Total tau and Phosphorylated tau 181 Levels in the Cerebrospinal Fluid of Patients With Frontotemporal Dementia Due to P301L and G272V tau Mutations

Sonia M. Rosso, MD, PhD; Esther van Herpen; Yolande A. L. Pijnenburg, MD; Niki S. M. Schoonenboom, MD; Philip Scheltens, MD, PhD; Peter Heutink, PhD; John C. van Swieten, MD, PhD

Background: Frontotemporal dementia (FTD) is a pathologically heterogeneous group of presenile neurodegenerative disorders, with or without the deposition of hyperphosphorylated tau protein in affected brain regions. Mutations in the tau gene have been found in the familial form of FTD, linked to chromosome 17q21-22, showing a spectrum of tauopathy.

Objective: To evaluate levels of total tau, phosphorylated tau 181 (Ptau-181), and amyloid-β1-42 in the cerebrospinal fluid (CSF) of patients with FTD, with special emphasis on FTD due to tau mutations.

Design: Case-control study.

Setting: Outpatient neurology clinics at 2 university medical centers, in Rotterdam and Amsterdam (the Netherlands).

Patients: Twenty-six patients with FTD (9 with tau mutations 7 P301L and 2 G272V), 18 patients with Alzheimer disease (AD), and 13 nondemented controls.

Methods: Total tau, Ptau-181, and amyloid-β1-42 levels in CSF, obtained by lumbar puncture, were determined by sandwich enzyme-linked immunosorbent assay. Patients were diagnosed after clinical examination, neuropsychologic evaluation, and neuroimaging. Differences between patient groups were statistically evaluated using nonparametric tests.

Results: Although CSF levels of total tau were mildly increased in FTD patients compared with nondemented controls ($P=0.05$), median CSF total tau levels were low in the subgroup with tau mutations compared with AD patients. Furthermore, CSF levels of Ptau-181 and amyloid-β1-42 were not different in FTD patients, including the patients with tau mutations, compared with nondemented controls.

Conclusions: The tauopathy in P301L and G272V does not appear to be associated with an evident increase in CSF levels of Ptau-181 in FTD patients with these tau mutations, in contrast with findings in patients with AD.

Arch Neurol. 2003;60:1209-1213

Frontotemporal dementia (FTD) is a neurodegenerative disorder of the frontotemporal cortex, exhibiting presenile onset of behavioral changes and cognitive decline.1 Mutations in the tau gene have been identified in some patients with familial FTD. While only about 20% of patients with sporadic FTD show tau-containing Pick bodies at autopsy, tauopathy is nearly always found in neurons and glial cells in patients with FTD caused by tau mutations.2 The remaining FTD cases are characterized by neuronal loss, spongiosis, and gliosis with or without ubiquitin-positive inclusions in the frontotemporal cortex, and may occur in the sporadic as well as in the familial form.2,3 Because cerebrospinal fluid (CSF) is in direct contact with the extracellular space of the central nervous system, many studies have focused on CSF, in search of biomarkers with diagnostic significance in dementia. Most studies in FTD patients show a modest increase in total tau (t-tau) protein concentration in CSF.4,5 However, the level of tau protein in CSF has not yet been investigated in FTD patients with tau mutations. Therefore, we measured CSF levels of t-tau, tau phosphorylated at Thr181 (Ptau-181), and amyloid-β1-42 (Aβ1-42) in 26 FTD patients, 9 of whom showed missense mutations in the tau gene. We compared our findings with a group of patients with Alzheimer disease (AD) and nondemented controls. Our hypothesis was that CSF Ptau-181 levels would be elevated in FTDP-17 patients with tau mutations, as all known tau mutations lead to the deposition of hyperphosphorylated tau protein in neurons and/or glial cells, and these deposits are known to be phosphorylated at Thr181 in the P301L and G272V mutations.
Table 1. Clinical Data and Cerebrospinal Fluid Analyses per Diagnostic Category

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>No. of Patients</th>
<th>Age, Mean ± SD, y</th>
<th>Duration, Mean ± SD, y</th>
<th>t-tau, Median (25th-75th Percentile), pg/mL</th>
<th>Ptau-181, Median (25th-75th Percentile), pg/mL</th>
<th>Aβ1-42, Median (25th-75th Percentile), pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTD</td>
<td>26</td>
<td>54.7 ± 7.0</td>
<td>3.0 ± 1.8</td>
<td>299 (179-499)</td>
<td>33 (25-43)</td>
<td>683 (458-771)</td>
</tr>
<tr>
<td>Tau mutation</td>
<td>9</td>
<td>52.7 ± 6.9</td>
<td>2.1 ± 1.4</td>
<td>330 (184-338)</td>
<td>31 (28-42)</td>
<td>528 (409-708)</td>
</tr>
<tr>
<td>Sporadic</td>
<td>17</td>
<td>56.0 ± 6.6</td>
<td>3.5 ± 1.8</td>
<td>298 (178-706)</td>
<td>34 (22-71)</td>
<td>756 (441-831)</td>
</tr>
<tr>
<td>AD</td>
<td>18</td>
<td>66.0 ± 7.5</td>
<td>3.0 ± 2.1</td>
<td>479 (360-698)</td>
<td>80 (54-101)</td>
<td>280 (222-312)</td>
</tr>
<tr>
<td>Nondemented</td>
<td>13</td>
<td>57.3 ± 12.6</td>
<td>NA</td>
<td>171 (117-310)</td>
<td>51 (21-42)</td>
<td>547 (421-625)</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ1-42, β-amyloid1-42 protein; AD, Alzheimer disease; FTD, frontotemporal dementia; NA, not applicable; Ptau-181, tau phosphorylated at Thr181; t-tau, total tau.

RESULTS

The age of patients with FTD at examination was similar to that of nondemented controls (P = .4). The AD patients were significantly older (P < .001) (Table 1). The mean ± SD age of the 9 FTD patients with tau mutations (52.3 ± 7.0 years) did not differ significantly from that of the remaining FTD patients (56.0 ± 6.9 years; P = .2). The mean duration of disease on lumbar puncture in both FTD and AD patients was 3.0 years. Cerebrospinal fluid levels of t-tau, Ptau-181, and Aβ1-42 were similar in men and women. Total protein levels in CSF appeared to be highest in patients with AD (median, 0.51 g/L in patients with AD; 0.36 g/L in FTD patients with tau mutations; 0.37 g/L in patients with sporadic FTD; and 0.34 g/L in nondemented controls), although this difference did not reach statistical significance (P = 1).

Levels of t-tau in the CSF of FTD patients were slightly higher than in the nondemented controls (P = .05), whereas this difference was not significant in either of the 2 subgroups individually (Figure 1). Total tau levels in CSF were increased in patients with AD (P < .001) compared with nondemented controls. Cerebrospinal fluid levels of Ptau-181 in the entire FTD group, as well as in the 2 subgroups separately, did not differ from those in controls, while CSF levels of Ptau-181 in AD patients...
were significantly higher than in nondemented controls ($P<.001$). Neither the ratio of CSF Ptau-181 to CSF total protein nor the ratio of CSF Ptau-181 to CSF t-tau was statistically different in any of the groups. Patients with FTD, including those with tau mutations, had similar levels of CSF $\beta_{1-42}$ compared with nondemented controls, in contrast with AD patients, who had lower levels of CSF $\beta_{1-42}$ compared with nondemented controls ($P<.001$). There was no significant correlation between CSF t-tau, CSF Ptau-181, or CSF $\beta_{1-42}$, and age at lumbar puncture or duration of disease in any of the patient groups. The correlation between CSF t-tau and CSF Ptau-181 was high in all groups. There was no correlation between the duration of the symptoms in patients with tau mutations and levels of CSF t-tau or CSF Ptau-181 (Table 2).

**COMMENT**

To our knowledge, this study is the first to address CSF levels of tau in FTD patients with tau mutations. The levels of t-tau in CSF were slightly higher in FTD patients than in nondemented controls, although this elevation could not be confirmed in the subgroup of patients with P301L or G272V tau mutations. The levels of Ptau-181 in CSF were not increased in FTD patients, neither in those with FTD with tau mutations nor in those with sporadic FTD. At the same time, we confirmed previous findings of increased CSF t-tau and Ptau-181 levels, and lowered CSF $\beta_{1-42}$ in AD patients.

One of the drawbacks of this study is that pathologic confirmation was lacking in patients with sporadic FTD and AD. Despite this, the clinical diagnosis was firmly established using international clinical criteria and supported by neuroimaging and neuropsychologic examination findings. These clinical criteria have been shown to be highly specific for FTD. A second drawback of this study is the small sample size, which made it difficult to detect small differences among groups. However, although the group of FTD patients with tau mutations may be too small to detect statistically significant changes, the striking homogeneity in CSF Ptau-181 levels suggests that similar results would be achieved with larger patient numbers.

The observation of mildly increased levels of CSF t-tau in the entire FTD group is similar to findings in previous studies of FTD. Increased CSF t-tau has also been found in a variety of other neurologic disorders, including AD, corticobasal degeneration, Creutzfeldt-Jakob disease, and acute stroke. Therefore, these elevated levels probably reflect nonspecific neuronal and axonal degeneration and are not merely a consequence of neurofibrillary tauopathy. The finding of increased levels of CSF Ptau-181 in patients with AD and corticobasal degeneration suggests that CSF tau levels may be more useful in differentiating these conditions from other disorders without tauopathy. Several studies of CSF levels of Ptau-181, using antibodies directed against several different phosphorylated epitopes (threonine-181, serine-199, and threonine-231), have all shown an increase in CSF levels of Ptau-181 in AD patients.

Surprisingly, CSF Ptau-181 levels in the present study were low in FTD patients with tau mutations compared with AD patients. These findings indicate that accumulation of Ptau-181 in the brains of patients with tauopathy does not necessarily lead to an increase in CSF levels of Ptau-181. Additional factors are probably involved in determining why certain disorders with tauopathy, such as AD, are associated with...
an increase in CSF levels of Ptau-181, and others are not. A possible explanation for this observation may be that the tau deposits in P301L and G272V are located intracellularly (in the shape of pretangles or Pick-like inclusions, respectively) and might not reach the CSF, while the extracellular ghost tangles found in AD are not seen.20 It will be interesting to examine the CSF of patients with the R406W tau mutation, as the pathologic neurofibrillary change found in this mutation closely resembles that in AD.21 Alternatively, the difference in CSF Ptau-181 levels in these 2 conditions may be explained by different clearance mechanisms. The observation that calpain 2 activity co-localized with tau in the brains of patients with familial cases of frontotemporal degeneration strongly suggests that increased activity of this enzyme may promote tau synaptic aggregation, which may result in the development of Pick-related symptoms and pathology.22 In view of the above, it is tempting to speculate that the clinical picture of a frontotemporal tauopathy with dementia and parkinsonism may be explained by increased clearance of tau.22

In the current study, CSF was only available from patients with P301L and G272V missense mutations, both of which reduce the ability of mutant tau protein to interact with microtubules and other molecules.23 Intronic and some coding region mutations in exon 10 of tau have a primary effect at the messenger RNA level, resulting in a change in ratio of 3 to 4 repeat tau isoforms without affecting the binding properties of the protein.24 Because of the different mechanisms by which tau mutations lead to neurodegeneration, it is unpredictable whether CSF levels of tau or Ptau-181 may be altered in patients with tau mutations that affect the alternative splicing of exon 10. Analysis of the CSF of patients with different types of tau mutations, as well as various other types of tauopathies, may contribute to our understanding of which factors determine the selective increase in levels of different CSF proteins in neurodegenerative disorders in general.

Accepted for publication May 1, 2003.

Author contributions: Study concept and design (Drs Rosso and van Swieten); acquisition of data (Drs Rosso, Pijnenburg, Schoonenboom, Scheltens, and van Swieten, and Ms van Herpen); analysis and interpretation of data (Drs Rosso, Heutink, and van Swieten); drafting of the manuscript (Drs Rosso, Schoonenboom, Heutink, and van Swieten); critical revision of the manuscript for important intellectual content (Ms van Herpen and Drs Pijnenburg, Scheltens, Heutink, and van Swieten); statistical expertise (Dr Rosso); obtained funding (Drs van Swieten and Heutink); administrative, technical, and material support (Ms van Herpen, and Drs Schoonenboom, Scheltens, and Heutink); study supervision (Drs Scheltens, Heutink, and van Swieten).

This work was supported by a grant from the Netherlands Organization for Scientific Research (project 940-38-005), the Hague, the Netherlands, the Internationale Stichting Alzheimer Onderzoek, Maestricht, the Netherlands, and a generous donation by the van Zuijlen family.

We thank Eugen van Mellechelm, PhD, for the use of INNOTEST PHOSPHO-TAU(181P), and Michel Goedert, MD, PhD, for insightful discussion.

Corresponding author and reprints: Sonia M. Rosso, MD, PhD, Department of Neurology, Erasmus MC, Locatie Dijkzigt, Dr Molewaterplein 40, 3015 GD Rotterdam, the Netherlands (e-mail: s.rosso@erasmusc.nl).

Table 2. Characteristics of Patients With Tau Mutations

<table>
<thead>
<tr>
<th>Patient/Sex/Age, y</th>
<th>Duration, y</th>
<th>CSF t-tau, pg/mL</th>
<th>CSF Ptau-181, pg/mL</th>
<th>CSF-P301L, pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/49</td>
<td>0.5</td>
<td>266</td>
<td>27</td>
<td>528</td>
</tr>
<tr>
<td>2/M/58</td>
<td>2.0</td>
<td>345</td>
<td>44</td>
<td>674</td>
</tr>
<tr>
<td>3/M/52</td>
<td>0.8</td>
<td>569</td>
<td>42</td>
<td>725</td>
</tr>
<tr>
<td>4/F/62</td>
<td>5.0</td>
<td>214</td>
<td>34</td>
<td>475</td>
</tr>
<tr>
<td>5/F/53</td>
<td>1.1</td>
<td>332</td>
<td>31</td>
<td>692</td>
</tr>
<tr>
<td>6/M/93</td>
<td>2.0</td>
<td>155</td>
<td>28</td>
<td>324</td>
</tr>
<tr>
<td>7/F/45</td>
<td>2.3</td>
<td>331</td>
<td>28</td>
<td>478</td>
</tr>
<tr>
<td>8/M/45</td>
<td>2.2</td>
<td>330</td>
<td>42</td>
<td>748</td>
</tr>
<tr>
<td>9/M/45</td>
<td>2.2</td>
<td>123</td>
<td>20</td>
<td>343</td>
</tr>
</tbody>
</table>

P301L Mutation

G272V Mutation

Abbreviations: Aβ, β-amyloid; p, protein; CSF, cerebrospinal fluid; Ptau-181, tau phosphorylated at Thr181; t-tau, total tau.

REFERENCES


