SHORT REPORT

CSF biomarkers in frontotemporal lobar degeneration: relations with clinical characteristics, apolipoprotein E genotype, and neuroimaging

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In order to better understand the large variation in cerebrospinal fluid (CSF) tau and amyloid-beta(1–42) (A β 42) in frontotemporal lobar degeneration (FTLD), relations between these biomarkers and clinical parameters, neuroimaging characteristics, and apolipoprotein E (ApoE) genotype were studied in 31 patients with FTLD, including 16 patients with the frontal variant and 15 with the temporal variant. CSF tau was highest in FTLD with predominant temporal involvement. In the frontal subgroup, CSF tau level was influenced by the number of ApoE ϵ 3 alleles. In the temporal subgroup, CSF tau level was dependent on a combination of CSF A β 42, age, disease duration, and disease severity. No relation with degree of atrophy or asymmetry on neuroimaging could be established. CSF A β 42 variability remained unexplained. Future research could study the role of ApoE genotype and A β 42 in FTLD, as well as establish measures for disease intensity.

It is generally considered that the cerebrospinal fluid (CSF) marker tau reflects neuronal degeneration, while decreased CSF amyloid-beta(1–42) (A β 42) is associated with intracerebral plaque deposition.¹ The results of the limited number of studies of these biomarkers in frontotemporal lobar degeneration (FTLD) have been inconsistent. Some studies found an increase in CSF tau, while others reported normal CSF tau concentrations.^{2–6} CSF A β 42 has been reported to be normal or moderately decreased.^{4–6} Other studies investigated CSF biomarkers in more circumscribed FTLD subgroups such as semantic dementia (SD)⁷ or progressive non-fluent aphasia (PA).⁸ CSF biomarker variability in FTLD might (in part) be explained by clinical, pathological, and genetic heterogeneity in this disorder. The goal of the present study was to investigate CSF tau and A β 42 in FTLD in relation to clinical characteristics, apolipoprotein E (ApoE) genotype, and neuroimaging features, whereby the degree of cerebral atrophy might be an indicator of disease severity.

METHODS

Patients

Thirty one patients with FTLD were included in the study. The clinical diagnosis was based on international clinical diagnostic criteria⁹ and supported by structural and/or functional neuroimaging and clinical follow up of at least 1 year's duration. All patients underwent a standard battery of examinations including medical history, physical and neurological examination, screening laboratory tests, psychometric tests, and MRI or CT scan. In eight patients who were suspected of having FTLD but who had a normal structural

neuroimaging examination, ^{99m}Tc-hexamethyl propyleneamine oxide (HMPAO) SPECT demonstrated frontal/temporal hypoperfusion, defined as perfusion which is <80% of cerebellar perfusion. According to the distribution of atrophy and hypoperfusion on neuroimaging, 16 patients had predominant frontal involvement and 15 had predominant temporal involvement. These distributions corresponded with the clinical diagnoses whereby subjects with behaviour disturbances and a clinical diagnosis of frontotemporal dementia had predominant frontal abnormalities and subjects with the language based syndromes SD (n = 11) and PA (n = 4) had predominant temporal abnormalities. Most cases were sporadic. One patient had a P301L tau gene mutation. In two cases with a positive family history, mutation analysis had been refused by the patient or their families. Disease duration was calculated as the time between the first symptoms reported by the patient or caregiver and the time of lumbar puncture. Cognitive decline was rated using the Mini-Mental State Examination (MMSE).¹⁰ Dementia severity was assessed using the Clinical Dementia Rating (CDR).¹¹

Laboratory analysis

ApoE genotyping was performed after DNA isolation from leucocytes of peripheral blood, using the LightCycler ApoE Mutation Detection method (Roche Diagnostics, Mannheim, Germany). CSF acquisition and storage were performed according to our previously described method.¹² Levels of CSF tau and A β 42 were determined using sandwich ELISA.^{13–14} ApoE genotyping and CSF investigations were part of an ongoing study on CSF biomarkers in dementia and had been approved by the ethical review board of the VU University Medical Center. All patients gave written informed consent.

Neuroimaging analysis

MRIs were acquired on a 1.0 or 1.5 T scanner (Siemens, Forchheim, Germany) and included coronal three-dimensional T1 weighted and axial FLAIR images. Thirty MRI scans and one CT scan had been performed with a median time interval of 1 month (range 0–5) before or after CSF collection and were visually rated for cortical atrophy by lobe using a 0–3 scale.¹⁵ Asymmetry of frontotemporal atrophy was rated as present or absent. Rating was performed by a single rater (YP) who was blinded to the CSF results.

Abbreviations: A β 42, amyloid-beta(1–42); ApoE, apolipoprotein E; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; FTLD, frontotemporal lobar degeneration; MMSE, Mini-Mental State Examination; PA, progressive non-fluent aphasia; SD, semantic dementia; HMPAO, ^{99m}Tc-hexamethyl propyleneamine oxide

Figure 1 Scatterplots of CSF tau and Aβ42 levels in the FTLD subgroups.

Statistical analysis

The software package SPSS 10.0 was used for statistical analysis. The Mann-Whitney test was applied to compare levels of CSF markers, age, disease duration, CDR, and MMSE between the frontal and temporal subgroups. The relative frequencies of parameters were compared using the χ^2 test. Spearman rank correlation coefficients were computed between clinical and imaging characteristics. To obtain a normal distribution of the dependent variables CSF tau and Aβ42, logarithmic transformation of these variables was performed. We checked the normal distribution of the log transformed data using the Shapiro-Wilk test. Multiple backward regression analysis was performed to investigate determinants of CSF tau and CSF Aβ42 in FTLD. Statistical significance was set at $p < 0.05$ for all computations.

RESULTS

Clinical data and additional investigations

Clinical data, CSF and imaging parameters, and ApoE allele frequencies are displayed in table 1. The relative frequencies of ApoE alleles ε2, ε3, and ε4 in the total group of FTLD patients did not differ significantly from frequencies in the general population ($p = 0.56$).¹⁶ No patients were found to be homozygous with ε2/ε2 or ε4/ε4. The individual values of CSF tau and Aβ42 are displayed in fig 1.

Correlations between imaging parameters and age, disease duration, CDR, and MMSE

In the total group, CDR correlated with frontal atrophy ($r = 0.65$, $p < 0.001$), left parieto-occipital atrophy ($r = 0.38$, $p = 0.04$), and the sumscore of frontotemporal atrophy ($r = 0.44$, $p = 0.01$). When controlling for temporal and parieto-occipital atrophy and age, using Spearman rank order correlation, CDR was still significantly correlated with

frontal atrophy ($r = 0.60$, $p = 0.001$). A weak negative correlation was found between disease duration and frontal atrophy ($r = -0.38$, $p = 0.04$).

Regression

Applying multiple backward regression analysis with ln-CSF tau as the dependent variable, revealed that ln-CSF tau was dependent on either frontal or temporal lobar predominance ($F = 4.70$, $p = 0.04$). We were unable to create a model to predict ln-CSF Aβ42 by clinical or neuroimaging parameters or ApoE genotype. In the total group, we checked for significant interactions between subgroups and the other parameters and found that ln-CSF tau was influenced by an ApoE ε3×group interaction ($p = 0.02$). Univariate linear regression in the frontal subgroup yielded ApoE ε3 as a significant determinant of ln-CSF tau ($F = 9.13$, $p = 0.01$), which was also the only significant determinant in the multiple regression analysis. In the temporal subgroup, univariate linear regression revealed that onset age ($F = 9.70$, $p = 0.01$) and age ($F = 6.23$, $p = 0.03$) significantly determined ln-CSF tau. Applying multiple backward regression analysis, ln-CSF tau was best predicted by the combination of age ($p = 0.007$), CSF Aβ42 ($p = 0.007$), duration ($p = 0.005$), and CDR ($p = 0.008$), with the equation $\ln\text{-CSF tau} = 5.835 - 0.056 \times \text{duration} - 0.528 \times \text{CDR} - 0.0005 \times \text{Aβ42} + 0.02 \times \text{age}$, explaining 82.7% of the variance of ln-CSF tau.

DISCUSSION

We found that CSF tau was higher in the temporal FTLD subgroup than in the frontal subgroup. In the frontal subgroup, the number of ApoE ε3 alleles influenced CSF tau levels. In temporal FTLD patients, CSF tau was determined by a combination of CSF Aβ42 and clinical

Table 1 Clinical and CSF characteristics and ApoE genotyping

Parameter	Frontal, n = 16	Temporal, n = 15	p value
Age, years	62 (54–76)	66 (55–85)	0.12
Onset age, years	59.5 (49–75)	61 (51–83)	0.35
Disease duration, years	2.5 (1–10)	4 (1–11)	0.20
MMSE	24 (3–30)	25 (3–28)	0.74
CDR	1 (0.5–2)	1 (0.5–2)	0.14
CSF tau, pg/ml	255 (49–2225)	396 (220–906)	0.01*
CSF Aβ42, pg/ml	549 (245–1257)	649 (247–1408)	0.55
Sumscore of frontal atrophy	3 (0–6)	2 (0–4)	0.12
Sumscore of temporal atrophy	2 (0–4)	4 (0–6)	0.07*
Sumscore of frontotemporal atrophy	4 (0–10)	6.5 (2–10)	0.50
Presence of asymmetric atrophy, number of cases	3	11	0.03*
ApoE ε2:ε3:ε4	3:23:6	1:22:7	0.60

Values are displayed as medians (range).

*Significant differences.

parameters. No independent predictors could be identified for CSF A β 42.

CSF tau is regarded as a state marker, reflecting the intensity of neuronal degeneration.¹ The mere presence of intracerebral tau pathology does not necessarily result in higher CSF tau levels, as is evidenced by the normal CSF tau levels in FTLD patients with tau mutations and in patients with progressive supranuclear palsy.^{17,18} One might hypothesise that asymmetric FTLD takes place during active disease, whereas end stage neuroimaging is often symmetric. Although the presence of asymmetry was more prevalent in the temporal than the frontal FTLD subgroup, with the former having higher CSF tau concentrations, asymmetry was not a statistical determinant of CSF tau in FTLD or either of the subgroups. Frontotemporal atrophy scores, which were (non-significantly) higher in the temporal subgroup than in the frontal subgroup, were not a statistical determinant either.

We found that within the frontal FTLD subgroup, patients with two ApoE ϵ 3 alleles tended to have higher CSF tau levels than patients with one ApoE ϵ 3 allele. ApoE genotype influences amyloid precursor protein metabolism, in that ApoE3 is relatively protective against the formation of amyloid plaques. Also, ApoE3, in contrast to ApoE4, can form stable complexes with tau and neurofilaments in vitro, thus interfering with hyperphosphorylation and the formation of paired helical filaments.¹⁹ We speculate that ApoE3 binding to tau in the frontal variant of FTLD evolves differentially, facilitating pathological transformation of tau and leakage into the CSF.

Based on regression analysis in the temporal subgroup where higher CSF tau is correlated with lower CSF A β 42 levels and with higher age, we might have included some subjects with concomitant Alzheimer's disease pathology in this group.²⁰ A limitation of our study is indeed that pathological or genetic confirmation is missing in most cases. However, as the clinical diagnosis was made in conference in a tertiary referral setting and confirmed by stability during a follow period of at least 1 year, we are confident a high diagnostic accuracy has been achieved. Apart from possible concomitant pathology, it remains intriguing how A β 42 relates to tau in FTLD. Recently, it has been shown that soluble A β 42 and A β 40 are increased in FTLD with tau mutations, suggesting A β peptides are associated with tau pathology in this disorder.²¹

In conclusion, the variability of CSF biomarkers in FTLD is still largely not understood and deserves the attention of future research. Tau levels were dependent on lobar localisation, and according to FTLD subgroup, on ApoE genotype, A β 42, and a number of clinical parameters but were independent of the degree of cerebral atrophy. The role of ApoE and A β 42 in the pathophysiology of FTLD as well as a more accurate measure of disease intensity such as cerebral atrophy rate, might be interesting topics to be studied in relation to CSF biomarkers.

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