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Cerebrospinal Fluid Tau in Frontotemporal Lobar Degeneration: Clinical, Neuroimaging, and Prognostic Correlates

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Abstract. Frontotemporal lobar degeneration (FTLD) refers to heterogeneous clinical and biological conditions. In FTLD, cerebrospinal fluid (CSF) tau levels have been reported highly variable. The aim of the present study was to evaluate whether CSF tau might be the hallmark of a distinct FTLD phenotype. Fifty-five FTLD patients, who underwent CSF analysis, were considered in the present study. In each patient, a wide standardized neuropsychological evaluation, and CSF tau, phospho-tau, and amyloid-β (Aβ) dosages were performed. Each patient was followed-up to five years, and outcomes carefully recorded. In a subgroup of patients ($n = 24$), magnetic resonance imaging scanning was performed, by using voxel-based morphometry, for grey matter investigation. The higher the CSF tau levels, the worse the neuropsychological and neuroimaging pattern, mainly characterized by greater language disturbances and left temporal grey matter loss. The same pattern, even if less significant, was associated with CSF phospho-tau, while CSF Aβ levels did not play any influence on FTLD phenotype. FTLD patients with high CSF tau showed poor prognosis compared to those with low CSF tau ($p = 0.031$). In FTLD, CSF tau levels might be considered a marker of neurodegeneration, associated with a specific clinical and neuroimaging picture, and significantly related to poor outcome. Further studies aimed at defining the biological underpinnings of these findings are warranted.

Keywords: Biological marker, cerebrospinal fluid, frontotemporal dementia, frontotemporal lobar degeneration, tau

INTRODUCTION

Frontotemporal lobar degeneration (FTLD) is an heterogeneous clinical and biological disorder characterized by language deficits, impairment of executive functions, and behavioral disturbances [1]. FTLD is a more common form of dementia than previously recognized, with prevalence of up to 17 cases per 100,000 inhabitants [2]. Despite clear-cut neuroimaging features, affecting frontal and temporal lobes [3], no diagnostic biological markers are available yet. Several studies have evaluated the usefulness of cerebrospinal fluid (CSF) total tau and phospho-tau levels in patients with FTLD, but with contrasting findings [4–8]. Indeed, while it has been widely demonstrated that CSF tau, phospho-tau, and amyloid-β (Aβ) markers are reliable tools to identify Alzheimer's disease in the preclinical stages [9–11], in FTLD, the results have been highly variable. Some studies have shown

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statistically increase of CSF tau, whereas others have shown unremarkable levels [4–8].

Different hypotheses for such a finding may be addressed. Firstly, CSF tau levels might be related to heterogeneous FTLD neuropathology, but no autopsy study investigating this issue has given definitive results. Second, CSF tau variability might be influenced by genetic variations within *Microtuble Associated Protein Tau (MAPT)*, i.e., H1/H2 haplotype [12], or other genes that regulate Tau expression. Finally, tau in CSF might represent an aspecific marker of axonal damage, as increased levels are reported in many other conditions associated with neurodegeneration [13–17].

It has been widely demonstrated that neuroimaging is a promising tool to assess *in vivo* the potential role played by biological markers. Voxel-based morphometry (VBM) is a spatially-specific and unbiased method of analysis of magnetic resonance images reflecting the regional gray matter volume at a voxel scale, by anatomical definition of regional brain tissue damage/preservation [18,19].

In the present work, we examined the usefulness of CSF biomarkers, namely CSF tau and phospho-tau, in defining a) distinct clinical and neuroimaging correlates in FTLD patients by a wide standardized neuropsychological assessment and VBM analysis, respectively, and b) in clarifying whether CSF biomarkers may reflect the degree of axonal damage and could predict the clinical outcome.

METHODS

Subjects

FTLD patients fulfilling current clinical criteria [1] were consecutively recruited from the Centre for Neurodegenerative Diseases, University of Brescia, Italy.

All subjects underwent a physical evaluation, a routine laboratory examination, a lumbar puncture for cerebrospinal fluid analyses, and a brain structural imaging study.

The diagnostic assessment involved a review of full medical history, a semi-structured neurological examination, and a complete mental status evaluation by at least two independent and experienced reviewers (B.B., G.B., A.P.). Only patients with full consensus agreement by the reviewers were enrolled. No patient carrying *MAPT* mutations was included, while three patients carried *Progranulin* mutations.

Demographic characteristics, the estimated age at onset of symptoms, and family history were carefully recorded. The age at onset of symptoms was based on a family report of the earliest persistently abnormal clinical feature in the domains of language, social function or personality change, executive functioning, or movement disorder. Patients considered to have a positive family history were those who had a first-degree relative with dementia, parkinsonism, or motor neuron disease. No patients belonging to the same family were included.

Each patient was followed-up over a 5-year period from the time of the study enrollment/diagnosis, and entry to nursing home or other long-term care facility (institutionalization) and death, and otherwise, was considered. This was determined by clinical periodic follow-up when possible, or by a telephone semi-structured interview.

All participants were made fully aware about the aims of the research and informed consent was sought from all subjects. The work was conducted in accordance with local clinical research regulations and conformed to the Helsinki Declaration.

Exclusion criteria

Stringent exclusion criteria were applied as follows: a) cerebrovascular disorders, previous stroke, hydrocephalus, and intra-cranial mass documented by magnetic resonance imaging; b) a history of traumatic brain injury or another neurological disease; c) significant medical problems (e.g., poorly controlled diabetes or hypertension; cancer within the past 5 years; clinically significant hepatic, renal, cardiac, or pulmonary disorders); d) history of major depressive disorder, bipolar disorder, schizophrenia, substance abuse disorder, or mental retardation according to criteria of the DSM-IV; e) cerebrospinal fluid analyses not available.

Cognitive, behavioral, and functional assessment at enrollment and at follow-up

At first evaluation, each patient underwent a global cognitive function assessment according to a standardized battery, including the Mini-Mental State Examination (MMSE) [20] and FTD Clinical Dementia Rating (FTD-CDR) scale [21]. The neuropsychological assessment was carried out through the following tests: Story Recall Test [22], Raven Coloured Progressive Matrices [23], Rey Complex Figure Copy and Recall [24], Controlled Oral Word Association Test and Category Fluency [25], Digit Span [26], Token Test [27], Trail Making Test A and B [28], Clock's Drawing test [29], and De Renzi Imitation [30]. Instrumental Activities of Daily Living (IADL) and Basic Activities

of Daily Living (BADL) were assessed as well. Motor impairment was evaluated using the motor subscale of Unified Parkinson Disease Rating Scale (UPDRS, part III). Behavioral and psychiatric disturbances were evaluated by Neuropsychiatry Inventory (NPI) [31], and Frontal Behavioral Inventory (FBI) [32].

The same standardized neuropsychological assessment was performed every year, when possible.

Cerebrospinal fluid analyses

CSF was obtained at the time of enrollment. Lumbar puncture was performed according to a standardized protocol, in the outpatient clinic, after fasting, from 9.30 a.m. to 10.30 a.m., after informed written consent had been obtained. CSF was collected in sterile polypropylene tubes and gently mixed to avoid gradient effects. Routine chemical measures were determined. The remaining CSF was centrifuged for 3 min at 3,000 rpm, and aliquots were stored at –80°C or in liquid nitrogen for subsequent total-tau, phospho-tau and Aβ dosages. CSF concentrations were measured in duplicate by ELISA test (Innotest hTau Antigen kit and Innotest PHOSPHO-TAU 181P, Innogenetics, Ghent, Belgium). Interassay variability was less than 7%.

According to the reference cut-off scores of our laboratory obtained on control subjects ($n = 48$) and Alzheimer's disease patients ($n = 28$), CSF tau levels >400 pg/ml, CSF phospho-tau >35 pg/ml, and CSF Aβ <300 pg/ml are considered to be highly suggestive for Alzheimer's disease.

MRI data acquisition

Magnetic resonance imaging was performed on a 1.5 T Siemens (Simphony) scanner.

For VBM analysis, 3D MPRAGE T1-weighted images were acquired using the following parameters: TE = 3.93 ms, TR = 2010 ms, flip angle = 15, and field of view (FOV) = 250 mm. This yielded 176 contiguous 1-mm-thick slices. Both pre-processing and statistical analyses were implemented in the SPM2 software package (Wellcome Department of Imaging Neuroscience, London; http://www.fil.ion.ucl.ac.uk/spm) running on Matlab 6.5.1 (MathWorks, Natick, MA). Optimized-VBM analysis was performed according to Good et al. [33], and grey matter and total intracranial volume were considered, as previously published [3]. Age and gender were considered as nuisance variables. Correlation involved a regression of CSF markers on grey matter atrophy. Threshold was set at $p < 0.001$, uncorrected, and the reliability of the statistical analysis was confirmed using an extent threshold of 100 adjacent voxels.

Statistical analyses

Comparison between clinical subgroups was carried out using Pearson χ^2, Student-*t* test (unpaired), and Analysis of Variance (ANOVA), as appropriate. Spearman correlation analysis was performed to test the correlation between CSF markers and both demographic characteristics and neuropsychological tests.

Survival analyses were carried out by Cox proportional hazard models. Hazard ratios (HR) are given with their respective 95% confidence intervals (CI), while the significance level was established at $p < 0.05$, two-sided. Kaplan Meier curves with log-rank *post-hoc* testing were also performed. The analyses were conducted by SPSS software version 16 (SPSS Inc, Chicago, Ill).

RESULTS

Subjects

Sixty FTLD patients who underwent lumbar puncture for CSF analysis were consecutively enrolled and entered the study. From this sample, five patients with the diagnosis of FTLD but with low CSF Aβ levels (<300 pg/ml), thus resembling Alzheimer's disease profile, were excluded.

The present study was conducted considering 55 FTLD. Demographic and clinical characteristics are shown in Table 1.

Overall, FTLD patients had a mean age of 62.8 (standard deviation, ±7.3), and 50.9% were female. The mean age at disease onset was 60.7 (±7.0). FTLD patients were mild for global cognitive decline (MMSE = 22.1 ± 6.5). Behavioral variant of FTD (bvFTD) diagnosis was the most prevalent (81%); semantic dementia (SD) and progressive non-fluent aphasia (PNFA) diagnoses were less frequent (19%).

CSF profile in FTLD patients and in bvFTD, SD, PNFA subgroups is reported in Table 1. CSF markers showed a wide range of variability. No significant differences of CSF total tau, phospho-tau, or Aβ levels among groups were found.

CSF marker correlations with neuropsychological and behavioral assessment

CSF tau, phospho-tau, and Aβ levels did not correlate with demographic characteristics, such as age

Table 1
Demographic and clinical characteristics of FTLD patients

Variable	FTLD (all)	bvFTD	SD	PNFA	p^*
n (%)	55	45	4	6	0.730
Age, years	62.8 ± 7.3	63.1 ± 7	65.5 ± 9.2	58.8 ± 8.4	0.294
Gender, F%	50.9%	48.9%	75%	50%	0.605
Onset, years	60.7 ± 7.0	60.9 ± 6.6	64 ± 8.9	57 ± 7.8	0.272
Education, years	7.1 ± 3.4	6.8 ± 3.3	11.5 ± 4.3	6.0 ± 1.5	0.023
Family history, %	43.1%	40.5%	50.0%	60.0%	0.678
MMSE	22.1 ± 6.5	22.5 ± 6.5	19.3 ± 7	21 ± 7.4	0.652
NPI	16.4 ± 13.5	17.7 ± 14.3	16 ± 4.0	8.1 ± 6.2	0.279
FBI, AB	16.4 ± 11.8	17.5 ± 12.6	18.3 ± 5.8	8.8 ± 2.8	0.244
CSF markers					
CSF tau (pg/ml)	464.4 ± 392.5	472.6 ± 413.5	287.3 ± 131.3	521 ± 346.1	0.628
CSF phosho-tau (pg/ml)	88.7 ± 94.5	86.6 ± 95.9	53.6 ± 23.0	133.4 ± 115.6	0.438
CSF Aβ (pg/ml)	744.4 ± 376.0	711.0 ± 329.0	534.9 ± 143.2	1060.5 ± 580.2	0.057

FTLD: Frontotemporal Lobar Degeneration; bvFTD: behavioral variant Frontotemporal Dementia; SD: Semantic Dementia; PNFA: Non-Fluent Progressive Aphasia; MMSE: Mini-Mental State Examination; NPI: Neuropsychiatry Inventory; FBI: Frontal Behavioral Inventory; CSF: cerebrospinal fluid.
$^*p$-values refer to comparisons across groups, namely bvFTD, SD, PNFA.

(at CSF), age at symptom onset, gender, or education.

As reported in Table 2, correlation analysis between CSF markers, namely total tau, phospho-tau, and Aβ, and neuropsychological performances was carried out.

CSF tau was significantly associated with language comprehension, the higher the CSF tau the worse the Token test scores ($p = 0.006$). The same results, even if the *p*-values were less significant, were obtained when CSF phospho-tau levels were considered. Conversely, CSF Aβ significantly correlated with verbal and non-verbal performances, lower Aβ levels being associated with worse short story ($p = 0.019$) and recall of Rey figure ($p = 0.044$) scores, and with semantic fluency performances ($p = 0.02$).

No significant correlations of CSF markers and behavioral abnormalities were detected.

CSF marker levels and brain atrophy

To obtain evidence validating CSF marker correlation to neuropsychological profile, we correlated CSF data with grey matter in a subset of patients. Twenty-four patients out of 55 underwent a magnetic resonance imaging scan and VBM analysis. We evaluated the linear correlation between CSF markers and regional brain atrophy; the higher the CSF scores the greater the atrophy in specific brain regions.

As shown in Fig. 1 and in Table 3, when CSF total tau was considered, higher CSF tau levels were specifi-

Table 2
Correlations between CSF markers and neuropsychological assessment

Test	CSF tau		CSF phospho-tau		CSF Aβ	
	rho	*p*	rho	*p*	rho	*p*
Short story	**–0.288**	**0.035**	**–0.351**	**0.014**	**0.342**	**0.019**
Rey figure, copy	–0.153	0.264	–0.123	0.398	0.228	0.119
Rey figure, recall	–0.127	0.357	–0.171	0.240	**0.292**	**0.044**
Semantic fluency	–0.244	0.073	–0.267	0.063	**0.325**	**0.024**
Phonological fluency	–0.207	0.133	–0.195	0.184	0.125	0.402
Digit span	–0.231	0.093	–0.189	0.198	0.206	0.165
Raven Coloured Matrices	–0.016	0.909	–0.047	0.748	0.201	0.170
Token test	**–0.377**	**0.006**	**–0.323**	**0.028**	0.115	0.454
Trail Making test, A	–0.009	0.946	0.288	0.052	–0.282	0.054
Trail Making test, B	–0.186	0.181	–0.196	0.86	–0.118	0.423
Clock's drawing	–0.204	0.207	–0.071	0.680	0.295	0.091
NPI	–0.246	0.089	–0.190	0.217	–0.030	0.848
FBI, A	–0.104	0.487	–0.187	0.236	0.123	0.449
FBI, B	–0.283	0.054	–0.203	0.197	0.082	0.615
FBI, AB	–0.223	0.133	–0.261	0.095	0.112	0.492

CSF: Cerebrospinal fluid; MMSE: Mini-Mental State Examination; NPI: Neuropsychiatry Inventory; FBI: Frontal Behavioral Inventory. $p < 0.05$ are highlighted.

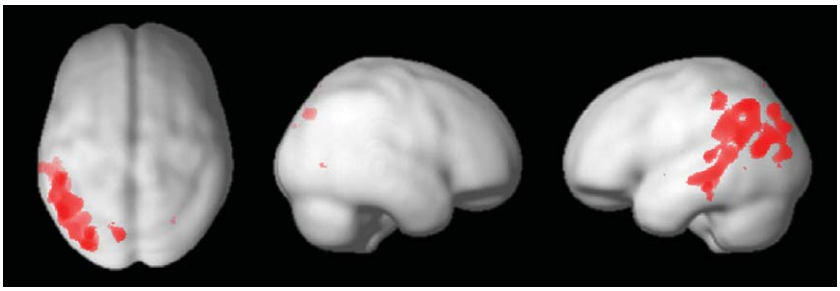

Fig. 1. Correlation analysis of CSF total Tau on grey matter atrophy ($p < 0.001$). See Table 3 for coordinates.

Table 3
Location of the peaks of cerebral brain atrophy in FTLD patients associated with CSF tau levels

Region	*x*	*y*	*z*	*T*	*p*	Cluster size
L middle temporal gyrus	–67	–33	–13	4.210	<0.001	320
L middle temporal gyrus	–36	–70	17	7.800	<0.001	16223
L inferior parietal lobule	–53	–39	46	4.730	<0.001	475

L: Left.

cally associated with greater atrophy in language areas, namely left middle temporal gyrus and left inferior parietal lobule.

The inverse association, i.e., the lower the CSF tau the greater the atrophy, did not show any voxel above the pre-established threshold.

In the same manner, even if with less voxel extent, CSF phospho-tau levels correlated with cortical atrophy in left inferior parietal lobule ($x, y, z = –54,–38,56$; $p < 0.001$) and superior temporal gyrus (–49, –11,1; $p < 0.001$).

No significant association between Aβ and brain atrophy as measured by magnetic resonance imaging was detected at the pre-established threshold.

Survival analysis

Out of 55 patients, 10 had been institutionalized or died throughout the 5-year observation. The median survival time from the onset of symptoms was 4.5 years (±2.6). Median values of CSF markers were considered for Cox proportional estimates using time at study enrollment/diagnosis. Compared to low CSF tau dosage (≤400 pg/ml), high tau dosage group (>400 pg/ml) had an increased risk of mortality/early institutionalization (HR = 4.73, 95% CI = 1.15–19.3, $p = 0.031$).

Figure 2 displays the corresponding Kaplan Meier survival curves.

CSF phospho-tau and CSF Aβ did not significantly correlate with rate of survival when this was calculated from time of disease onset. Age at onset of symptoms, gender, years of schooling, positive family history for dementia, and comorbidities also did not significantly correlate with rate of survival.

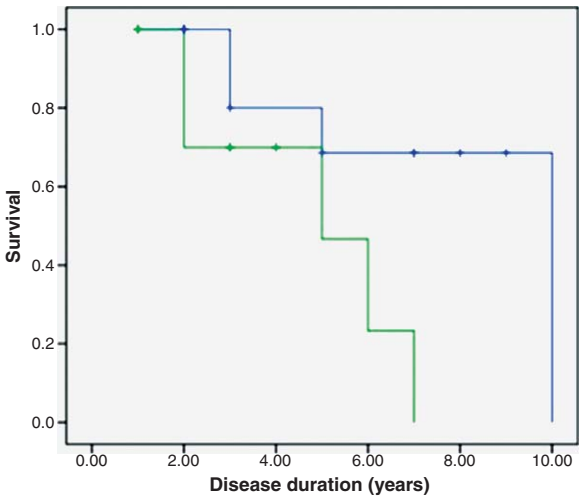

Fig. 2. Survival curves of FTLD groups defined by high versus low CSF tau levels. Kaplan Maier curves according to low CSF tau (blue) and high CSF tau (green) in FTLD patients ($p = 0.031$).

DISCUSSION

In the present study, we showed that CSF total tau levels are associated with a specific clinical phenotype within the FTLD spectrum, namely characterized by greater language impairment. This was corroborated by neuroimaging data, and a significant correlation between CSF tau levels and grey matter atrophy in the left posterior temporal and inferior parietal lobes was

reported. Finally, CSF tau levels were also associated with poor outcomes over time.

Tau is a microtubule-associated protein primarily localized in neuronal cells. In damaged brain, tau is released into the CSF from the neuronal cytoplasm, and it has been established that the concentration of CSF tau can reflect the degree of neuronal abnormalities in central nervous system disorders, such as Alzheimer's disease, Creutzfeldt-Jakob disease, encephalitis, Guillain-Barre syndrome, stroke, and active multiple sclerosis [13–17,34,35].

In FTLD, reports of CSF tau levels have been widely variable [6–8], but the meaning of such a finding needs to be further elucidated. The results of the present work suggest that CSF tau might be considered a marker of neurodegeneration, and higher levels of tau protein in CSF might be associated with increased vulnerability of specific brain areas, thus leading to defined neuropsychological deficits and brain atrophy pattern as compared to patients with lower CSF tau.

Language comprehension impairment is characteristically present in patients with SD, but it might be detected even in the other clinical phenotypes, at onset or during disease course. Language deficits are disabling both for patients and carers, and this clinical feature is still unpredictable across the FTLD spectrum. In our series, we sought independent validation in living patients by evaluating the correlation between this biomarker and the pattern of cortical atrophy. We found that the higher the CSF tau levels, the greater the atrophy in left posterior temporal lobe and, with less extent, in left inferior parietal lobule. Imaging data cannot substitute histopathological evidence, but these results argue that CSF tau is significantly related to another marker that is often taken to reflect the underlying disease process [5], and this is in agreement with neuropsychological findings of a specific involvement of language functions.

The results herein reported might be related to the topographical distribution of CSF protein concentrations during the disease process, with higher CSF tau values related to degeneration involving cortical areas not remote from ventricular and lumbar spaces [4]. Accordingly, previous work has demonstrated that levels of CSF tau were specifically associated with greater left temporal cortical atrophy in FTLD [5]. However, the selective involvement of left cortical temporal areas related to high CSF tau should be matter of future evaluations, as a proper answer should be still searched out.

Our series must be interpreted with caution because the lack of histopathological diagnosis. Nevertheless, the results of CSF total tau in autopsy-proven patients with FTLD have been inconsistent [7]. One autopsy study reported significantly increased CSF tau compared to normal controls [36], while another study showed CSF tau within normal range [37]. The major limitation of the above works is the small sample size and the lack of a careful evaluation of the pathological FTLD spectrum, with varying number of patients with Pick's disease, FTLD tau-positive, or FTLD 43-kDa transactivation-responsive DNA-binding protein (TDP43)-positive disorders.

Indeed, low CSF tau levels might be associated to either FTLD tau-negative or to FTLD tau-positive pathology with the possibility that tau is sequestered into the brain in the form of filamentous inclusions or Pick's bodies [5]. In the same view, high CSF tau might be related either to FTLD tau-positive or to a more aggressive disease independent of neuropathology, as tau is an aspecific marker of axonal damage.

Moreover, CSF tau levels seem to be quite specific as compared to phospho-tau and Aβ, which led to less significant findings. In fact, CSF tau reflects the intensity of neuronal degeneration [13–17,34], while phospho-tau mirrors the hyperphosphorylation of tau with subsequent formation of tangles [38], and Aβ is the marker of deposition of amyloid into plaques [39,40]. Accordingly, in our clinical series, that likely included both FTLD tau-positive and FTLD tau-negative cases, a marker of tangles formation as well as a marker of Alzheimer's disease cannot be of help. In particular, in the present series, we carefully excluded patients with low Aβ levels, as suggestive of ongoing Alzheimer's disease pathology, to avoid possible misdiagnoses and confounds. Moreover, in regard to phospho-tau evaluation, we considered tau phosphorylated in P181 which is mainly typical of Alzheimer's disease profile, thus might being less sensitive to FTLD pathology.

CSF tau was not only a marker of clinical phenotype but was also associated with worse prognosis over time. The association between CSF tau and poor outcome might be due to a greater aggressiveness of the disease, with higher values of the neurodegeneration marker, or to the specific involvement of language function that would lead to an earlier institutionalization.

Several caveats should be kept in mind when interpreting our results. Neuropathological data are missing; furthermore, a large sample size and confirmation studies are warranted.

In conclusion, we suggest that biomarkers might be used not only as diagnostic tools across neurodegenerative disorders, but as markers of clinical phenotype

and prognosis. CSF tau levels might be considered in clinical grounds and in future pharmacological trials to define FTLD with poor outcome. Association studies between CSF markers and autopsy proven cases are mandatory.

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