconds immediately before being loaded into the corresponding wells. In our experience, CSF AD-related peptides become more insoluble with time in vitro, resulting in variable loss of measured levels if the vortexing immediately before well loading is omitted (ranging from 10% in t-Tau and p-Tau_{181} to nearly 50% for Aβ42). The ratio of p-Tau_{181} to t-Tau was calculated by dividing p-Tau_{181} by t-Tau.

Levels of other candidate CSF FTLD-TDP biomarkers were measured by modifying commercially available immunossays.
Agouti-related peptides and adrenocorticotropic hormones were measured in a multiplex assay (75 µL CSF, overnight primary antibody incubation at 4°C; Millipore, Billerica, MA), while eotaxin-3 (200 µL CSF, overnight primary antibody incubation at 4°C; Millipore), Fas (100 µL CSF, 1-hour primary antibody incubation at room temperature; Affymetrix/Procarta, Santa Clara, CA), and interleukin (IL)-23 (200 µL, 2-hour primary antibody incubation at room temperature; R&D Systems, Minneapolis, MN) were measured in singleplex assays. IL-17 measurements were tried in 5 commercially available kits (Millipore; Life Technologies, Grand Island, NY; Affymetrix/Procarta; R&D Systems; and Affymetrix/El Bioscence, San Diego, CA) with no reliably detectable levels. IL-17 in the original biomarker panel was thus replaced by IL-23 because IL-23 is an upstream effector of IL-17 and CSF IL-23 levels were significantly decreased in FTLD-TDP compared with FTLD-Tau in our original study.¹

**Effects of preanalytical factors on analyte levels.** Preanalytical factors may influence CSF analyte levels, including age,⁰ sex,¹ duration of freezer storage,² and freeze-thaw cycles. The effects of age, sex, and storage duration were assessed statistically (see below). Freeze-thaw effects were determined empirically by having CSF samples from 5 randomly chosen subjects undergo up to 3 freeze-thaw cycles (figure e-1 on the Neurology® Web site at www.neurology.org).

**Statistical analysis.** Statistical analysis was performed in IBM SPSS 20 (Chicago, IL). The χ² test and Student t test (for 2 subgroups) or analysis of variance (for 3 or more subgroups) were used to detect univariate differences between subgroups. Mann-Whitney U tests were used to determine whether levels of agouti-related peptides, adrenocorticotropic hormones, eotaxin-3, Fas, IL-23, t-Tau, and p-Tau₁₈₁ differed between FTLD-TDP and FTLD-Tau in the first validation cohort. Receiver operating characteristic (ROC) curve analysis was used to determine the area under the curve (AUC) including 95% confidence interval (CI) values, and cutoff points were chosen to achieve sensitivity and specificity greater than 80%.¹⁴ Data from the validation cohort 1 (Emory) were used to calculate the necessary sample size in the 2-center validation cohort 2 (Emory and Penn, with no overlap between the 2 validation cohorts) using G*Power 3.1.5 (Kiel, Germany). With a calculated effect size of 0.93 from validation cohort 1 for p/Tau, a sample size of 28 FTLD-TDP and 18 FTLD-Tau has power of 0.90 in detecting a difference in CSF p/Tau between the 2 groups at α = 0.05. In validation cohort 2, ROC curve analysis was performed with and without the inclusion of AD subjects with increased t-Tau/AB42 ratio to determine whether the overall predictive accuracy could be improved by incorporating CSF AD biomarkers¹⁶ into the diagnostic algorithm.¹⁹

To determine the effects of preanalytical factors, Mann-Whitney U test was used to compare the distribution of p/Tau ratio between categorical factors (sex, presence of APOE ε4 allele, autopsy status), and linear regression analysis was used to determine the effects of age and collection year.

**Levels of evidence.** We set out to determine whether there is Class II evidence that candidate CSF biomarkers can reliably distinguish between FTLD-TDP and FTLD-Tau in a 2-center study.

**RESULTS** We sought to validate putative CSF biomarkers of FTLD subtypes in a single-center validation cohort 1 (n = 30) or a 2-center validation cohort 2 (n = 100, table). In validation cohort 1, FTLD-TDP cases had lower p-Tau₁₈₁ levels than FTLD-Tau cases (mean 12.3 vs 19.4 pg/mL, p = 0.031, figure 2), and a trend of increased Fas levels and decreased IL-23 levels (p = 0.158, p = 0.152, figure 2). Levels of the other biomarkers did not differ between FTLD-TDP and FTLD-Tau. Decreased p-Tau₁₈₁ levels alone had moderate performance as a biomarker for FTLD-TDP, with an AUC of 0.750 (95% CI 0.581–0.926) in the ROC curve analysis (figure 3A).

Because previous studies have noted a trend of decreased t-Tau levels in FTLD-Tau,²³ we further analyzed the ratio of p-Tau₁₈₁ to t-Tau (p/t-Tau ratio) to account for possible interindividual differences in the relative Tau phosphorylation at threonine 181. FTLD-TDP cases had significantly lower p/t-Tau ratio than FTLD-Tau cases (mean 0.27 vs 0.47, p = 0.005, figure 2), with AUC of 0.804 (95% CI 0.625–0.983) in the ROC curve analysis (figure 3A).

As further validation, we measured CSF levels of Fas, IL-23, p-Tau₁₈₁, and t-Tau in validation cohort 2 including subjects recruited from Emory (no overlap with validation cohort 1 from Emory) and Penn. Validation cohort 2 included patients with FTLD-TDP (n = 33), FTLD-Tau (n = 20), as well as subjects with AD and elevated CSF ratio of t-Tau to Aβ42 (t-Tau/Aβ42 >0.39, n = 25) and normal cognition (22, including 13 with PN). We included subjects with other central (AD) and peripheral (PN) neurologic disorders to determine whether the observed p/t-Tau phenomenon is specific to FTLD-TDP or merely reflective of brain or peripheral nerve disease. In validation cohort 2, patients with AD were older than patients with FTLD-TDP and FTLD-Tau at the time of symptom onset and time of CSF collection, but all groups were otherwise similar in age at onset, age and disease duration at CSF collection, sex, and education. CSF Fas and IL-23 levels no longer associated with FTLD-TDP in validation cohort 2 (figure e-2). ROC curve analysis showed that p/t-Tau ratio <0.372 differentiated FTLD-TDP cases from all non-FTLD cases with 82% sensitivity and 82% specificity (AUC of 0.838, 95% CI 0.752–0.925, figure 3A; AUC of 0.835 if AD cases were excluded [95% CI 0.739–0.931]), and FTLD-TDP cases from FTLD-Tau with 82% sensitivity and 62% specificity (AUC of 0.731, 95% CI 0.589–0.874).

The observed performance in validation cohort 2 may be attributable to preanalytical factors such as site of collection. We thus determined whether CSF p/t-Tau was influenced by center (Emory vs Penn), age, sex, year of collection, and autopsy status. This analysis revealed that a decreased CSF p/t-Tau ratio in FTLD was not associated with the center of collection (p = 0.607), age (p = 0.391, figure 3B), sex (p = 0.440), or autopsy status (p = 0.193). However,
while CSF p/t-Tau was stable in the FTLD-TDP cases regardless of number of years in −80°C storage (p = 0.257 in linear regression model), FTLD-Tau cases from before 2009 had lower CSF p/t-Tau levels than FTLD-Tau cases collected in 2009 or after (p = 0.017, figure 3C). This was likely due to higher t-Tau levels in the pre-2009 FTLD-Tau cohort (71 pg/mL vs 50 pg/mL, p = 0.017 by Mann-Whitney U test). When only samples collected in 2009 or after were analyzed (figure 3D), CSF p/t-Tau ratio < 0.37 was associated with a high diagnostic accuracy in distinguishing FTLD-TDP from FTLD-Tau cases only (ROC = 0.849, 95% CI 0.725–0.973) or all non-FTLD-TDP cases (ROC = 0.908, 95% CI 0.832–0.983).

Because most autopsy cases had longer freezer storage duration (n = 25, mean 7.7 years) than mutation (n = 21, mean 1.85 years) or clinical (n = 37, mean 0.90 years) cases, the difference in p/t-Tau ratio between FTLD-TDP and FTLD-Tau may be attributable to the inclusion of clinical cases. Therefore, we determined whether the CSF p/t-Tau ratio distinguished between FTLD-TDP and FTLD-Tau within each subgroup as autopsy and mutation confirmation are both criteria for definite FTLD.21 Compared with FTLD-Tau cases, FTLD-TDP cases had lower CSF p/t-Tau ratio in both the mutation (n = 0.046) and clinical (n < 0.001) series, but only showed a trend of lower CSF p/t-Tau ratio in the autopsy (n = 0.209) series.

**DISCUSSION**

The design of disease-modifying FTLD clinical trials has been largely hampered by the clinical inability to distinguish patients with FTLD-TDP and FTLD-Tau. In this study, we demonstrated CSF p/t-Tau ratio as a reproducible biomarker for FTLD-TDP in a large number of patients with FTLD recruited from 2 academic centers with known or high-confidence pathology. The performance of reduced CSF p/t-Tau ratio approximates that of the well-established CSF biomarker of t-Tau/β42 for AD,18 although fluctuations after long-term freezer storage may limit its use in old samples. Assays for the 2 components of this ratio, p-Tau181 and t-Tau, are well established in many neurodegenerative disease research centers, and an international standardization effort is already underway given their importance in AD diagnosis and disease-modifying AD trials.22 Our validation of reduced p/t-Tau ratio as an FTLD-TDP biomarker permits the rapid translation of this marker into current and future clinical trials for FTLD-TDP and FTLD-Tau.

The pathophysiologic change that results in a decreased p/t-Tau ratio in FTLD-TDP is unknown at this time. This is likely not due to increased p-Tau181 in FTLD-Tau as these cases had lower p-Tau181 levels and p/t-Tau ratio than healthy
control subjects and AD cases. Alternatively, there may be altered Tau phosphorylation in the brain or CSF of patients with FTLD-TDP that leads to the absence of hyperphosphorylated Tau in patients with FTLD because of the accumulation of pathologic FTLD-TDP. However, there is insufficient evidence to support this possibility, because our immunoassays measured the absolute levels of t-Tau and p-Tau\textsubscript{181} instead of global phosphorylation within each Tau peptide, and we have not examined phosphorylation status at other Tau residues (e.g., p-Tau\textsubscript{231}). Mass spectrometry methods would be useful to further investigate this issue, but Tau remains poorly detectable in CSF through these methods. Finally, measured levels of p-Tau\textsubscript{181} and t-Tau include both full-length and cleaved Tau isoforms containing the antigenic sites targeted by the capturing and detecting antibodies, and differential degradation of p-Tau\textsubscript{181} may occur in different FTLD subtypes.

Another important finding in our study is the differential effects of preanalytical factors on CSF analytes. A major hurdle in the bench-to-bedside translation of promising biomarkers is their technical and biological validation.\textsuperscript{23,24} Failure to replicate results may be attributable to preanalytical factors (e.g., collection tubes, assay format [immunoassays vs mass spectrometry], biological heterogeneity, and statistical approaches. In the 2 smaller single-center cohorts (n = 23 in our earlier work\textsuperscript{3} and n = 30 in validation cohort 1), we found trends of higher Fas in FTLD-TDP. However, this association disappeared in the validation cohort 2 (n = 53) at least in part because of the age-associated changes. Age is known to influence levels of CSF biomarkers such as A\textsubscript{β}\textsubscript{42}\textsuperscript{25} and α-synuclein,\textsuperscript{26} but its effect is only detectable with a sufficiently powered cohort. Age of the samples also altered CSF p/t-Tau ratio values and IL-23 levels. This effect from sample age reduced the ability of p/t-Tau to distinguish between autopsy-confirmed FTLD-TDP and FTLD-Tau with long freezer storage time, but p/t-Tau still distinguished between the 2 FTLD subtypes with pathogenic mutations fulfilling criteria of definite FTLD, confirming the notion that p/t-Tau reflects the FTLD pathology instead of clinical syndromes.\textsuperscript{21} Sample age is not a new preanalytical factor, as we previously found 4 CSF analytes to undergo age (of the sample) dependent changes in levels.\textsuperscript{4} Whether this is attributable to slow protein turnover, release from interacting proteins, or another mechanism is unclear. Caution is thus warranted when using older stored CSF samples to perform biomarker discovery or validation studies. Because cases in long-term storage are more likely to have autopsy confirmation, future studies must account for storage time and possibly identify alternate gold standards such as pathogenic mutations.

We propose that CSF p/t-Tau ratio is a reproducible CSF biomarker to distinguish between FTLD-TDP and FTLD-Tau. The same ratio can be potentially used to identify cases of ALS without cognitive impairment. In a follow-up study at Penn, one of us (M.G.) determined that ALS cases without dementia showed decreased CSF p/t-Tau compared with control subjects with p-Tau\textsubscript{181} and t-Tau levels. While characterizing the clinical FTD syndromes remains important in symptomatic management and potentially tracking longitudinal progression,\textsuperscript{27} the use of a simple, accurate, and minimally invasive biomarker can significantly enhance the design of therapeutic trials focused on abnormal inclusions containing TDP-43, or to exclude subjects with high-likelihood FTLD-TDP from trials that target Tau pathology in FTLD-Tau patients. A previous tauopathy trial limited its enrollment only to patients with PSP because of the poor reliability of using clinical syndromes to predict FTLD-TDP or FTLD-Tau.\textsuperscript{28} With measures of CSF p/t-Tau ratio readily available in most laboratories involved in AD biomarker research, future clinical trials of drugs that target Tau or TDP can enrich their study population.

Figure 2 CSF biomarker levels in FTLD-TDP and FTLD-Tau

Levels of Fas (A), IL-23 (B), p-Tau\textsubscript{181} (C), and p/t-Tau ratio (D) in validation cohort 1 from Emory between FTLD-TDP and FTLD-Tau. FTLD-TDP = frontotemporal lobar degeneration with TAR DNA-binding protein 43 (TDP-43) inclusions; IL = interleukin; p/t-Tau = Tau phosphorylated at threonine 181 (p-Tau\textsubscript{181})/total Tau ratio.
with patients with FTD syndromes and normal or low p/t-Tau ratio. Finally, in asymptomatic subjects from families with FTLD-TDP–related mutations, a decrease in CSF p/t-Tau levels may herald early biochemical changes in the brain of these clinically normal subjects, similar to the early decrease in CSF Aβ42 levels in asymptomatic subjects with autosomal dominant AD mutations.29 If so, CSF p/t-Tau can be used as a biomarker to identify subjects at very high risk of symptomatic FTLD-TDP for prevention trials similar to those ongoing in familial AD.30,31

AUTHOR CONTRIBUTIONS

Dr. Hu: study concept and design, acquisition of data, analysis and interpretation, statistical analysis, drafting/revision of the manuscript. Ms. Watts, Dr. Grossman, Dr. Glass, Dr. Lah, Dr. Hales, and Mr. Shelnutt: acquisition of data, analysis and interpretation. Dr. Van Deerlin: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Trojanowski and Dr. Levey: study concept and design, critical revision of the manuscript for important intellectual content, study supervision.

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DISCLOSURE

W. Hu has received research support from the Association for Frontotemporal Degeneration, the Alzheimer’s Drug Discovery Foundation, the NIH, and the ALS Association. Dr. Glass has consulted for Forest and Allon. J. Lah has received research support from the NIH. C. Hales and M. Shelnutt have nothing to disclose. V. Van Deerlin has received research support from the NIH; has a patent on the Compositions and Methods for the Treatment of Frontotemporal Lobar Degeneration with p-Tau43; and has consulted for Allon Therapeutics, Biokao, and Biodesign ASA.

Figure 3  Diagnostic performance of Tau-related biomarkers in identifying FTLD-TDP

(A) ROC curve analysis of CSF p-Tau181 levels (gray dashed line) and CSF p/t-Tau ratio (blue solid line) in validation cohort 1, and the CSF p/t-Tau ratio (black solid line) in validation cohort 2. (B) Analysis of both validation cohorts together showed no significant effect of age on the CSF p/t-Tau ratio. (C) CSF samples collected before 2009 had lower p/t-Tau ratio than CSF samples collected in or after 2009 in FTLD-Tau subjects (red line) but not FTLD-TDP subjects (blue line). (D) When subjects whose CSF was collected before 2009 were excluded, the CSF p/t-Tau ratio remained an accurate biomarker to distinguish FTLD-TDP from FTLD-Tau (black solid line) or all non-TDP cases (black dashed line). FTLD-TDP = frontotemporal lobar degeneration with TAR DNA-binding protein 43 (TDP-43) inclusions; p/t-Tau = Tau phosphorylated at threonine 181 [p-Tau181]/total Tau ratio; ROC = receiver operating characteristic.

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