Cerebrospinal Fluid Tau, p-Tau 181 and Amyloid-β_{38/40/42} in Frontotemporal Dementias and Primary Progressive Aphasias

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Key Words
Frontotemporal dementias · Primary progressive aphasias · Alzheimer’s dementia · Cerebrospinal fluid · Amyloid-β peptides · Biomarkers · Tau · p-Tau

Abstract
Background/Aims: We determined cerebrospinal fluid (CSF) concentrations of amyloid-β (Aβ), total tau and phospho-tau (p-tau) in order to study their differential expression in frontotemporal dementia (FTD, n = 25) and primary progressive aphasia (PPA, n = 12) as compared to Alzheimer’s dementia (AD, n = 25) and nondemented controls (n = 20). Methods: Commercially available ELISA and electrochemiluminescence methods were applied. Results: High CSF p-tau and low ratios of Aβ_{38}/Aβ_{40} and Aβ_{42}/Aβ_{38}, respectively, were specific for AD. CSF Aβ_{38} was reduced in FTD as compared to each of the other diagnostic groups, including PPA. CSF tau and p-tau levels were elevated in PPA as compared to FTD. Conclusion: This is the first detailed report on biomarker patterns in PPA, indicating distinct CSF biomarker patterns in FTD and PPA as major subgroups of frontotemporal lobar degeneration. The diagnostic and pathophysiological implications of our results warrant further studies on larger and neuropathologically diagnosed patient populations.

Introduction

Over the past 10 years, characteristic cerebrospinal fluid (CSF) biomarker patterns have been established to support the clinical diagnosis of Alzheimer’s dementia (AD). The main protagonists are amyloid-β (Aβ)_{42}, tau and its phosphorylated forms (e.g. p-tau 181). In contrast, the literature about specific biomarkers for other common neurodegenerative disorders, such as frontotemporal lobar degeneration (FTLD), is sparse. FTLD is defined as a generic term to summarize heterogeneous clinical phenotypes that may appear sporadically or be caused by various genetic mutations. There is also great heterogene-
ity in neuropathologic findings, but the present study focuses on the clinical definition of diagnostic groups. Three sets of criteria for clinically diagnosing FTLD have been published so far. The clinical criteria by Neary et al. [1] are most helpful when focussing on the 3 prototypic clinical subtypes of FTLD: frontotemporal dementia (FTD), primary progressive aphasia (PPA) and semantic dementia. However, clinical diagnosis among these subgroups often remains crucial in a definite case. Thus, biomarkers for applicable diagnostic testing are warranted and still deserve intensive investigation. There are previous reports about the aforementioned AD-specific biomarkers in FTLD and FTD, revealing rather unspecific and still deserve intensive investigation. There are previous reports about the aforementioned AD-specific biomarkers in FTLD and FTD, revealing rather unspecific and still deserve intensive investigation. There are previous reports about the aforementioned AD-specific biomarkers in FTLD and FTD, revealing rather unspecific and still deserve intensive investigation. There are previous reports about the aforementioned AD-specific biomarkers in FTLD and FTD, revealing rather unspecific and still deserve intensive investigation. There are previous reports about the aforementioned AD-specific biomarkers in FTLD and FTD, revealing rather unspecific and still deserve intensive investigation. There are previous reports about the aforementioned AD-specific biomarkers in FTLD and FTD, revealing rather unspecific and still deserve intensive investigation. There are previous reports about the aforementioned AD-specific biomarkers in FTLD and FTD, revealing rather unspecific and still deserve intensive investigation. There are previous reports about the aforementioned AD-specific biomarkers in FTLD and FTD, revealing rather unspecific and still deserve intensive investigation. There are previous reports about the aforementioned AD-specific biomarkers in FTLD and FTD, revealing rather unspecific and still deserve intensive investigation. There are previous reports about the aforementioned AD-specific biomarkers in FTLD and FTD, revealing rather unspecific and still deserve intensive investigation. There are previous reports about the aforementioned AD-specific biomarkers in FTLD and FTD, revealing rather unspecific and still deserve intensive investigation. There are previous reports about the aforementioned AD-specific biomarkers in FTLD and FTD, revealing rather unspecific and still deserve intensive investigation. There are previous reports about the aforementioned AD-specific biomarkers in FTLD and FTD, revealing rather unspecific and still deserve intensive investigation. There are previous reports about the aforementioned AD-specific biomarkers in FTLD and FTD, revealing rather unspecific and still deserve intensive investigation. There are previous reports about the aforementioned AD-specific biomarkers in FTLD and FTD, revealing rather unspecific and still deserve intensive investigation.

Two reports have focussed on \( \alpha \beta_{1-40} \) in FTLD, one of which showed a decrease in comparison to controls and AD [5]. The other did not include a comparison group, but reported an inverse correlation of CSF \( \alpha \beta_{1-40} \) with frontal lobe volume in 11 FTD patients [6]. Our group reported decreased \( \alpha \beta_{1-37} \) and \( \alpha \beta_{1-38} \) levels as part of disease-specific CSF \( \alpha \beta \) peptide patterns in FTLD and FTD [7, 8], using the \( \alpha \beta \)-SDS-PAGE with Western immunoblot (\( \alpha \beta \)-SDS-PAGE/immunoblot). Interestingly, electrochemiluminescence measurements confirmed decreased CSF \( \alpha \beta_{1-38} \) levels in FTD, but with considerably lower test accuracy for diagnosing the disease in a single case [9]. Other biomarker findings for FTD include slightly elevated levels of TAR DNA-binding protein 43 and differences in processing soluble ectodomain of the amyloid precursor protein [10, 11].

PPA represents another major subgroup of FTLD, but very little is known about its CSF biomarker patterns. This prompted us to determine the major \( \alpha \beta \) species in CSF 1–40, 1–38 and 1–42 in addition to total tau and p-tau 181 in patients with FTD (n = 25) and PPA (n = 12), as compared to AD (n = 25) and nondemented disease controls (NDC, n = 20).

**Patients and Methods**

Eighty-two CSF samples were referred to our laboratory between 1999 and 2004 and investigated. CSF concentrations of \( \alpha \beta_{1-38} \) (n = 82), \( \alpha \beta_{1-40} \) (n = 78), \( \alpha \beta_{1-42} \) (n = 73), p-tau 181 (n = 78) and tau (n = 58) were measured. Aliquots of these samples had been studied previously under another objective, focussing on a distinct issue of differentially diagnosing dementias [8]. CSF of AD and other dementia and depressive patients came from the memory clinic of the University of Göttingen or from wards. Cognitive impairment was assessed at least by Mini-Mental State Examination (MMSE). More detailed neuropsychological testing including clock drawing and the CERAD (Consortium to Establish a Registry for Alzheimer’s Disease) test battery was additionally carried out on the majority of patients with cognitive complaints (46/72). Specifically, 5/10, 10/25, 21/25 and 10/12 patients underwent neuropsychological testing in the groups of depressive cognitive complainers (DCC), and AD, FTD and PPA patients, respectively. Detailed neuropsychological assessment was hindered in 2 patients with FTD and 2 patients with PPA by severe lingual or cognitive deficits.

A psychiatrist, a neurologist and a neuropsychologist rendered diagnoses based on a thorough medical history, clinical examination, neuropsychological assessment, clinical records and best clinical judgment. The investigators were blinded to the neurochemical outcome measures. Investigations were carried out with the informed consent of patients or their authorized caregivers. The study was conducted under the guidelines of the Declaration of Helsinki [12] and approved by the ethics committee of the University of Göttingen.

**Patients**

**Nondemented Disease Controls.** The NDC group consisted of 2 subgroups: (1) patients with peripheral neurological diseases (PND) without organic brain affection, and (2) DCC. The 10 patients in the PND subgroup underwent lumbar puncture to investigate central nervous affection in case of polynoeruphathy (n = 7), benign paroxysmal positioning vertigo (n = 1), intervertebral disk herniation (n = 1), autosomal dominant hereditary spinal muscular atrophy (n = 1). The 10 DCC underwent lumbar puncture for differential diagnosis of cognitive complaints during the course of disease. The diagnosis of depression was made according to the criteria of the DSM-IV, and cognitive impairment was assessed at least by the MMSE. Patients with persistent cognitive decline for more than 6 months, an MMSE score below 26 or clear focal atrophy in brain imaging (CT or MRI) were excluded.

**Patients with AD.** Twenty-five patients fulfilled the DSM-IV criteria and NINCDS-ADRDA criteria for clinical diagnosis of AD [13]. Structural (CT or MRI) or functional (single-photon-emission CT or positron emission tomography) brain imaging displayed global cortical atrophy, or temporal, parietotemporal or frontotemporal focal atrophy, or marked hypometabolism of these regions.

**Patients with FTD and PPA.** FTD (n = 25) and PPA (n = 12) were diagnosed according to the consensus criteria [1]. Structural (CT or MRI) or functional (single-photon-emission CT or positron emission tomography) brain imaging revealed frontal or frontotemporal focal atrophy or marked hypometabolism in case of FTD, and left anterior temporal focal atrophy or marked hypometabolism in case of PPA.

**Test Methods**

Preanalytical Treatment of CSF. CSF was drawn by lumbar puncture into polypropylene vials and centrifuged (1,000 g, 10 min, 4°C). Aliquots of 200 µl were kept at room temperature for a maximum of 24 h before storage at –80°C for subsequent p-tau, \( \alpha \beta_{1-38} \) and \( \alpha \beta_{1-40} \) analysis. CSF for \( \alpha \beta_{1-42} \) and total tau ELISA analysis was stored at +4°C and analyzed within 2 days.

ELISA for p-Tau, Total Tau Protein and \( \alpha \beta_{1-42} \) and \( \alpha \beta_{1-40} \). ELISA for p-tau at Thr181 was conducted as previously described [14]. Briefly, the HT7 monoclonal antibody (Mab) directed against both normal tau and p-tau was used for capturing, and biotinylated MAb AT8270 for detection. According to published standard methods [15], the Innotest hTAU Antigen ELISA and
Innotest β-Amyloid_{1–42} (ELISA Innogenetics, Ghent, Belgium) served for quantification of CSF tau and Aβ_{1–42}, respectively. For the quantification of Aβ_{1–40}, the ELISA of The Genetics Company was conducted similarly, except that before application to a microtiter plate, the samples were prediluted 1:5 with diluting buffer.

**Electrochemiluminescence Detection of Aβ_{1–38}**. Electrochemiluminescence detection of Aβ_{1–38} in CSF was performed according to the manufacturer’s recommendations (Meso Scale Discovery). In brief, Multi-Spot 4-spot 96-well plates, precoated with MAb 6E10, were blocked with solution A. The plate was then incubated with a reference peptide dilution series or 100 μl CSF for 1 h, followed by incubation with C-terminal Sulfo-Tag Aβ_{1–38} antibody and finally Read Buffer, for 1 h each. Washing steps with 1 × Tris buffer were performed in between. The emitted light was measured at approximately 620 nm.

**Statistical Analysis**

Aβ peptides, tau and p-tau were expressed as absolutes (in nanograms per milliliter). Patient groups were characterized by mean and SD. The Mann-Whitney U test was employed for comparisons of diagnostic groups. Correlations were estimated by Spearman’s rho. The two-sided level of significance was taken as p < 0.05. The statistical software package SPSS, version 12.0, served for computations.

**Results**

**Test Results**

The mean age of FTD and PPA patients was significantly below that of the AD group (p < 5 × 10^{-2}). Otherwise, there was no significant difference in age among the diagnostic groups. The mean MMSE score did not significantly differ between the dementia groups. There was no significant difference among PND patients and DCC in any of the parameters investigated. For the following statistical evaluation, the 2 groups were therefore considered as one (NDC). The respective CSF concentrations underlying the following comparisons are displayed in figures 1–5.

**Neurochemical Phenotype of AD versus NDC.** Aβ_{1–42} was selectively decreased in AD (p = 1.3 × 10^{-7}), where-
as Aβ1–40 levels were virtually unchanged between the 2 groups. Aβ1–38 tended to be increased in AD, but missed the level of significance. Consequently, the ratios of Aβ1–42/Aβ1–40 (p = 8.0 × 10⁻⁶) and Aβ1–43/Aβ1–38 (p = 2.0 × 10⁻⁸) showed a decrease in AD. Aβ1–38/Aβ1–40 was significantly elevated in AD (table 1). CSF total tau (p = 2.4 × 10⁻⁴) and p-tau (p = 1.4 × 10⁻⁶) were elevated in AD.

**Neurochemical Phenotype of FTD versus NDC.** FTD patients showed lower levels of Aβ1–38 (p = 4.1 × 10⁻⁴), Aβ1–42 (p = 3.2 × 10⁻⁵) and Aβ1–40 (p = 9.7 × 10⁻⁶) than NDC. The Aβ ratios remained virtually unchanged between FTD and NDC. CSF total tau did not significantly differ, whereas p-tau was lowered in FTD (p = 5.3 × 10⁻³).

**Neurochemical Phenotype of FTD versus AD.** In comparison to AD, FTD showed lower levels of Aβ1–38 (p = 1.9 × 10⁻⁵) and Aβ1–40 (p = 4.5 × 10⁻³), but higher lev-

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**Table 1.** Total and p-tau, and Aβ peptides 1–38, 1–40 and 1–42 in CSF of diagnostic groups

<table>
<thead>
<tr>
<th></th>
<th>NDC (n = 20)</th>
<th>AD (n = 25)</th>
<th>FTD (n = 25)</th>
<th>PPA (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65.05 ± 9.4</td>
<td>71.56 ± 8.6</td>
<td>58.92 ± 10.2</td>
<td>62.33 ± 10.1</td>
</tr>
<tr>
<td>Sex (m/w), n</td>
<td>11/9</td>
<td>5/20</td>
<td>17/8</td>
<td>10/2</td>
</tr>
<tr>
<td>In-/outpatients, n</td>
<td>10/10</td>
<td>10/15</td>
<td>13/12</td>
<td>6/6</td>
</tr>
<tr>
<td>MMSE score</td>
<td>28.27 ± 1.7</td>
<td>17.06 ± 6.2</td>
<td>19.74 ± 10.1</td>
<td>17.50 ± 12.8</td>
</tr>
<tr>
<td>p-tau ELISA 1, ng/ml</td>
<td>0.055 ± 0.02</td>
<td>0.114 ± 0.04</td>
<td>0.041 ± 0.01</td>
<td>0.058 ± 0.03</td>
</tr>
<tr>
<td>Tau ELISA 1, ng/ml</td>
<td>0.252 ± 0.14</td>
<td>0.601 ± 0.31</td>
<td>0.252 ± 0.25</td>
<td>0.370 ± 0.22</td>
</tr>
<tr>
<td>Aβ1–38, ng/ml</td>
<td>0.857 ± 0.20</td>
<td>0.984 ± 0.28</td>
<td>0.623 ± 0.20</td>
<td>0.806 ± 0.20</td>
</tr>
<tr>
<td>Aβ1–40, ng/ml</td>
<td>6.492 ± 1.63</td>
<td>6.225 ± 1.82</td>
<td>4.603 ± 1.60</td>
<td>5.503 ± 1.51</td>
</tr>
<tr>
<td>Aβ1–42, ng/ml</td>
<td>0.971 ± 0.30</td>
<td>0.384 ± 0.16</td>
<td>0.709 ± 0.20</td>
<td>0.754 ± 0.26</td>
</tr>
<tr>
<td>Aβ1–38/Aβ1–40, ng/ml</td>
<td>0.134 ± 0.02</td>
<td>0.165 ± 0.03</td>
<td>0.143 ± 0.04</td>
<td>0.155 ± 0.06</td>
</tr>
<tr>
<td>Aβ1–42/Aβ1–38, ng/ml</td>
<td>1.177 ± 0.39</td>
<td>0.377 ± 0.16</td>
<td>1.198 ± 0.43</td>
<td>1.009 ± 0.39</td>
</tr>
<tr>
<td>Aβ1–42/Aβ1–40, ng/ml</td>
<td>0.158 ± 0.05</td>
<td>0.064 ± 0.02</td>
<td>0.158 ± 0.07</td>
<td>0.148 ± 0.06</td>
</tr>
</tbody>
</table>

¹ Aβ peptide concentrations as measured by electrochemiluminescence detection (Meso Scale Discovery).
² Aβ peptide concentrations as measured by ELISA.

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![Fig. 4. Means and 95% CI of CSF Aβ1–40 concentrations for each diagnostic group. * p < 0.05.](image1)

![Fig. 5. Means and 95% CI of CSF Aβ1–42 concentrations for each diagnostic group. * p < 0.05.](image2)
els of Aβ1–42 (p = 8.7 × 10^{-7}). Consequently, the ratios of Aβ1–42/Aβ1–40 (p = 2.8 × 10^{-7}) and Aβ1–42/Aβ1–38 (p = 1.9 × 10^{-8}) were decreased in AD, while Aβ1–38/Aβ1–40 was lowered in FTD (p = 2.3 × 10^{-2}) (table 1). CSF total tau (p = 6.3 × 10^{-6}) and p-tau (p = 4.2 × 10^{-9}) were elevated in AD.

**Neurochemical Phenotype of PPA versus NDC.** PPA displayed lower overall Aβ levels (p = 4.5 × 10^{-2}). There was a tendency toward lower levels of Aβ1–40 and Aβ1–42 than in NDC, which missed the level of significance. The Aβ ratios as well as tau and p-tau levels were unaltered.

**Neurochemical Phenotype of PPA versus AD.** In comparison to AD, PPA displayed a tendency toward lower levels of Aβ1–38, but this missed the level of significance. Aβ1–40 did not differ significantly, but Aβ1–42 was decreased in AD (p = 2.0 × 10^{-4}). Consequently, the ratios of Aβ1–43/Aβ1–40 (p = 5.9 × 10^{-5}) and Aβ1–42/Aβ1–38 (p = 1.0 × 10^{-6}) were decreased in AD. In contrast, the ratio of Aβ1–38/Aβ1–40 was lowered in PPA (p = 4.5 × 10^{-2}). CSF p-tau (p = 6.2 × 10^{-6}), but not total tau, was significantly elevated in AD.

**Correlations**

Throughout all investigated patient groups, the different Aβ peptides were strongly correlated with each other, except for NDC and FTD, where a correlation of Aβ1–42 to Aβ1–40 and Aβ1–38, respectively, was lacking. Tau and p-tau were negatively correlated with Aβ1–42. We found higher tau levels in younger AD patients, but levels of p-tau and tau increased with age in NDC. Otherwise, none of the markers investigated, alone or in combination, were correlated with sex, age or severity of dementia in any of the groups investigated. All reported correlations reached the level of significance (p < 0.05).

**Discussion**

In order to investigate disease-specific biomarker patterns in FTLD subgroups, we evaluated CSF Aβ peptides 1–40, 1–38 and 1–42 as well as total tau and p-tau 181 in patients with FTD and PPA in comparison with AD patients and NDC.

The NDC group consisted of two subgroups, one with PND, the other DCC, which did not differ in any of the parameters investigated. The results of the AD group as compared to the NDC confirm our own previous results [8, 16] and those from studies of others [17]. The overlapping CSF tau and Aβ1–42 levels between AD and the other dementia groups indicate a limited differential diagnostic value of these biomarkers.

**Aβ Peptide Patterns in FTD**

FTD patients presented with low levels of Aβ1–38 as compared to NDC. Using electrochemiluminescence as an independent method, these results confirm our findings from the Aβ-SDS-PAGE/immunoblot [7, 8]. Although less pronounced, CSF Aβ1–40 was reduced in FTD as measured by electrochemiluminescence. In previous studies, the Aβ-SDS-PAGE/immunoblot revealed no significant change in Aβ1–40, which may be due to methodological differences [9]. Conflicting results of Aβ1–40 in FTD also arise from other studies. A recent study found a significant decrease in Aβ1–40 in FTLD compared with AD and control subjects [5]. Another study reported a linear correlation between CSF Aβ1–40 levels and the degree of frontal atrophy as measured by MRI in FTD, suggesting higher CSF Aβ1–40 levels in FTD patients with more pronounced frontal atrophy [6]. However, the results of the latter study are limited by the lack of a control group, which hampers a direct comparison to our results and those of others. The moderate decrease in Aβ1–42 in FTLD as compared to NDC in the present study confirms our previous findings by Aβ-SDS-PAGE/immunoblot [7, 8], as well as results from ELISA-based investigations of others [3, 17].

In comparison to AD, FTD displayed lower levels of Aβ1–38 and Aβ1–40 accompanied by a less pronounced decrease in Aβ1–42. Accordingly, FTD could be differentiated from AD by either a decreased ratio of Aβ1–38/Aβ1–40 or increased ratios of Aβ1–42/Aβ1–40 and Aβ1–42/Aβ1–38, respectively. These results match those of our previous reports [7–9] and the study by Pijnenburg et al. [5]. They underline the diagnostic usefulness not only of the ratios of Aβ1–42/Aβ1–40 and Aβ1–42/Aβ1–38, but also of the ratio of Aβ1–38/Aβ1–40 in differentiating FTD from AD. Within these ratios, decreased CSF Aβ1–38 may be considered as the most specific parameter of FTD as moderately diminished concentrations of Aβ1–42 and Aβ1–40 could also be found in other dementias such as dementia with Lewy bodies [18] and vascular dementia [19].
**Tau and p-Tau Proteins in FTD**

The results of unchanged CSF tau levels and mildly decreased p-tau levels in FTD as compared to controls are in line with previous studies by others [17, 20]. The decrease in CSF p-tau in FTD as compared to controls may be explained by disturbances of tau phosphorylation regulatory mechanisms in FTD [20]. Another explanation may be an underlying AD pathology in NDC, especially in the subgroup of DCC, as depression in the elderly may also be a prodromal state of AD. Compared to AD, FTD presented with both lower tau and lower p-tau levels in CSF. These findings are in accordance with the literature [2, 23, 24].

**Ab Peptide Patterns in PPA**

None of the investigated Ab peptides differed significantly between PPA and NDC. The major differences between PPA and AD were the decreased CSF levels of Ab1–42 and, subsequently, the ratios of Ab1–42/Ab1–40 and Ab1–42/Ab1–38 in the latter. Due to stable CSF Ab1–40 levels in both groups, paralleled by a tendency toward higher and lower CSF Ab1–38 levels in AD and PPA, respectively, the ratio of Ab1–38/Ab1–40 differed between the two diagnostic groups.

When comparing the CSF Ab peptide patterns of PPA and FTD, the only difference was lower levels of Ab1–38 in the latter. This may somehow indicate a specificity of decreased CSF Ab1–38 levels in FTD as compared to other subgroups of the FTLD spectrum. However, due to the lack of a confirmative neuropathological diagnosis, the pathophysiological implications of this finding remain to be elucidated in further investigations. Nevertheless, there is evidence of three distinct presenilin 1 mutations causing a clinical phenotype of FTD [21, 22], indicating a role of Ab peptide metabolism in the neurodegenerative process of FTD. Interestingly, presenilin mutations are also the most common cause of familial AD.

To the best of our knowledge, this is the first study on the three major CSF Ab peptides 1–40, 1–38 and 1–42 in the distinct group of PPA. A multiple case evaluation of patients with PPA (n = 3) reported CSF Ab1–42 to be in the normal range [23]. A subgroup evaluation of a study on the CSF biomarkers tau, p-tau and Ab1–42 in 34 patients with FTLD in comparison to AD and control subjects found PPA to have the smallest overlap with AD-typical CSF biomarker patterns [24]. Despite large methodological differences between those studies, the results indicate Ab1–42 to be in the normal range in most patients with PPA, which is in line with our results. Although it missed the level of significance, we noted a weak tendency toward lower CSF Ab1–42 levels in PPA than in NDC. This may be caused by overlapping AD pathology in PPA and may become more evident in a larger cohort of PPA patients. However, we cannot completely exclude the possibility that AD and PPA diagnoses have been mixed up. We did not find any previous report on CSF Ab1–38 and Ab1–40 in PPA.

**Limitations of the Study**

The reliance on clinical diagnosis limits the validity of our results because of potential misclassification. Another point of concern is that the methods used for measurement varied between Ab1–38 and Ab1–40 or Ab1–42. However, an ELISA for Ab1–38 was not yet available at the time of measurement. Moreover, the analyses of p-tau, Ab1–38 and Ab1–40 were made with frozen samples, whereas Ab1–42 and total tau ELISA were conducted with unfrozen CSF samples.
Conclusions

This is the first detailed report on biomarker patterns in PPA including the three most prominent Aβ peptides in CSF (1–40, 1–38 and 1–42) in addition to the widely accepted AD CSF biomarkers tau and p-tau. The evaluation of these markers in PPA as compared to AD, FTD and NDC confirmed high p-tau levels and low levels of Aβ1–42/Aβ1–40 and Aβ1–42/Aβ1–38 as specific features of AD as compared to other dementias. Moreover, the finding of low CSF Aβ1–38 levels in FTD could be confirmed. Interestingly, PPA did not show this feature. In addition, PPA patients showed higher levels of CSF tau and p-tau than did FTD patients. Thus, our results show distinct CSF biomarker patterns for FTD and PPA. Further studies on larger patient groups will have to clarify the diagnostic value of this finding. Otherwise, a distinct clinical presentation may be related to different kinds of neuropathology. Thus, the investigation of more homogeneous patient groups with neuropathologically confirmative diagnoses may display CSF biomarker changes even more precisely. This approach may also elucidate the pathophysiological implications of our results. We are convinced that these aspects deserve further investigation in appropriately designed studies.

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