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CSF biomarkers in frontotemporal lobar degeneration with known pathology

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Abstract

Objective—To evaluate the diagnostic value of CSF biomarkers in patients with known pathology due to frontotemporal lobar degeneration (FTLD).

Background—It is important to distinguish FTLD from other neurodegenerative diseases like Alzheimer disease (AD), but this may be difficult clinically because of atypical presentations.

Methods—Patients with FTLD ($n = 30$) and AD ($n = 19$) were identified at autopsy or on the basis of genetic testing at University of Pennsylvania and Erasmus University Medical Center. CSF was obtained during a diagnostic lumbar puncture and was analyzed using assays for total tau and amyloid-beta 1-42 ($A\beta_{42}$). Patients also were assessed with a brief neuropsychological battery.

Results—CSF total tau level and the ratio of CSF total tau to $A\beta_{42}$ ($\text{tau}/A\beta_{42}$) were significantly lower in FTLD than in AD. Receiver operating characteristic curve analyses confirmed that the CSF $\text{tau}/A\beta_{42}$ ratio is sensitive and specific at discriminating between FTLD and AD, and is more successful at this than CSF total tau alone. Although some neuropsychological measures are significantly different in autopsy-proven FTLD and AD, combining these neuropsychological measures with CSF biomarkers did not improve the ability to distinguish FTLD from AD.

Conclusions—The ratio of CSF $\text{tau}/A\beta_{42}$ is a sensitive and specific biomarker at discriminating frontotemporal lobar degeneration from Alzheimer disease in patients with known pathology.

It is important to distinguish between progressive neurodegenerative conditions such as frontotemporal lobar degeneration (FTLD) and Alzheimer disease (AD) for many reasons. They appear to have distinct underlying causes that may require different etiologically based treatments, for example, and patient counseling would benefit since clinical features such as survival may differ in these conditions. There are two definite ways to confirm the diagnosis of FTLD. One depends on brain pathology at autopsy; the other identifies a genetic mutation known to cause FTLD. In 1998, mutations in the microtubule-associated protein tau (*MAPT*)

gene were first discovered in some FTDP-17 families,¹⁻³ and patients with MAPT mutations consistently have tau-positive inclusion pathology at autopsy.^{4,5} More recently, mutations of the progranulin (*PGRN*) gene were confirmed as the cause of autosomal dominant tau-negative FTLN with ubiquitin-positive but tau-negative inclusions (FTLD-U) linked to chromosome 17.^{6,7} In this study, we examine the usefulness of CSF biomarkers obtained during life in distinguishing patients with autopsy evidence or with a genetic mutation causing known FTLN pathology from AD.

Among currently available CSF biochemical markers of neurodegenerative diseases, the protein tau appears most promising for differentiating FTLN from AD. Several studies of CSF tau levels have been reported in patients clinically diagnosed with FTLN. The results have been inconsistent. Some studies found statistically increased CSF tau levels,⁸⁻¹⁰ while others reported normal CSF tau concentrations.¹¹ In our previous clinical study, we found that CSF tau levels are significantly lower in FTLN than AD. Moreover, a receiver operating characteristic (ROC) curve analysis showed that tau is more sensitive than amyloid or isoprostane at distinguishing between FTLN and AD.¹² Differences between reported studies may be due in part to the fact that clinical diagnosis does not always correspond to pathologic findings. Diagnosis may be difficult because of atypical presentations, such as frontal variant AD^{13,14} or FTLN presenting with memory difficulty.¹⁵ The current study examines CSF biomarker levels in cases with known pathology found at autopsy or genetic ascertainment. We hypothesized that FTLN would have a lower CSF tau level and lower tau/A β ₄₂ ratio than AD.

Attempts to distinguish FTLN and AD during life also have focused on cognitive biomarkers. AD is characterized by memory decline, for example, while changes in personality/behavior and progressive aphasia are the most prominent features of FTLN.¹⁶ However, these broad descriptions have proven to be only modestly reliable in clinical-pathologic correlation studies.^{17,18} Neuropsychological measures such as category naming fluency, confrontation naming, and episodic memory appear to differ in autopsy-proven FTLN and AD, so we also assessed whether neuropsychological results can improve the diagnostic value of CSF biomarkers.

METHODS

Subjects

From among 113 patients with CSF samples, we identified 36 in whom we also had known pathologic evidence for a specific diagnosis. This included patients with FTLN determined at autopsy (n = 15), FTLN with a known genetic mutation (n = 2), and autopsy-proven AD (n = 19) recruited from the Department of Neurology at the University of Pennsylvania. CSF samples from another 13 patients with autopsy-proven FTLN (n = 4) or a genetically determined mutation (n = 9) causing FTLN were obtained from the Department of Neurology at Erasmus University Medical Center of the Netherlands. The clinical diagnosis of an FTLN spectrum disorder or AD was established through a consensus mechanism following a clinical evaluation by an experienced neurologist and was consistent with the results of serum studies (e.g., normal levels on studies such as B12, thyroid functioning, and sedimentation rate), the absence of clinically significant MRI or CT changes suggesting vascular pathology or hydrocephalus, normal clinical studies of CSF (when available), and functional neuroimaging studies such as SPECT or PET (when available). The demographic characteristics of these subjects are summarized in table 1. In the FTLN series, histopathologic and genetic mutation diagnoses were as follows: 13 tau-positive patients, including corticobasal degeneration (CBD, n = 2), dementia with Pick bodies (PiD, n = 1), tangle predominant senile dementia (TPSD, n = 1), FTDP-17 (n = 1), G272V mutation (n = 2), and P301L mutation (n = 6); and 17 tau-negative patients, including FTLN-U (n = 9), dementia lacking distinctive histopathology

(DLDH, $n = 3$), FTL with motor neuron disease (FTLD-MND, $n = 2$), and PGRN mutation ($n = 3$).

CSF from 13 cognitively normal seniors established the range of normal CSF tau and $A\beta_{42}$. All patients and their legally authorized caregivers participated in an informed consent procedure approved by the Institutional Review Board at the University of Pennsylvania or Erasmus University Medical Centre.

Materials and procedures

CSF was obtained during routine diagnostic lumbar puncture. After the collection of 10 mL CSF for clinical diagnostic purposes, an additional 2 mL was collected in a red top tube, separated into small aliquots of fluid, and immediately frozen at -80°C . As described in detail elsewhere,¹² CSF was analyzed in duplicate using a sandwich ELISA for total tau level with a specific kit used at both sites (Innotest hTAU-Antigen kit; Innogenetics, Ghent, Belgium). CSF levels of $A\beta_{42}$ were also assayed in duplicate with a sandwich ELISA using specific monoclonal antibodies, as described previously.¹⁹

Neuropsychological assessment was based on a brief battery of standardized tests administered in the same manner at both institutions. We assessed working memory (forward and backwards digit span)²⁰; letter category naming fluency (number of words beginning with a specified letter F, A, S produced in 1 minute)²¹; confrontation naming (15-item version of the Boston naming test)²²; animal category naming fluency (as many names of animals as possible in 60 s)²³; geometric figure copy (copy four geometric designs)²³; Verbal Serial List Learning Test (10-word list administered over three trials, delayed free recall, and delayed recognition).²⁴

To establish a neuropathologic diagnosis, board-certified neuropathologists (M.S.F., J.Q.T.) reviewed all cases, and we established diagnoses according to consensus criteria including the recent Workgroup on Frontotemporal Dementia and Pick's Disease, as described previously.^{16,25} Immunohistochemistry was performed using standard and previously published protocols with antibodies that detect phosphorylated tau (PHF126, provided by Dr P. Davies); β -amyloid (i.e., 4G8; Senetek, Maryland Heights, MO); α -synuclein (Syn30327); ubiquitin (Chemicon International, Temecula, CA, and Dako Cytomation, Glostrup, Denmark); phosphorylated NF subunits (RMO2428); and α -internexin (Zymed Laboratories, San Francisco, CA). In instances where multiple distinct pathologies were present ($n = 1$), a primary diagnosis was assigned based on the density and distribution of the observed pathology in relation to the clinical phenotype of the patient.

Statistical analysis

All statistical analyses were performed using SPSS version 12.0 (SPSS, Chicago, IL). Descriptive statistics were used to characterize the entire cohort, as well as each pathologic subgroup. Student t tests were used to investigate differences in demographics and levels of CSF tau, $A\beta_{42}$, and ratio of tau/ $A\beta_{42}$ between the two pathologic groups. χ^2 statistics were used to compare gender ratios and to compare ratios across different CSF tau level and tau/ $A\beta_{42}$ ratio groups. Performance on each measure of cognitive function was reported as a z-score relative to 25 age- and education-matched healthy seniors. Significance was set at -2.32 , equivalent to $p < 0.01$ (two-tailed), unless otherwise noted. The Spearman coefficient was used for correlation. ROC curves were used to evaluate the utility of various measures at distinguishing between groups.

RESULTS

Demographic features and CSF levels of total tau, $A\beta_{42}$, and tau/ $A\beta_{42}$ are summarized in table 1. Figure 1 illustrates CSF total tau, $A\beta_{42}$, and tau/ $A\beta_{42}$ ratio in FTLN, AD, and control groups. Relative to patients with AD, CSF total tau level [$t(47) = 4.05, p < 0.01$] and tau/ $A\beta_{42}$ ratio [$t(46) = 6.93, p < 0.001$] were reduced in patients with FTLN with known pathology. The CSF $A\beta_{42}$ level was higher in FTLN than AD [$t(46) = 4.13; p < 0.001$]. Similar findings were evident in an assessment of the subset of autopsy-confirmed patients, that is, lower CSF tau [$t(36) = 3.33, p < 0.01$] and lower tau/ $A\beta_{42}$ ratio [$t(35) = 5.33, p < 0.01$] in FTLN than AD, and elevated CSF $A\beta_{42}$ in FTLN relative to AD [$t(35) = 3.48, p < 0.01$]. Both CSF tau level [$t(34) = 3.52, p < 0.01$] and tau/ $A\beta_{42}$ ratio [$t(22) = 5.59, p < 0.01$] were lower in tau-negative patients than patients with AD. Similarly, CSF tau level [$t(26) = 2.94, p < 0.01$] and tau/ $A\beta_{42}$ ratio [$t(19) = 5.66, p < 0.01$] were lower in tau-positive patients than patients with AD. CSF total tau, $A\beta_{42}$ and tau/ $A\beta_{42}$ ratio were lower in tau-negative than tau-positive patients, but this difference was not significant. Patients with AD had elevated CSF tau level [$t(30) = 3.12, p < 0.01$] and tau/ $A\beta_{42}$ ratio [$t(30) = 3.87, p < 0.01$], and lower CSF $A\beta_{42}$ level [$t(30) = 3.79, p < 0.01$] compared to the control group, but FTLN and controls did not differ in these measures.

Figure 2A shows the scatter plot of the raw values of the CSF tau level and tau/ $A\beta_{42}$ ratio in FTLN and AD. Figure 2B illustrates the ROC curves for CSF total tau, $A\beta_{42}$, and tau/ $A\beta_{42}$ ratio in FTLN and AD based on these raw values. The area under the curve (AUC) for CSF tau was 0.79 ($p = 0.001$). For tau/ $A\beta_{42}$, the AUC was 0.93 ($p < 0.001$). Using a cutoff value of 1.06, CSF tau/ $A\beta_{42}$ ratio has a sensitivity of 78.9% and a specificity of 96.6% at distinguishing FTLN from AD. Using a cutoff value of 403.05 pg/mL, total CSF tau has a sensitivity of 68.4% and a specificity of 89.7% at distinguishing FTLN from AD. In evaluating FTLN and controls, the AUC for CSF tau was 0.52 ($p = 0.817$), and the AUC for tau/ $A\beta_{42}$ ratio was 0.42 ($p = 0.422$), showing modest ability to distinguish FTLN from controls based on CSF biomarkers.

An analysis of total CSF tau levels was performed in individual patients using z-scores derived from the control sample obtained using the same CSF analyses. This was necessary to combine CSF and cognitive results in the diagnostic evaluation of FTLN and AD (see below). The range of normal CSF total tau is 81-445 pg/mL ($z < -1.96$, equivalent to a p value of < 0.05 , two-tailed), based on this control group. Using these z-score values, we found that 4 (13.3%) of the 30 patients with FTLN have a significantly reduced CSF total tau level. Of the four cases with significantly reduced CSF tau levels, all were tau-negative patients: three had FTLN-U, and the remaining case had DLN. All four patients with a low CSF tau level presented with a social/executive impairment. Three FTLN cases with significantly reduced tau were so low that they could not be detected by the kit we used. A significantly reduced level of CSF tau was never seen in individual patients with AD, according to these z-score analyses. However, a much higher proportion of patients with AD (10 of 19, or 52.6%) had an elevated CSF total tau level compared to FTLN (3 of 30, or 10.0%) [$\chi^2(2) = 12.03; p = 0.002$]. Of the three patients with FTLN with an elevated tau level, two were tau-positive (one with Pick disease presenting with a social/executive impairment and one with a P301L mutation presenting with mixed social impairment and primary progressive aphasia), and the other had FTLN-U presenting with a social/executive impairment. An analysis of individual patient tau/ $A\beta_{42}$ ratios, using z-scores derived from the control sample, revealed that none of the patients with FTLN have an elevated tau/ $A\beta_{42}$ ratio, while more than half (10 of 19, or 52.6%) of the patients with AD have an elevated tau/ $A\beta_{42}$ ratio [$\chi^2(1) = 19.28, p < 0.001$].

Table 2 shows the z-score of cognitive tests in patients with known pathology due to FTLN or AD. Using a z-score criterion of -2.32 ($p < 0.01$) based on 25 healthy seniors, the mean z-score of confrontation naming is significantly impaired in FTLN but not in AD. In contrast, the z-

score of visual constructions is impaired in AD but not FTLT. Animal category naming fluency and delayed free recall memory were significantly impaired in both FTLT and AD.

There were several correlations between CSF biomarkers and neuropsychological tests in FTLT and AD. As summarized in table 2, the ratio of tau/ $A\beta_{42}$ correlated with confrontation naming and delayed recall memory in FTLT. In AD, tau and the tau/ $A\beta_{42}$ ratio correlated with animal naming fluency output, and the ratio of tau/ $A\beta_{42}$ also correlated with confrontation naming accuracy.

ROC curves for the Boston Naming Test and animal naming fluency in FTLT and AD showed that the AUC for Boston Naming test was 0.62 ($p = 0.22$) and the AUC for animal fluency was 0.48 ($p = 0.85$). Thus, performance on these neuropsychological measures alone does not distinguish effectively between FTLT and AD.

Because of the correlations of CSF tau and tau/ $A\beta_{42}$ ratio with neuropsychological tests, and because of the differences between FTLT and AD in autopsy-proven cases, we tried to combine CSF tau and tau/ $A\beta_{42}$ with neuropsychological measures such as animal category naming fluency and confrontation naming in an attempt to improve sensitivity and specificity at distinguishing FTLT from AD. The results showed that only the combination of CSF total tau with confrontation naming improved the ROC marginally (AUC 0.81, $p = 0.002$) compared to CSF tau alone. The combinations of tau/ $A\beta_{42}$ ratio with confrontation naming (AUC = 0.81, $p = 0.002$) and with animal category naming fluency (AUC = 0.76, $p = 0.009$) were statistically robust, but these combined measures showed no improvement compared to the tau/ $A\beta_{42}$ ratio alone.

DISCUSSION

CSF tau is a potentially valuable biomarker for differentiating FTLT from AD. Based on analyses of clinically diagnosed cohorts, reports of CSF total tau levels in patients with FTLT have been highly variable, ranging from normal¹¹ to significantly low¹² and significantly high⁸⁻¹⁰ compared with AD and normal senior controls. In this study, we examined a large group of patients with known pathology confirmed by autopsy or genetic testing to evaluate the usefulness of CSF biomarkers in diagnosing FTLT during life. We found that CSF tau and the ratio of tau/ $A\beta_{42}$ are significantly lower in FTLT than in AD. The ratio of tau/ $A\beta_{42}$ appears to be a particularly sensitive and specific biomarker at discriminating FTLT from AD.

The impression that CSF tau level and CSF tau/ $A\beta_{42}$ ratio may be valuable in differentiating FTLT from AD is confirmed by individual patient analyses. We found significantly reduced CSF tau level in FTLT, but none of the autopsy-proven patients with AD had a significantly reduced CSF total tau level. Likewise, none of the patients with FTLT had a high tau/ $A\beta_{42}$ ratio, although more than half of the patients with AD had a significantly elevated tau/ $A\beta_{42}$ ratio.

Several factors probably contribute to the inconsistent comparative CSF findings reported in previous articles. First, most of these studies included patients with a clinical diagnosis instead of autopsy-proven diagnosis, and only a few cases with a neuropathologically proven diagnosis have been reported, raising concern about the possibility of misdiagnosis. Clinical-pathologic correlation studies show that between 15% and 33% of patients with a clinical diagnosis of FTLT in fact have AD at autopsy.²⁶⁻³² Nevertheless, the results of CSF total tau level in autopsy-proven patients with FTLT have been inconsistent. One study reported significantly increased CSF total tau in autopsy-proven patients with FTLT compared with normal controls⁸ while another study showed no significant difference between FTLT and controls.³³ However, these were very small samples. Another contributing factor may be related to the pathologic diversity of FTLT, with varying numbers of patients with PiD, CBD, or FTLT-U

included in these studies. Larger studies of patients with diagnoses such as these are needed to clarify the role of these specific pathologies on CSF biomarker values.

The reason that some patients with FTLN have low CSF tau remains unclear. One possible explanation is that the soluble tau level in the brain is depleted, leaving no source for CSF tau. This may be seen in the four tau-negative patients with FTLN (one case with DLN and three cases with FTLN-U) with low CSF tau levels in this study. Another possibility is that tau is sequestered in the brain, possibly in the form of filamentous inclusions such as Pick bodies or in balloon cells.¹² This finding may also be related to the topographic distribution of CSF protein concentrations, especially during early clinical stages, where the degenerating process in FTLN may be confined to small cortical areas that are remote from ventricular and lumbar CSF spaces.¹⁰ It is less likely that low CSF tau level is related to longer disease duration at the time of assessment since the patients with FTLN in fact had marginally shorter disease duration than the patients with AD. Regardless of the basis for low CSF tau in FTLN, ROC curves showed that both CSF tau and tau/A β ₄₂ ratio were able to discriminate between FTLN and AD.

The tau/A β ₄₂ ratio has better sensitivity and specificity compared to CSF tau alone in distinguishing patients with FTLN from those with AD. This may be related in part to the pathogenic roles of tau and A β ₄₂ in FTLN and AD.³⁴ It has been suggested that CSF total tau reflects the intensity of neuronal degeneration,^{35,36} while CSF A β ₄₂ reflects the deposition of A β into plaques,^{37,38} and phosphorylated tau reflects the hyperphosphorylation of tau with subsequent formation of tangles.³⁹ The latter two are major neuropathologic characteristics of AD.⁴⁰ In FTLN, however, amyloid plaque deposition, even if present in some cases, is not a common feature.^{41,10} This may be the main reason that patients with FTLN usually have higher A β ₄₂ level compared to AD, and why the ratio of tau/A β ₄₂ is superior at discriminating between FTLN and AD. Indeed, the tau/A β ₄₂ ratio discriminated between FTLN and AD in our cohort with a sensitivity of 79% and a specificity of 97%. According to a consensus report, a useful diagnostic biomarker should have sensitivity approaching or exceeding 80% for detecting AD and a specificity greater than 80% for distinguishing other dementias.⁴² The ratio of tau/A β ₄₂ thus appears to fulfill these requirements, because both high sensitivity and specificity were obtained at a cutoff value of 1.06.

A reliable and reproducible diagnostic biomarker also should be stable over time. Previous studies have indicated that CSF tau and A β ₄₂ levels remain stable in patients with AD when CSF samples are compared over an average interval of 6 to 18 months.⁴³⁻⁴⁵ In a cross-sectional correlation analysis with disease duration in the present study, we found no correlation between disease duration and CSF tau levels and the tau/A β ₄₂. However, the stability of these biomarkers in the course of FTLN remains to be documented using a within-patient longitudinal design.

The results of neuropsychological measures in this study indicate that distinct cognitive profiles also can differentiate between patients with known pathology due to FTLN and AD. Patients with FTLN showed greater deficits on tests of confrontation naming and category naming fluency, but relatively better performance on memory and visuospatial tasks than patients with AD. These findings are consistent with clinical observations that FTLN predominantly affects executive skills and language function, while memory and visuospatial functioning are more likely to be impaired in AD. Other comparative studies of patients with autopsy-confirmed FTLN and AD also report these findings.^{17,18,32} This may reflect the distinct regional brain pathology that underlies these conditions. MRI studies in FTLN associate orbitofrontal, dorsolateral, and anterior temporal cortical atrophy with impairment of personality, behavior, and social conduct, and with poor performance on cognitive tasks that involve executive and language functions.^{46,47} Other work relates cognitive measures such as these directly to the

anatomic distribution of histopathologic disease in FTLN using correlation analyses.¹⁸ In contrast, patients with AD have extensive medial temporal and parietal lobe involvement that is consistent with the prominent episodic memory dysfunction and visuospatial impairments that occur in the disorder.⁴⁸⁻⁵²

CSF protein levels and neuropsychological measures are two promising biomarkers for distinguishing FTLN from AD because of their quantitative nature. The significant correlation of tau/A β ₄₂ with recall in FTLN indicates that poor memory performance is associated with an abnormally elevated tau/A β ₄₂ ratio. Likewise, the significant correlation of tau/A β ₄₂ ratio with confrontation naming in AD indicates that better naming performance is associated with an abnormally elevated tau/A β ₄₂ ratio. Since an elevated tau/A β ₄₂ ratio occurs in more than half of patients with AD but rarely in FTLN, poorer performance on recall memory and better performance on confrontation naming tasks may be a clinical indication that a patient is less likely to have FTLN.

CSF tau and tau/A β ₄₂ ratio have been linked directly to histopathologic disease, just as specific neuropsychological measures have been related to known pathology in FTLN.^{17,18,32} We sought to determine whether the combination of these two measures would be more informative than either one alone at distinguishing FTLN from AD. The combination of neuropsychological measures with CSF biomarkers in fact did not improve the ability to distinguish FTLN from AD. Although a ROC curve showed that the combination of CSF tau level with confrontation naming had a relatively higher specificity than CSF tau alone, the overall sensitivity and specificity of this combination is still less than the tau/A β ₄₂ ratio alone. None of the neuropsychological measures, when combined with the tau/A β ₄₂ ratio, improved the AUC associated with the ratio measure alone. Thus the ratio of tau/A β ₄₂ appears to be the most effective biomarker at discriminating FTLN from AD.

Several caveats should be kept in mind when interpreting our results. First, the CSF tau/A β ₄₂ ratio is a valuable biomarker at discriminating between neurodegenerative conditions with clinically detectable abnormalities such as FTLN and AD. However, no statistical difference was found between FTLN and the control group in the CSF tau level and tau/A β ₄₂ ratio. These biomarkers thus are useful only in the setting of an abnormal neurologic examination, and are not helpful at differentiating patients with FTLN from healthy controls. Second, both academic medical centers participating in this study used the same kit to analyze CSF and administered the same neuropsychological tests in a standard manner. However, minor methodologic differences in data analysis in the two centers can not be completely excluded. Third, most CSF samples were typically collected soon after the patients were first seen in our clinics, but there was often a delay between symptom onset and initial evaluation. Although we failed to find a correlation between CSF biomarkers and disease duration in a cross-sectional analysis, it is important to be cautious about generalizing our observations to the earliest stage of a neurodegenerative disease. In addition, not all types of pathology were included in the FTLN group, such as progressive supranuclear palsy and argyrophilic grain disease, and this may influence the CSF tau level and cognitive test results of the FTLN group. Finally, only a subset of the patients performed the cognitive tests, and the relatively small number of cases with known pathology included in this study limited the interpretability of these results. With these caveats in mind, our findings suggest that FTLN and AD have relatively distinct CSF biomarker profiles. Relative to patients with AD, patients with FTLN are characterized by lower levels of CSF tau and tau/A β ₄₂ ratio. The ratio of tau/A β ₄₂ appears to be the most sensitive and specific biomarker at discriminating FTLN from AD.

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GLOSSARY

AD, Alzheimer disease; AUC, area under the curve; CBD, corticobasal degeneration; FTLT, frontotemporal lobar degeneration; FTLT-U, FTLT with ubiquitin-positive but tau-negative inclusions; MAPT, microtubule-associated protein tau; MND, motor neuron disease; PiD, dementia with Pick bodies; ROC, receiver operating characteristic; TPTD, tangle predominant senile dementia.

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Figure 1. CSF total tau, $A\beta_{42}$, and tau/ $A\beta_{42}$ ratio in frontotemporal lobar degeneration (FTL), Alzheimer disease (AD), and control groups

Figure 2.

Scatterplot and receiver operating characteristic curves of CSF tau, $A\beta_{42}$, and $\tau/A\beta_{42}$ ratio in patients with frontotemporal lobar degeneration (FTLD) and Alzheimer disease (AD) (A) Scatterplot of CSF tau and $A\beta_{42}$ levels in patients with FTLD and AD. (B) Receiver operating characteristic curves of CSF tau, $A\beta_{42}$, and $\tau/A\beta_{42}$ ratio in patients with FTLD and AD. Using the raw data depicted in the figure, the CSF $\tau/A\beta_{42}$ ratio at a cutoff of 1.06 has sensitivity = 78.9%, specificity = 96.6%, positive predictive value = 93.75%, and positive likelihood ratio = 23.21 to distinguish between FTLD and AD. CSF tau, at a cutoff of 403.05 pg/mL, has sensitivity = 68.4%, specificity = 89.7%, positive predictive value = 81.25%, and positive likelihood ratio = 6.64 to distinguish between FTLD and AD.

Table 1
Demographic features and CSF biomarker levels of patients with known pathology due to FTLD or AD

	FTLD autopsy and genetic combined, n = 30	FTLD autopsy, n = 19	AD autopsy, n = 19	Control, n = 13
Age at onset (SD), y [*]	59.13 (12.23)	60.12 (13.49)	68.53 (10.04)	70.46 (6.63)
Duration at time of testing (SD), mo [†]	29.70 (23.11)	33.13 (23.95)	49.11 (38.48)	—
Gender (M/F) [‡]	10/20	4/15	8/11	10/3
MMSE (SD), § max = 30	22.00 (6.65)	19.79 (7.05)	17.24 (7.25)	29.27 (1.01)
CSF tau (SD), pg/mL [¶]	265.94 (150.51)	271.90 (149.81)	522.56 (291.89)	260.42 (93.75)
CSF Aβ ₄₂ (SD), pg/mL	531.97 (266.23)	533.42 (316.24)	265.24 (110.72)	429.46 (133.83)
Tau/Aβ ₄₂ [#]	0.52 (0.30)	0.56 (0.34)	2.22 (1.28)	0.74 (0.63)

FTLD = frontotemporal lobar degeneration; AD = Alzheimer disease; MMSE = Mini-Mental State Examination.

^{*} Data available in 27 patients with FTLD, 18 patients with AD, and 13 normal controls; patients with FTLD differ from patients with AD and controls ($p < 0.01$). No correlations with CSF biomarkers.

[†] Data available in 26 patients with FTLD and 18 patients with AD. No correlations with CSF biomarkers.

[‡] Data available in 30 patients with FTLD, 19 patients with AD, and 13 controls; autopsy patients with FTLD differ from controls ($p < 0.01$).

[§] Data available in 21 patients with FTLD, 17 patients with AD, and 11 controls; all patients with FTLD, autopsy patients with FTLD, and patients with AD differ from controls ($p < 0.01$). No correlations with CSF biomarkers.

[¶] Data available in 30 patients with FTLD, 19 patients with AD, and 13 controls; see text for statistical comparisons between groups.

^{||} Data available in 29 patients with FTLD, 19 patients with AD, and 13 controls; see text for statistical comparisons between groups.

[#] Data available in 29 patients with FTLD, 19 patients with AD, and 13 controls; see text for statistical comparisons between groups.

Table 2
Mean z-scores of cognitive function, and relationship between CSF biomarker and neuropsychological measures in patients with FTLD and AD

Cognitive Tests	FTLD			AD				
	z-Score	Correlation (tau)	Correlation (tau/ $A\beta_{42}$)	Regression (tau/ $A\beta_{42}$)	z-Score	Correlation (tau)	Correlation (tau/ $A\beta_{42}$)	Regression (tau/ $A\beta_{42}$)
Figure copy	-1.31 (n=17)	-0.248	-0.311	—	-2.39 (n=14)	0.004	0.270	—
Confrontation naming	-2.51 (n=18)	-0.730 [*]	-0.491 [†]	0.23	-1.37 (n=16)	0.354	0.533 [†]	0.21
Animal fluency	-2.49 (n=19)	-0.157	-0.385	—	-2.60 (n=16)	0.674 [*]	0.735 [‡]	0.46
Delayed recall	-2.52 (n=15)	-0.419	-0.595 [†]	0.08	-3.07 (n=15)	0.110	-0.009	—
Recognition memory	-1.12 (n=14)	-0.411	-0.425	—	-2.10 (n=15)	0.135	-0.031	—

A z-score of -2.32 is equivalent to a two-tailed *p* value of 0.01; a z-score of -1.96 is equivalent a two-tailed *p* value of 0.05.

FTLD = frontotemporal lobar degeneration; AD = Alzheimer disease.

^{*} Significant correlation with total CSF tau level at *p* < 0.01.

[†] Significant correlation with CSF tau/ $A\beta_{42}$ at *p* < 0.05.

[‡] Significant correlation with CSF tau/ $A\beta_{42}$ at *p* < 0.01.