Serum neurofilament light chain protein is a measure of disease intensity in frontotemporal dementia

ABSTRACT

Objective: To investigate serum neurofilament light chain (NfL) concentrations in frontotemporal dementia (FTD) and to see whether they are associated with the severity of disease.

Methods: Serum samples were collected from 74 participants (34 with behavioral variant FTD [bvFTD], 3 with FTD and motor neuron disease and 37 with primary progressive aphasia [PPA]) and 28 healthy controls. Twenty-four of the FTD participants carried a pathogenic mutation in C9orf72 (9), microtubule-associated protein tau (MAPT; 11), or progranulin (GRN; 4). Serum NfL concentrations were determined with the NF-Light kit transferred onto the single-molecule array platform and compared between FTD and healthy controls and between the FTD clinical and genetic subtypes. We also assessed the relationship between NfL concentrations and measures of cognition and brain volume.

Results: Serum NfL concentrations were higher in patients with FTD overall (mean 77.9 pg/mL [SD 51.3 pg/mL]) than controls (19.6 pg/mL [SD 8.2 pg/mL]; p < 0.001). Concentrations were also significantly higher in bvFTD (57.8 pg/mL [SD 33.1 pg/mL]) and both the semantic and nonfluent variants of PPA (95.9 and 82.5 pg/mL [SD 33.0 and 33.8 pg/mL], respectively) compared with controls and in semantic variant PPA compared with logopenic variant PPA. Concentrations were significantly higher than controls in both the C9orf72 and MAPT subgroups (79.2 and 40.5 pg/mL [SD 48.2 and 20.9 pg/mL], respectively) with a trend to a higher level in the GRN subgroup (138.5 pg/mL [SD 103.3 pg/mL]). However, there was variability within all groups. Serum concentrations correlated particularly with frontal lobe atrophy rate (r = 0.53, p = 0.003).

Conclusions: Increased serum NfL concentrations are seen in FTD but show wide variability within each clinical and genetic group. Higher concentrations may reflect the intensity of the disease in FTD and are associated with more rapid atrophy of the frontal lobes.

GLOSSARY

bvFTD = behavioral variant frontotemporal dementia; FTD = frontotemporal dementia; GENFI = Genetic Frontotemporal Dementia Initiative; lvPPA = logopenic variant of primary progressive aphasia; MND = motor neuron disease; NfL = neurofilament light chain; nfvPPA = nonfluent variant of primary progressive aphasia; PPA = primary progressive aphasia; PPA-NOS = primary progressive aphasia not otherwise specified; Simoa = single-molecule array; svPPA = semantic variant of primary progressive aphasia.

Frontotemporal dementia (FTD) is a common cause of early-onset dementia.1 Clinically, patients present with either changes in personality (behavioral variant FTD [bvFTD]) or impaired language (primary progressive aphasia [PPA]), although overlap with motor neuron disease (FTD-MND) is not uncommon.1 FTD has an autosomal dominant genetic cause in around a quarter of people, with mutations in the progranulin (GRN), chromosome 9 open reading frame 72 (C9orf72), and microtubule-associated protein tau (MAPT) genes being commonest.2

Few fluid biomarkers have been investigated in FTD, although there have now been a number of studies of neurofilament concentration in the CSF.3–11 Higher neurofilament light chain

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article. The Article Processing Charge was paid by Medical Research Council.

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Abbreviations: bvFTD = behavioral variant of frontotemporal dementia; FTD = frontotemporal dementia; FTD-MND = frontotemporal dementia with motor neuron disease; lPPA = logopenic variant of primary progressive aphasia; NA = not applicable; NfL = neurofilament light chain; nPPA = nonfluent variant of primary progressive aphasia; PPA-NOS = primary progressive aphasia not otherwise specified; svPPA = semantic variant of primary progressive aphasia.

Total FTD does not include lvPPA.

<table>
<thead>
<tr>
<th>Disease group</th>
<th>Controls</th>
<th>Total FTD</th>
<th>bvFTD</th>
<th>FTD-MND</th>
<th>nfvPPA</th>
<th>svPPA</th>
<th>lvPPA</th>
<th>PPA-NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>28</td>
<td>67</td>
<td>34</td>
<td>3</td>
<td>13</td>
<td>10</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>63.9 (7.2)</td>
<td>64.5 (7.9)</td>
<td>63.0 (8.3)</td>
<td>65.0 (0.3)</td>
<td>67.5 (9.7)</td>
<td>65.2 (6.4)</td>
<td>65.6 (5.9)</td>
<td>63.9 (5.2)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>54.6</td>
<td>61.2</td>
<td>73.5</td>
<td>66.7</td>
<td>23.1</td>
<td>60.0</td>
<td>71.4</td>
<td>71.4</td>
</tr>
<tr>
<td>Disease duration, mean (SD), y</td>
<td>NA</td>
<td>5.5 (3.7)</td>
<td>6.2 (4.6)</td>
<td>6.0 (4.6)</td>
<td>3.8 (1.5)</td>
<td>6.0 (2.1)</td>
<td>6.4 (2.9)</td>
<td>4.5 (2.9)</td>
</tr>
<tr>
<td>Serum NfL, mean (SD), pg/mL</td>
<td>19.6 (8.2)</td>
<td>77.9 (51.3)</td>
<td>57.8 (33.1)</td>
<td>195.0 (69.9)</td>
<td>82.5 (33.8)</td>
<td>95.9 (33.0)</td>
<td>49.5 (19.4)</td>
<td>91.2 (86.6)</td>
</tr>
</tbody>
</table>

Abbreviations: NfL = neurofilament light chain; NFT = neurofibrillary tangle; PPA-Nos = primary progressive aphasia not otherwise specified; PPA-NOS = primary progressive aphasia; svPPA = semantic variant of primary progressive aphasia.
Psychometric assessment. Forty-seven participants had psychometric testing at baseline, usually on the same day as serum sampling but at a maximum of 6 months from the time of sample collection (mean interval 0.2 years [SD 0.2 years]). Eighteen had bvFTD, 19 had FTD-MND, and 14 had PPA (6 with nfvPPA, 7 with svPPA, and 1 with PPA-NOS). Twenty-nine participants had follow-up psychometric testing at an interval of 1 year (SD 0.2 years): 11 with bvFTD, 2 with FTD-MND, and 16 with PPA (5 with nfvPPA, 7 with svPPA, and 4 with PPA-NOS). Testing included the Wechsler Abbreviated Scale of Intelligence, Vocabulary, Block Design, Similarities, and Matrices subscales; the Recognition Memory Tests for Faces and Words; the Graded Naming Test; the Delis-Kaplan Executive Function System Color-Word Interference Test, as well as the Mini-Mental State Examination.

Neuromaging analysis. Forty-six of the participants with FTD had volumetric T1 brain MRI on a 3T Siemens Trio scanner performed usually on the same day as serum sampling but at a maximum of 6 months from the time of sample collection (mean interval 0.2 years [SD 0.2 years]): 22 with bvFTD, 2 with FTD-MND, and 23 with PPA (9 with nfvPPA, 9 with svPPA, and 5 with PPA-NOS). Twenty-nine participants had follow-up volumetric T1 brain MRI on a 3T Siemens Trio scanner performed usually on the same day as serum sampling but at a maximum of 6 months from the time of sample collection (mean interval 0.2 years): 11 with bvFTD, 2 with FTD-MND, and 16 with PPA (5 with nfvPPA, 7 with svPPA, and 4 with PPA-NOS). Testing included the Wechsler Abbreviated Scale of Intelligence, Vocabulary, Block Design, Similarities, and Matrices subscales; the Recognition Memory Tests for Faces and Words; the Graded Naming Test; the Delis-Kaplan Executive Function System Color-Word Interference Test, as well as the Mini-Mental State Examination.

Statistical analysis. Serum NfL concentrations were initially compared between the control group and the total FTD group. The Levene test for homogeneity demonstrated unequal variances between these 2 groups (Levene statistic = 22.8; p < 0.001); therefore, the Welch test (without assumptions for equal variance) was used to compare the groups. Serum NfL data were normally distributed (Kolmogorov-Smirnov test), so an analysis of variance was used to compare mean serum NfL concentrations across each of the clinical subgroups (bvFTD, FTD-MND, nfvPPA, svPPA, and PPA-NOS) and across the genetic FTD subgroups (MAPTGRN, and C9orf72) and to compare each of these subgroups with the control group. To allow for unequal variance, the Games-Howell correction was used for post hoc pairwise comparisons between groups. The same statistical methods were also used to compare NfL levels between the genetic subgroups and between each of these groups and the control group. The Pearson correlation coefficient was used to examine the association
### Table 2 Comparison of serum neurofilament light chain concentrations between the disease subgroups and control group

<table>
<thead>
<tr>
<th>Group</th>
<th>bvFTD</th>
<th>FTD-MND</th>
<th>nfvPPA</th>
<th>svPPA</th>
<th>lvPPA</th>
<th>PPA-NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>−38.2 (5.9)</td>
<td>−175.3 (40.4)</td>
<td>−62.9 (9.5)</td>
<td>−76.2 (10.5)</td>
<td>−29.9 (7.5)</td>
<td>−71.6 (32.8)</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>0.185</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.053</td>
<td>0.413</td>
</tr>
<tr>
<td>bvFTD</td>
<td>−137.2 (40.8)</td>
<td>−24.7 (10.9)</td>
<td>−38.1 (11.9)</td>
<td>8.3 (9.3)</td>
<td>−71.6 (32.8)</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.276</td>
<td>0.308</td>
<td>0.070</td>
<td>0.968</td>
<td>0.413</td>
<td></td>
</tr>
<tr>
<td>FTD-MND</td>
<td>112.4 (41.5)</td>
<td>99.1 (41.7)</td>
<td>145.4 (41.0)</td>
<td>103.8 (51.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.374</td>
<td>0.451</td>
<td>0.248</td>
<td>0.509</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nfvPPA</td>
<td>−13.3 (14.0)</td>
<td>33.0 (11.9)</td>
<td>−8.7 (34.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.959</td>
<td>0.136</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>svPPA</td>
<td>463 (12.7)</td>
<td>4.7 (34.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.032</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lvPPA</td>
<td>−41.7 (33.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.857</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: bvFTD = behavioral variant of frontotemporal dementia; FTD-MND = frontotemporal dementia with motor neuron disease; nfvPPA = nonfluent variant of primary progressive aphasia; lvPPA = semantic variant of primary progressive aphasia; PPA-NOS = primary progressive aphasia not otherwise specified; svPPA = semantic variant of primary progressive aphasia.

Values are given as mean difference in serum neurofilament concentration between groups (SEM) and refer to comparison of rows vs columns.

Mean NfL concentrations were higher than controls in each of the genetic subgroups (figure 1B, table 3): 138.5 pg/mL (SD 103.3 pg/mL) in GRN, 79.2 pg/mL (SD 48.2 pg/mL) in C9orf72, and 40.5 pg/mL (SD 20.9 pg/mL) in MAPT mutations. However, only the MAPT subgroup (mean difference from controls = 20.8, 95% confidence interval = 1.4–40.3, p = 0.035) and the C9orf72 subgroup (mean difference from controls = 59.5, 95% confidence interval = 8.0–111.0, p = 0.025) were significantly different, with the lack of difference in the GRN subgroup likely due to small sample size (table 3).

Baseline and longitudinal cognitive and imaging measures are shown in table 4. Serum NfL concentrations...
with faster rates of brain atrophy. These findings suggest that serum NfL concentrations reflect the intensity of the disease in FTD and that higher concentrations are associated with a more rapid disease progression. Within the FTD subtypes, there was a tendency for groups with probable TDP-43 pathology (svPPA and FTD-MND clinically, GRN and C9orf72 mutations genetically) to have raised levels compared with those associated with tau pathology (MAPT mutations), although within all groups there is substantial variability. With a lower limit of quantification of 0.26 pg/mL, all samples, including those from normal controls, could be reliably quantified, which is an advantage over earlier studies on serum NfL in other conditions.14,30–52

The results of this study are consistent with those found in previous CSF studies of NfL concentrations in FTD: levels are consistently higher in patients with FTD411 and tend to be increased in those with probable TDP-43 pathology.30,11 Certainly for genetic FTD, for which GRN and C9orf72 mutations are associated with TDP-43 pathology, this is consistent with the more rapid progression (and shorter disease duration) seen in many patients within these 2 mutation groups (independent of clinical syndrome) compared with the relatively slower progression of patients with MAPT mutations (which is associated with tau pathology).83 One previous study also suggested a correlation of CSF NfL with measures of disease severity and, consistent with our study, showed an association of levels with frontal lobe atrophy.11

We found that serum NfL levels were correlated with the rate of subsequent brain atrophy but not with the baseline brain volumes. Measures of brain atrophy are likely to be better measures of the disease intensity than just a single cross-sectional measure of the whole-brain or lobar volumes, which reflect disease duration and normal variation as well as disease activity. Serum NfL levels correlated with baseline measures of executive function but not with longitudinal changes in psychometric measures. However, no cognitive measures survived correction for multiple comparisons. There were also no significant correlations with baseline brain volumes. However, serum NfL levels were correlated with rates of whole brain (r = 0.46, p = 0.01), frontal lobe (r = 0.53, p = 0.003; figure 2), and parietal lobe (r = 0.38, p = 0.04) atrophy, although not with other lobar atrophy rates. Only the correlation with frontal lobe atrophy rate survived correction for multiple comparisons.

**DISCUSSION** Using an ultrasensitive immunoassay, we show that serum NfL concentrations are raised in FTD and that higher concentrations are associated

| Cognitive and imaging characteristics of the frontotemporal dementia study participants |
|---------------------------------|-----------------|-----------------|
| **Cognitive measures**          | Baseline, mean (SD) | Longitudinal, mean (SD) |
| Participants, n                 | 47               | 29               |
| MMSE                            | 23.8 (5.7)       | –1.7 (5.0)       |
| WASI vocabulary                 | 4.4 (4.4)        | –0.9 (2.9)       |
| WASI block design               | 8.7 (4.3)        | –0.4 (2.6)       |
| WASI similarities               | 5.9 (4.3)        | –1.5 (3.1)       |
| WASI matrices                   | 9.4 (4.3)        | 0.1 (2.6)        |
| RMT faces                       | 5.2 (4.1)        | –0.9 (3.7)       |
| RMT words                       | 6.1 (4.5)        | –1.5 (4.1)       |
| Graded naming test              | 4.2 (4.4)        | –1.7 (3.0)       |
| Graded difficulty calculation test | 7.8 (5.0)       | –0.9 (2.4)       |
| D-KEFS Color-Word Interference Test | 6.1 (5.1)  | –1.7 (2.5)       |

**Imaging measures**

| Participants, n | 46 | 29 |
| Whole brain     | 72.6 (5.0) | 1.9 (1.5) |
| Frontal         | 10.4 (1.0) | 2.2 (2.7) |
| Temporal        | 7.0 (0.9)  | 2.7 (2.4) |
| Parietal        | 6.0 (0.5)  | 1.2 (2.9) |
| Occipital       | 4.9 (0.4)  | 0.7 (2.5) |
| Insula          | 0.8 (0.1)  | 2.6 (2.6) |
| Cingulate       | 1.6 (0.1)  | 1.2 (2.0) |

Abbreviations: D-KEFS = Delis-Kaplan Executive Function System; MMSE = Mini-Mental State Examination; RMT = Recognition Memory Test; WASI = Wechsler Abbreviated Scale of Intelligence.

Baseline cognitive measures are standard scores except for the MMSE (out of 30). Longitudinal cognitive scores are annualized change in standard score (or change in MMSE score); a negative score is a decrease in score. Baseline brain volumes are expressed as a percentage of total intracranial volume (measured in Statistical Parameter Mapping [SPM12]). Longitudinal imaging measures are annualized rates of atrophy (%).
Serum NfL concentrations are correlated with frontal lobe atrophy rates (Neurology 87 September 27, 2016 1334). Points indicate individual patient values, and the straight line indicates the line of best fit from a linear regression model of serum NfL on annualized frontal lobe atrophy rate.

**Figure 2** Relationship of serum neurofilament light chain (NfL) concentrations to frontal lobe atrophy rate

Serum NfL concentrations are correlated with frontal lobe atrophy rates ($r = 0.53$, $p = 0.003$). Points indicate individual patient values, and the straight line indicates the line of best fit from a linear regression model of serum NfL on annualized frontal lobe atrophy rate.

**REFERENCES**


**DISCLOSURE**

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**AUTHOR CONTRIBUTIONS**

J.D.R., K.D.M., E.B., S.M., J.M.S., N.C.F., and J.D.W. were involved in patient recruitment and collection of data. J.T., R.D., N.N., U.A., K.B., and H.Z. were involved in assay development, sample processing, and analysis. J.D.R., I.O.C.W., K.M.D., E.B., E.G., A.F., M.J.C., and S.O. were involved in analysis of the psychometric and imaging data. J.D.R. and I.O.C.W. drafted the initial version and figures. J.D.R., I.O.C.W., and J.M.S. performed the statistical analysis. All authors contributed to reviewing and editing the manuscript.

**DISCLOSURE**

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Comment:

“If you can’t measure it, you can’t improve it” (Lord Kelvin)

In clinical practice, disability and its progression are notoriously difficult to quantify, urging the need for reliable soluble biomarkers for neuroaxonal damage. Neurofilament light chain (NfL) is a scaffolding protein of the neural cytoskeleton with important roles in axonal and dendritic branching and growth. After neuronal damage, NfL levels in the CSF increase and thus are considered a highly specific, real-time biomarker of axonal injury.

In the case of serum NfL, the single-molecule array technology substantially improves analytical sensitivity to an extent that measurements in blood-derived samples may be used as surrogate endpoints in neuroprotection trials or even in daily practice in the relatively near future. The ultrasensitive assay used by Rohrer and colleagues allowed reliable NfL measurements in all serum samples, including healthy controls, a giant stride for a biomarker that is independent of CSF and hence applicable in a routine clinical setting. Moreover, the authors found that their assay is quantitative: higher concentrations were associated with more rapid course of frontal lobe atrophy in a routine clinical setting. Moreover, the authors found that their assay is quantitative:


Jens Kuhle, MD, PhD

From Neurology, Departments of Medicine, Clinical Research and Biomedicine, University Hospital Basel, Switzerland.

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The terrorist inside my husband’s brain (see p. 1308)

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