Frontotemporal dementia: impact of P301L tau mutation on a healthy carrier

A Alberici, C Gobbo, A Panzacchi, F Nicosia, R Ghidoni, L Benussi, C Hock, A Papassotriopoulos, P Liberini, J H Growdon, G B Frisoni, A Villa, O Zanetti, S Cappa, F Fazio, G Binetti


Frontotemporal dementia (FTD) is the second commonest form of dementia after Alzheimer’s disease, but its clinical and biological features are less well known. To uncover its earliest signs, we studied the main clinical, neuroimaging, and biochemical findings in an asymptomatic carrier from a three generation FTD family, bearing the P301L pathogenic mutation in the tau gene. Except for selective impairment on the Verbal Fluency Test for letters, all cognitive tests were normal. The brain computed tomography scan was normal, but the brain single photon emission computed tomography and statistical parametric mapping (SPECT-SPM) scan revealed bilateral frontal lobe hypoperfusion. Levels of total tau, 181P-tau, and Aβ1-42 in the cerebrospinal fluid were increased compared with control values. We conclude that detection of these distinctive abnormalities should improve early diagnostic accuracy for FTD and help distinguish it from Alzheimer’s disease.

**METHODS**

**Clinical and cognitive examination**

We personally examined patient III;7 and his siblings III;8, III;9, and III;10 (fig 1A). They all underwent extensive clinical and neurological examinations, including neuroimaging investigations and a detailed cognitive assessment, as previously reported.14–16 In addition, we reviewed the medical records of all affected individuals in the family to reconstruct the main clinical features of the disease.

**Mutation analyses**

Blood samples for DNA were taken from III;6, III;7, III;8, III;9, and III;10 after informed consent was obtained. All exons of the tau gene were sequenced and APOE was genotyped as previously described.17

**Single photon emission computed tomography and statistical parametric mapping (SPECT-SPM)**

SPECT imaging of cerebral blood flow for the subjects III;10 and III;8 and for 21 control subjects (11 men, 10 women; mean age (SD) 51 (16) years) was performed using a maximum dose of 740 MBq 99mTc-ethyl cysteinate dimer (ECD), injected intravenously with the subjects supine in a resting state with eyes closed. Thirty minutes after the injection of the tracer, brain SPECT was performed using a triple-head SPECT system (PRISM 3000 Picker International, OH) with higher resolution fan beam collimators. For each camera, projection data were obtained in a 128×128 format for 24 angles of 120° at 40 seconds per angle. A Hanning filter (cut-off 0.5 cycle/cm) was used for SPECT image reconstruction. Attenuation correction was performed using Chang’s method. The data were analysed with statistical parametric mapping (SPM99) (using software from the Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 4.2 (Math-works Inc, Sherborn, MA, USA), running on a SUN Spare Station 20. The subjects’ scans were fit into a standard stereotactic space.17 Validation of statistical parametric mapping (SPM) for assessment of functional cerebral changes with SPECT was reported in a simulation study18 and in a clinical study.19

**Cerebrospinal fluid measurements**

After obtaining written consent, we collected cerebrospinal fluid (CSF) samples from subject III;10, two patients with sporadic AD and three age matched healthy control (HC) subjects. Levels of Aβ1-42 and tau protein in the CSF were determined by enzyme linked immunosorbent assay (Innogenetics, Belgium). CSF tau phosphorylated at threonine 181 was quantified using a prototype version of the INNOTEST phospho-tau (181P-tau) as described elsewhere.20

**RESULTS**

**Genealogical investigation and patient description**

Information about the family is summarised in fig 1A.

Patient III;7 was the index case of this family; at 50 years he had alien limb syndrome with associated extrapyramidal signs, initially diagnosed as corticobasal degeneration. Follow up evaluations documented rapid progression of the disease into overt FTD; he died after eight years of the illness. Enquiry into his family history revealed that six other family

**Abbreviations:** AD, Alzheimer’s disease; CSF, cerebrospinal fluid; FTD, frontotemporal dementia; HC, healthy controls; SPECT-SPM, single photon emission computed tomography and statistical parametric mapping
members over three generations had had neurological disorders ranging from psychiatric disturbances to motor deficits and dementia.

Subjects III;8 and III;9 were examined at the age of 58 years and 52 years, respectively, and their neurological and cognitive examinations, and neuroimaging investigations were normal. Subject III;10, at the age of 50 years, had a normal neurological examination, with no extrapyramidal deficit or frontal release sign. She was leading an appropriate social life, and she and her relatives had no complaints about behavioural disturbances or mood disorders. She was able to satisfy the requirements of her very demanding job, as she had been doing. On cognitive evaluation, her scores were normal on all tests, except for a reduction on the Verbal Fluency Test for letters. A total of 17 words were produced in one minute, compared with 30 and 34 by her two siblings (table 1). Her brain computed tomography (CT) scans were normal (data not shown).

**Mutation analysis**

Genetic analyses revealed an amino acid substitution P→L at position 301 of exon 10 of the \( \tau \) gene in the asymptomatic individual III;10. The same mutation was present in the index case III;7 and in the affected sibling III;6; no mutations were found in the healthy siblings III;8 and III;9. **APOE** genotype is given in fig 1A.

**SPECT-SPM**

In Subject III;10, SPECT abnormalities were not visible at gross inspection (data not shown). SPECT-SPM (fig 1B) analysis showed that significant reductions of cerebral blood flow were evident in the frontal lobes (p<0.001). These involved in particular the dorsolateral frontal cortex and the frontal poles, and the mesial frontal cortex. In subject III;8, SPECT-SPM was within normal range as compared with age matched controls.

**CSF determinations**

CSF Aβ1-42 levels of subject III;10 (1101 pg/ml) were higher than those of patients with sporadic AD (421; 412 pg/ml) and HC (658–924 pg/ml), and normative (SD) data (794 (218) pg/ml).21 In the same subject, the levels of CSF tau protein (303 pg/ml) and 181P-tau (45 pg/ml) were lower than those of the patients with AD (total tau 727; 562 pg/ml; 181P-tau 92; 69 pg/ml) and higher than those of HC (total tau 154–178 pg/ml; 181P-tau 32–38 pg/ml), and normative data (total tau 136 (89) pg/ml).22

**DISCUSSION**

We have documented distinctive regional brain dysfunction and biochemical pathological changes that precede onset of dementia in an asymptomatic carrier from a family with FTD caused by the P301L mutation in the \( \tau \) gene. Subject III;10
was 50 years old when first examined and just entering the decade when most of her family members developed the neurological symptoms. Two of her siblings had P→L mutation and overt neurological signs consistent with FTD; two other siblings did not have the mutation and were neurologically normal. When first seen, the sole deficit on formal cognitive testing in subject III;10 was the Verbal Fluency Test for letters. Language capacities are impaired very early on in the course of sporadic FTD and the presence of a deficit in verbal fluency in our subject underscores the primacy of language disturbances in the evolution of FTD. Previous studies have demonstrated that presymptomatic P301L mutation carriers not only have impaired verbal fluency but also frontal executive functions. Early diagnosis of FTD may be aided by an extensive assessment of language domains, in addition to executive functions.

Conventional brain CT scans did not show any morphological change in our asymptomatic subject, but a SPECT-SPM scan detected diminished blood flow in the frontal cortical regions. This evidence of frontal lobe dysfunction on physiologic neuroimaging is consistent with the cognitive deficit on the Verbal Fluency Test and in agreement with previous reports.

The silent neurodegenerative process detected by SPECT-SPM was associated with biochemical alterations of proteins in the CSF—that is, increased levels of Aβ1-42, total tau, and 181P-tau. Although it is somewhat surprising to find increased levels of tau in an asymptomatic person, this finding is expected in established AD, and is controversial in patients with FTD. The CSF formula in subject III;10 is that is, increased levels of Aβ1-42, total tau, and 181P-tau species might be even more informative in tracking the disease progression. In overt FTD patients, 181P-tau in CSF is almost undetectable, as tau might be first solubilised, then abnormally phosphorylated and eventually sequestered in tangle formation. Further longitudinal evaluation of these biological and imaging parameters may contribute to the establishment of an index of phenocorverion to follow the effects mediated by the mutation and leading to dementia.

### ACKNOWLEDGEMENTS

The authors wish to acknowledge the helpful and generous collaboration of the members of the family, which was essential for this study. We are grateful to Prof Daniela Perani for her scientific contribution. Mrs Eileen Johnston is acknowledged for her helpful editing.

### Authors’ affiliations

A Alberici, F Nicosia, R Ghidoni, L Benussi, A Villa, G Binetti, Neurobiology Lab, IRCCS S. Giovanni di Dio-FBF, Brescia, Italy
C Gobbo, A Panzacchi, S Cappa, F Fazio, Department of Nuclear Medicine, Institute H S Raffaele, Milan, Italy
J H Growdon, Department of Neurology, Massachusetts General Hospital, Boston, MA, USA
G B Frisoni, Epidemiology and Neuroimaging Lab, IRCCS S. Giovanni di Dio-FBF, Brescia, Italy
O Zanetti, Alzheimer Research Unit, IRCCS S Giovanni di Dio-FBF, Brescia, Italy
F Fazio, INB-CNR University of Milan-Bicocca, Milan, Italy
G Binetti, Memory Clinic, IRCCS S. Giovanni di Dio-FBF, Brescia, Italy

This work was supported by grant no. ICS030.13/RF97.46 from the Ministero della Salute, Italy.

Competing interests: none declared

Correspondence to: Dr G Binetti, Memory Clinic, IRCCS S. Giovanni di Dio-FBF, Via Pilastroni 4, 25123 Brescia, Italy; gbinetti@oh-fbf.it

Received 23 June 2003
In revised form 23 January 2004
Accepted 26 January 2004

---

### Table 1 Cognitive battery tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Subject</th>
<th>III;10</th>
<th>III;9</th>
<th>III;8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Raw</td>
<td>ES or</td>
<td>Raw</td>
<td>ES or</td>
</tr>
<tr>
<td></td>
<td>scores</td>
<td>(perc)</td>
<td>scores</td>
<td>(perc)</td>
</tr>
<tr>
<td>MMSE</td>
<td>29/30</td>
<td>–</td>
<td>29/30</td>
<td>–</td>
</tr>
<tr>
<td>GDS</td>
<td>7/30</td>
<td>–</td>
<td>2/30</td>
<td>–</td>
</tr>
<tr>
<td>Digit Span FW</td>
<td>8/4</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Digit Span BW</td>
<td>4</td>
<td>–</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Spatial Span</td>
<td>6</td>
<td>–</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Logical Memory Test</td>
<td>15/7/6</td>
<td>4</td>
<td>14/9/</td>
<td>4</td>
</tr>
<tr>
<td>Rey Figure Copy</td>
<td>36/36</td>
<td>4</td>
<td>33/36</td>
<td>4</td>
</tr>
<tr>
<td>Rey Figure Recall</td>
<td>18/36</td>
<td>4</td>
<td>28/36</td>
<td>4</td>
</tr>
<tr>
<td>Token Test</td>
<td>36/36</td>
<td>4</td>
<td>35/36</td>
<td>4</td>
</tr>
<tr>
<td>VFT for letters</td>
<td>17*</td>
<td>0</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>VFT for categories</td>
<td>52</td>
<td>3</td>
<td>58</td>
<td>4</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>28/30</td>
<td>–</td>
<td>29/30</td>
<td>–</td>
</tr>
<tr>
<td>Attention Matrices</td>
<td>59/60</td>
<td>4</td>
<td>48/60</td>
<td>4</td>
</tr>
<tr>
<td>Raven Coloured Matrices</td>
<td>33/36</td>
<td>4</td>
<td>33/36</td>
<td>4</td>
</tr>
<tr>
<td>WCST categories</td>
<td>5</td>
<td>–</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>perseverations</td>
<td>7</td>
<td>(70)</td>
<td>17</td>
<td>(70)</td>
</tr>
<tr>
<td></td>
<td>(perc)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes:

*Defective performance (age and education corrected).

BW, backward; ES, equivalent score; FW, forward; GDS, Geriatric Depression Scale; MMSE, Mini Mental State Examination; perc, percentile; VFT, Verbal Fluency Test; WSCT, Wisconsin Card Sorting Test.
REFERENCES

30 Alberici, Gobbo, Panzacchi, et al.
Frontotemporal dementia: impact of P301L tau mutation on a healthy carrier

A Alberici, C Gobbo, A Panzacchi, F Nicosia, R Ghidoni, L Benussi, C Hock, A Papassotriopoulos, P Liberini, J H Growdon, G B Frisoni, A Villa, O Zanetti, S Cappa, F Fazio and G Binetti

J Neurol Neurosurg Psychiatry 2004 75: 1607-1610
doi: 10.1136/jnnp.2003.021295

Updated information and services can be found at:
http://jnnp.bmj.com/content/75/11/1607

These include:

References
This article cites 25 articles, 7 of which you can access for free at:
http://jnnp.bmj.com/content/75/11/1607#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
Dementia (1020)
Memory disorders (psychiatry) (1390)
Radiology (1747)
Radiology (diagnostics) (1309)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/