Cognitive correlates of CSF biomarkers in Frontotemporal dementia

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Abstract

Objective
In this study we investigated the relationships between CSF biomarkers (tau and amyloid beta\textsubscript{1-42} (A\textbeta\textsubscript{1-42})) and cognition or behaviour in patients with Frontotemporal dementia (the behavioural variant, bvFTD).

Methods
We included 58 patients with bvFTD. All patients underwent a neuropsychological assessment and lumbar puncture. Relationships between CSF biomarkers and cognition or behaviour were assessed with linear regression analysis.

Results
After correction for age, gender and education, CSF tau levels were found to be negatively related to the visual association test (VAT) (standardized $\beta = -0.3$, $p < 0.05$), whereas CSF A\textbeta\textsubscript{1-42} levels were found to be positively related to the mini-mental-state examination (MMSE) ($\beta = 0.3$, $p < 0.05$), the frontal assessment battery (FAB) ($\beta = 0.5$, $p < 0.05$) and digit span backwards ($\beta = 0.3$, $p = 0.01$).

We did not find relations between CSF biomarkers and behaviour (measured by the neuropsychiatric inventory (NPI)). After excluding all patients with a CSF biomarker profile often seen in AD (high levels of tau and low levels of A\textbeta\textsubscript{1-42}), we still found relations between CSF A\textbeta\textsubscript{1-42} levels and VAT naming ($\beta = 0.4$, $p < 0.05$) as well as between CSF A\textbeta\textsubscript{1-42} levels and the FAB ($\beta = 0.5$, $p < 0.05$), but there was no relation between CSF tau and cognition.

Conclusion
Low CSF A\textbeta\textsubscript{1-42} levels are associated with worse general cognitive function and worse executive function in patients with bvFTD. Our results provide circumstantial evidence for a pathophysiological role of A\textbeta\textsubscript{1-42} in bvFTD.
Introduction

Frontotemporal dementia (behavioural variant, bvFTD), the most common form of frontotemporal lobar degeneration (FTLD), is a heterogeneous disorder, both clinically and neuropathologically. Clinically patients present with behavioural change often combined with executive dysfunction and language dysfunction. Cognitive dysfunction however, may vary between normal performance on neuropsychological assessment and the co-occurrence of episodic memory disturbances. On a cellular pathological level bvFTD is characterized by either tau positive inclusions (tauopathies) or tau-negative ubiquitin-positive inclusions (FTLD-U), which are frequently related with pathology of the TAR DNA-binding protein \( M_r 43 \text{ kDA} \) (TDP-43). A relatively smaller subgroup of bvFTD patients demonstrates DP43 negative FTLD-U pathology, immunoreactive for the fused in sarcoma protein (FTLD-FUS).

Alzheimer’s disease (AD) can be considered a tauopathy as one of its pathological hallmarks is the presence of neurofibrillary tau-containing tangles. In AD, the concentration of total tau in CSF is increased, whereas that of amyloid beta\(_{1-42}\) (A\(_\beta_{1-42}\)) is decreased. This combination has a high accuracy in discriminating AD patients from healthy elderly, whereas these biomarkers should be used more cautiously in the differential diagnosis of dementia. Several studies have investigated CSF biomarkers in either FTLD or the subgroup of bvFTD. In both groups a wide range of CSF tau concentrations has been found, whereas the concentration of A\(_\beta_{1-42}\) varies between normal to low values. This wide variability in levels of CSF biomarkers remains largely unexplained and might be related to the heterogeneity of underlying pathology or to varying neurodegenerative stages, particularly since it is known that disease duration in for example bvFTD varies between 2 until 20 years. PGRN mutations are a known cause of bvFTD, and PGRN or TDP43 could be potential biological markers for FTLD. However, not much is known about plasma or CSF levels of PGRN or TDP-43 in FTLD patients. One study found a strongly reduced CSF progranulin level in PGRN mutation carriers. Although they found that PGRN could be a useful marker for early identification of asymptomatic at risk subjects, PGRN could not be considered as a marker for PGRN negative FTLD subjects. In contrast to AD, a specific biomarker profile for FTLD or bvFTD has not yet been identified. However, low levels of CSF tau have been found in bvFTD and FTLD patients, but have never been reported in AD patients and a low tau/ A\(_\beta_{1-42}\) ratio seems to be able to discriminate FTLD from AD in patients with known pathology.

Assuming a relationship of cognitive decline to the degree of neurodegeneration and between CSF biomarkers and neurodegeneration, one would also expect a relationship between CSF biomarker levels and cognition. However, inconsistent results have been found in studies investigating relationships between CSF biomarkers and cognition in AD patients.
In FTLD one study described relationships between CSF tau and cognition, while others reported no relationships between CSF biomarkers and either cognition or behaviour\textsuperscript{10,12,14,15}.

The aim of our study was to investigate the relations between levels of the currently available CSF biomarkers (tau and Aβ\textsubscript{1-42}) and cognition or behavioural symptoms in patients with bvFTD. We hypothesized that particularly CSF tau, either as a marker of the degree of intracerebral tau-pathology or as a non-specific marker of neurodegeneration would be related with cognition or behavioural symptoms in bvFTD.

**Methods**

**Patients and clinical evaluation**

We included 66 consecutive patients with a diagnosis of bvFTD, who presented at the Alzheimer Center of the VU University Medical Center in Amsterdam. All patients underwent a standard battery of investigations including a medical history, physical and neurological examination including mini mental state examination (MMSE)\textsuperscript{21}, frontal assessment battery (FAB)\textsuperscript{22}, laboratory tests, neuropsychological assessment, behavioural assessment (neuropsychiatric inventory, NPI)\textsuperscript{23}, EEG and MRI of the brain. We excluded 8 patients, because there was a period of more than a year between the neuropsychological assessment and lumbar puncture (LP), resulting in a sample size of 58 patients. In all patients a LP was done within an average of 0.4 ± 3 months from neuropsychological assessment. The diagnosis of bvFTD was made according to the international consensus diagnostic criteria by a multidisciplinary team including a neurologist, psychiatrist, neurophysiologist, radiologist, neuropsychologist and specialist nurse\textsuperscript{1}. Patients were followed up to confirm their diagnosis for at least one year.

Post-mortem confirmation of the diagnosis was available for 5 patients.

CSF investigations were part of an ongoing study on CSF biomarkers in dementia, which has been approved by the ethical review board of the VU University Medical Center. All patients gave written informed consent.

**CSF analysis**

CSF samples were obtained by lumbar puncture between L3 and L4 or L4 and L5 intervertebral space, 12 ml was collected in polypropylene tubes and brought to the lab within two hours. Part of the CSF was used for routine analysis, including total cell count, as well as total protein determination. The remaining CSF was then centrifuged at 1800g for 10 minutes at 4°C. The CSF samples were aliquoted into polypropylene tubes and stored at -80°C until further analysis. Aβ\textsubscript{1-42} and tau were measured in CSF with Innotest sandwich ELISAs as described previously\textsuperscript{19}. As the manufacturer does not supply controls, the performance of the assays was monitored with pools of surplus CSF specimens. In the study period multiple specimens with various concentrations which were included in 7-18 runs, have been used for this purpose. The interassay coefficient of variation (mean ± SD) was 11.3% ± 4.9% for CSF Aβ\textsubscript{1-42} and 9.3% ± 1.5% for CSF tau.
The team of the department of Clinical Chemistry of the VU University Medical Center involved in the CSF analysis was not aware of the clinical diagnosis. Conversely, the results of CSF analysis were not known when the clinical diagnosis was made. The following cut off values are used for this study: CSF Aβ1-42 ≥ 550 pg/ml and CSF tau ≤ 375 mg/ml.

ApoE DNA was isolated from 10ml blood samples in ethylenediaminetetraacetic acid (EDTA). The ApoE genotype was determined at the department of Clinical Chemistry of the VU University Medical Center with the LightCyclerAPOEmutation detection method (Roche Diagnostics GmbH, Mannheim, Germany). ApoE data was analysed according to the presence or absence of an ApoE ε4 allele. ApoE data were available for 51 patients.

Neuropsychological assessment
Several neuropsychological tests were used to screen the major cognitive functions. Over time there was a variation in tests which were used and therefore not all patients received the same test battery. This neuropsychological test battery included the Visual Association Test (VAT) and digit span backwards for evaluating memory and animal fluency (production of animals in 1 minute) for semantic memory. For executive dysfunction the Trail Making Test (TMT) B and the Stroop colour word test were used. VAT naming was used for naming, the Rey-Osterrieth Complex Figure Copying test for evaluating visuospatial function and the forward condition of the digit span test for attention.

Statistical analysis
For statistical analysis SPSS version 15.0 was used. Values of CSF tau and Aβ1-42, TMT and Stroop were log-transformed before analysis, since they were not normally distributed. Basic demographic data were examined using Chi-squared test for categorical data and t-tests for continuous data. Linear regression analysis was used to analyse relations between CSF biomarkers and different neuropsychological tests and the NPI. In the first model the relationship of each CSF biomarker (independent variable) with each cognitive test or NPI score (dependent variable) was assessed. In the second model the same relationships were assessed adjusted for age, gender and education. In the third model concentrations of both CSF biomarkers were entered simultaneously, together with age, gender and education as covariates. In an additional fourth model we assessed the relationship of each CSF biomarker with each cognitive test or NPI additionally adjusted for ApoE ε4 status (presence or absence of ApoE ε4 allele). We repeated these analyses in a subgroup of patients, after excluding all patients with a CSF biomarker profile often seen in AD (high levels of tau and low levels of Aβ1-42). Results are presented as standardized regression coefficients (βs) to allow comparison of effect sizes. Statistical significance was set at p < 0.05.
Results
Table 1 shows the demographic characteristics of the patient group. The mean age was 63 ± 8 years and 33% was female. Mean CSF Aβ1-42 was in the normal range according to the cut-off values used in the VU University Medical Center, mean levels of CSF tau, however, were above the cut-off value (CSF Aβ1-42 ≥ 550 pg/ml and CSF tau ≤ 375 mg/ml).

Table 1. Demographic and clinical characteristics

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Age (at first symptoms)</td>
<td>63 (8)</td>
</tr>
<tr>
<td>Females</td>
<td>19 (33%)</td>
</tr>
<tr>
<td>MMSE a</td>
<td>23 (7)</td>
</tr>
<tr>
<td>Follow up duration (years)</td>
<td>1.7 (1.6)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>3.9 (3.8)</td>
</tr>
<tr>
<td>NPI total score b</td>
<td>29 (16)</td>
</tr>
<tr>
<td>CSF tau, pg/mL</td>
<td>447 (337)</td>
</tr>
<tr>
<td>CSF Aβ1-42, pg/mL</td>
<td>824 (278)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) or N (%)

a MMSE available for 53 patients
b NPI available for 20 patients

Table 2 shows the linear regression coefficients between the two CSF biomarkers and the raw scores of the different neuropsychological tests. CSF tau was found to be negatively related with the VAT (β = -0.3, p< 0.05), whereas CSF Aβ1-42 was found to be positively related with the MMSE (β = 0.3, p < 0.05) (figure 1A), FAB (β = 0.6, p < 0.01) (figure 1B), VAT (β = 0.3, p < 0.05), VAT naming (β = 0.4 p < 0.05) and digit span backwards (β = 0.3, p < 0.05). After correction for age, gender and education relationships remained largely unchanged, except for the relation between CSF Aβ1-42 and the VAT and VAT naming, which no longer reached statistical significance.
Table 2. Linear regression analysis between CSF biomarkers and neuropsychological tests

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Raw Scores</th>
<th>Aβ \textsubscript{1-42}</th>
<th>Tau</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Model 1</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Model 2</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>53</td>
<td>23 (7)</td>
<td>0.3#</td>
<td>-0.2</td>
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<td></td>
<td></td>
<td></td>
<td>0.3#</td>
<td>-0.1</td>
</tr>
<tr>
<td>FAB</td>
<td>20</td>
<td>12 (5)</td>
<td>0.6*</td>
<td>-0.02</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.5#</td>
<td>0.2</td>
</tr>
<tr>
<td>VAT</td>
<td>48</td>
<td>4 (2)</td>
<td>0.3#</td>
<td>-0.3#</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.2</td>
<td>-0.3#</td>
</tr>
<tr>
<td>VAT Naming</td>
<td>38</td>
<td>11 (2)</td>
<td>0.4#</td>
<td>-0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Digit span forward</td>
<td>51</td>
<td>11 (3)</td>
<td>0.2</td>
<td>-0.04</td>
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<td></td>
<td></td>
<td></td>
<td>0.2</td>
<td>-0.02</td>
</tr>
<tr>
<td>Digit span backward</td>
<td>49</td>
<td>6 (3)</td>
<td>0.3#</td>
<td>-0.06</td>
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<td></td>
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<td>0.3</td>
<td>-0.05</td>
</tr>
<tr>
<td>Animal fluency</td>
<td>48</td>
<td>14 (6)</td>
<td>0.02</td>
<td>-0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
<td>-0.1</td>
</tr>
<tr>
<td>TMTA \textsuperscript{a}</td>
<td>45</td>
<td>72 (62)</td>
<td>-0.3</td>
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<td></td>
<td></td>
<td></td>
<td>-0.2</td>
<td>-0.1</td>
</tr>
<tr>
<td>TMTB \textsuperscript{a}</td>
<td>46</td>
<td>247 (184)</td>
<td>-0.3</td>
<td>-0.1</td>
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<td></td>
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<td>-0.2</td>
<td>-0.1</td>
</tr>
<tr>
<td>Stroop-1 \textsuperscript{a}</td>
<td>31</td>
<td>58 (16)</td>
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<tr>
<td></td>
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<td></td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Stroop-2 \textsuperscript{a}</td>
<td>32</td>
<td>115 (165)</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Stroop-3 \textsuperscript{a}</td>
<td>27</td>
<td>250 (277)</td>
<td>-0.005</td>
<td>0.3</td>
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<td></td>
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<td>0.08</td>
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<td>Rey-Osterrieth Figure</td>
<td>32</td>
<td>30 (7)</td>
<td>-0.1</td>
<td>0.1</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>-0.1</td>
<td>0.04</td>
</tr>
<tr>
<td>NPI</td>
<td>20</td>
<td>29 (16)</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.2</td>
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</table>

N represents the total number of patients for which the different tests were available. Raw scores are presented as mean (SD). Results of the linear regression analysis are presented as standardized regression coefficients ($\beta$s) to allow comparison of effect sizes. Model 1 shows unadjusted associations, in the second model there was a correction for age, gender and education. For statistical analysis CSF biomarkers Aβ\textsubscript{1-42} and tau and neuropsychological tests TMT and Stroop were log transformed. \textsuperscript{a} Results in seconds: lower scores signify better (i.e. faster) performance.

\* $p < 0.01$ \quad \dagger p = 0.05 \quad \# p < 0.05 \quad \° p = 0.01
Figure 1A shows a scatter plot of CSF Aβ_{1-42} levels in relation to MMSE scores in bvFTD. Figure 1B shows a scatter plot of CSF Aβ_{1-42} levels in relation to FAB scores in bvFTD. Low CSF Aβ_{1-42} levels were associated with lower scores on the MMSE and the FAB. Please note the logarithmic scale on the y-axis.
Furthermore, we found that CSF Aβ₁₋₄₂ was related to digit span backwards (β = 0.4, p = 0.01) and to the MMSE (β = 0.3, p < 0.05) independently of CSF tau, whereas CSF tau was related to the VAT (β = -0.3, p < 0.05) independently of CSF Aβ₁₋₄₂ (data not shown). We did not find relations between CSF biomarkers and behaviour abnormalities, measured using the NPI.

Data on ApoE were available for 51 patients and 16 patients (31%) were ApoE ε4 carriers. When we additionally adjusted for ApoE status we still found relations between high levels of CSF Aβ₁₋₄₂ and lower scores on the digit span backwards (β = 0.4, p < 0.05), the FAB (β = 0.8, p < 0.05) and the MMSE (β = 0.4, p < 0.05). Furthermore high levels of CSF tau were associated with low scores on the VAT (β = - 0.3, p < 0.05).

We performed a second set of analyses in which we excluded patients (N = 7, 12%) with a CSF profile often seen in AD patients (a combination of low CSF Aβ₁₋₄₂, ≤ 550 pg/mL and high CSF tau, ≥ 375 pg/mL: N = 7, 12%). These patients performed worse on the MMSE (mean MMSE score 18 ± 9), but there were no differences in mean disease duration or follow up duration between patients with and without this specific CSF profile. In the remaining sample (N = 51) we found relations (corrected for age, gender and education) between CSF Aβ₁₋₄₂ and VAT naming (β = 0.4, p < 0.05) and the FAB (β = 0.5, p < 0.05), but there was no longer a relation with the MMSE, VAT and digit span backwards. In this sample of patients there was no relation between CSF tau and cognition.

Discussion
In this study we studied relations between the currently available CSF biomarkers (tau and Aβ₁₋₄₂) and cognition or behaviour in bvFTD. We found that low CSF Aβ₁₋₄₂ levels correlated with worse general cognitive performance, working memory performance and executive function. We did not find relations between CSF biomarkers and severity of behaviour symptoms.

Not many studies have investigated the possible relationship between cognitive functioning or behavioural symptoms and CSF biomarkers in FTLD or bvFTD and their results are inconsistent. One study reported negative relations between CSF tau and confrontation naming in FTLD patients, while others did not describe correlations between CSF tau and MMSE score or tests for executive function. We found that high CSF tau levels were correlated with worse memory performance. However, caution must be taken into account with the interpretation of these results, since the correlations disappeared when patients with an AD-like CSF profile were excluded. No relations have been reported between CSF Aβ₁₋₄₂ and cognition in bvFTD, whereas in AD patients low CSF Aβ₁₋₄₂ was associated with lower scores on the MMSE. One study found a relation between CSF Aβ₁₋₄₂ and aggression in AD patients, but did not find such relations in patients with FTD.
We cannot fully compare our results with the previous studies, as we only looked at bvFTD patients, whereas in literature most studies focus on FTLD patients. We choose to include only patients with bvFTD to create a clinically homogeneous patient group. Furthermore, language impairment could very well influence results on cognitive examination and therefore we excluded patients with the language variants of FTLD (semantic dementia and progressive non-fluent aphasia). We believe that our study gives a good representation of the relations between cognition and CSF biomarkers in bvFTD patients.

It remains unclear whether in our sample low CSF Aβ_{1-42} and high CSF tau reflect a more progressed disease stage or disease intensity or represent underlying pathology. Tau is believed to reflect the intensity of neurodegeneration in the brain and is known to be increased not only in AD patients, but also after ischaemic stroke or in patients with Creutzfeld Jacob Disease (CJD). High values of CSF tau in bvFTD could also be a reflection of possible tau pathology like Pick’s disease or MAPT gene mutations, although it has been found that patients with a known tau mutation did not have increased CSF tau levels. In contrast, CSF Aβ_{1-42} is suggested to reflect the disease stage with decreasing levels when the disease progresses in AD patients. This seems to be supported by the finding that CSF Aβ_{1-42} is correlated with lower MMSE scores in AD patients, which could indicate that a lower level of CSF Aβ_{1-42} is associated with more severe cognitive impairment. This hypothesis, however, is contradicted by longitudinal measurement of CSF Aβ_{1-42} in AD, showing no decline over time.

We performed an additional analysis (data not shown) to investigate the relationship between CSF biomarker values and disease duration in our study group. We also did not find any correlations between CSF biomarker values and disease duration.

Surprisingly, the main finding of our study was the existence of robust relations between CSF Aβ_{1-42} and cognition. Amyloid plaque deposition, however, is not a pathological hallmark of bvFTD and it remains intriguing which role Aβ_{1-42} plays in bvFTD pathology. Soluble Aβ_{42} and Aβ_{40} have been found to be increased in FTLD with tau mutations, suggesting Aβ peptides are associated with tau pathology in this disorder. It has been suggested that amyloid beta and tau abnormalities are linked through common upstream drivers. In this pathway, common upstream drivers (ApoE4 and glycogen synthase kinase, GSK3) cause both elevation in amyloid beta and tau hyperphosphorylation through independent but parallel mechanisms. Furthermore, one other study found that mutations in the GSK3B gene are a potential genetic risk factor for AD and FTD. Although the exact mechanism in which amyloid beta relates to tau in bvFTD remains unclear, these studies suggest pathophysiological involvement of amyloid beta in bvFTD. This suggestion is also strongly supported by our results, as entering both CSF biomarkers in the same model, we still found a relation between CSF Aβ_{1-42} and the MMSE, FAB and digit span backwards independently of CSF tau, whereas CSF tau related with the VAT independently of CSF Aβ_{1-42}. 
It could be argued that the patients with a combination of low levels of CSF Aβ\textsubscript{1-42} and high levels of CSF tau as well as lower MMSE scores are less likely to have underlying FTLD pathology and more likely to have AD pathology. As none of these 7 patients came to autopsy, this is only one possible hypothesis. On the other hand these patients fulfilled clinical criteria for bvFTD and were followed for at least one year (mean follow up 1.7 ± 1.6 years) in which the clinical diagnosis remained stable. Combinations of high CSF tau and low CSF Aβ\textsubscript{1-42} have been described in other studies in bvFTD, which might as well represent a subgroup of bvFTD (12;14). We therefore did not exclude these patients from our main analyses. Moreover, even after omitting cases with an AD-like CSF profile, associations between Aβ\textsubscript{1-42} and global cognition remained essentially the same. In the remaining sample we found correlations between Aβ\textsubscript{1-42} and tests for language (VAT-naming) and executive function (FAB), two domains often impaired in bvFTD. These results suggest a possible role for Aβ\textsubscript{1-42} in bvFTD pathology. Although we cannot fully exclude other underlying pathology, we think it is highly unlikely that misdiagnosis would account for all our results.

It has been found that cognition is more impaired in AD patients and patients with mild cognitive impairment (MCI), when they possess one or more ApoE ε4 alleles \textsuperscript{39,40}. It could therefore be argued that the presence of ApoE ε4 could be responsible for the relationships we found between CSF Aβ\textsubscript{1-42} and CSF tau and cognition. However, when we corrected for the presence of an ApoE ε4 allele, our results did not essentially change. We therefore do not believe that the presence of ApoE ε4 carriers are responsible for the relationships between CSF biomarkers and cognition in this study group.

It might be hypothesized that more neurodegeneration in turn leads to more cognitive impairment. The most common manifestation of bvFTD is a profound change in behaviour and personality, characterized by apathy and loss of initiative or social disinhibition and distractibility. Cognitive deficits consist of impairment in abstraction, planning and problem solving (dysexecutive syndrome), whereas memory, language and spatial functions are relatively preserved \textsuperscript{1}. However, a presentation with prominent memory impairment in patients with pathologically confirmed bvFTD has been reported by several studies and has been associated with the presence of hippocampal atrophy \textsuperscript{2,41,42}. In addition, it has been found that patients with bvFTD perform more poorly than patients with AD on verbal ability and picture naming \textsuperscript{43}. Finally, a small proportion of bvFTD patients does not have prominent behavioural abnormalities or cognitive impairment at presentation \textsuperscript{3}. It has been found that less severe cognitive impairment typically occurs in bvFTD patients without atrophy on MRI \textsuperscript{44}. We extend on these former findings, by showing that a more abnormal CSF profile (low levels of Aβ\textsubscript{1-42} and high levels of tau) correlates with a relatively stronger impairment of cognition. Unfortunately, we did not find relations between CSF biomarkers and behavioural symptoms.
However, further longitudinal research with standardized behavioural questionnaires and a larger, preferably pathologically confirmed patient group is essential to determine exact relations between CSF biomarkers and behavioural deterioration or cognition in bvFTD.

Reference list


