Cerebrospinal fluid sTREM2 levels in frontotemporal dementia differ by genetic and pathological subgroup

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Background

Frontotemporal dementia (FTD) is a clinically and pathologically very diverse disease. Reliable biomarkers of disease onset, intensity and pathology are lacking. Chronic neuroinflammation occurs in FTD, particularly in familial FTD associated with progranulin (GRN) mutations. Inflammatory biomarkers are therefore of interest.

Triggering receptor expressed on myeloid cells 2 (TREM2) is a microglial expressed gene. Homozygous mutations produce an FTD-like syndrome and TREM2 variants increase the risk of Alzheimer’s disease (AD) or FTD. When cleaved, soluble TREM2 (sTREM2) is released into the CSF.

Levels of CSF sTREM2 are raised in AD and correlate with CSF markers of neuronal injury. This has not been explored in FTD.

We measured CSF sTREM2 levels in individuals with sporadic and familial FTD and healthy controls to assess whether levels differ by clinical subtype of FTD, gene mutation, or underlying pathology. We also explored relationships between CSF sTREM2 and validated CSF neurodegenerative biomarkers: total tau (T-tau), phosphatidyl at position threonine-181 (P-tau), and amyloid beta 1-42 (Aβ42).

Participants

17 healthy controls and 64 individuals with dementia consistent with FTD were recruited from the Specialist Cognitive Disorders Clinic at the National Hospital for Neurology and Neurosurgery or from UCL FTD cohort studies. Those with FTD had either behavioural variant FTD (bvFTD) or a variant of primary progressive aphasia (PPA) leading to five clinical subtypes (Table 1). Ten cases had familial FTD, with mutations in one of three genes: GRN (n=3), C9orf72 (n=3) or MAPT (n=4).

Methods

CSF samples were collected by lumbar puncture in polypropylene tubes, centrifuged, the supernatant aliquoted and stored at -80C until analysis. CSF levels of T-tau, P-tau and Aβ42 were measured using commercially available INNOTEST sandwich ELISAs. CSF sTREM2 levels were measured using an immunoassay (Figure 1).

CSF sTREM2 levels were compared using multivariable linear regressions adjusted for age, gender and, for disease groups, disease duration, as follows:

1. Between FTD and control groups
2. Across clinical and genetic FTD subgroups and with controls
3. Between pathological subgroups – the FTD group was split by CSF T-tau/Aβ42 ratio into two groups: 1) ‘AD biomarker positive’ group (ratio >1, AD like FTD, often GRN); 2) ‘AD biomarker negative’ group (ratio <1, non-AD like FTD; n=49); both subgroups were also compared with controls (ratio <1).

CSF sTREM2 levels vs. age, disease duration, and CSF T-tau, P-tau and Aβ42 levels were assessed in each group and subgroup.

Table 1. Demographics of participants

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Control</th>
<th>FTD</th>
<th>bvFTD</th>
<th>sTREM2</th>
<th>pTREM2</th>
<th>sTREM2</th>
<th>pTREM2</th>
<th>sTREM2</th>
<th>pTREM2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>17</td>
<td>44</td>
<td>20</td>
<td>16</td>
<td>11</td>
<td>14</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender (n (%) total)</td>
<td>6 (54.5)</td>
<td>45 (50.6)</td>
<td>19 (95.0)</td>
<td>9 (56.2)</td>
<td>7 (63.6)</td>
<td>7 (50.0)</td>
<td>3 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at CSF (years, mean (SD))</td>
<td>63.7 (6.9)</td>
<td>64.8 (5.9)</td>
<td>65.0 (7.1)</td>
<td>64.5 (5.9)</td>
<td>64.8 (6.9)</td>
<td>65.0 (5.9)</td>
<td>64.5 (4.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset (years, mean (SD))</td>
<td>58.5 (6.6)</td>
<td>61.6 (5.7)</td>
<td>62.7 (6.1)</td>
<td>61.5 (6.1)</td>
<td>63.0 (6.7)</td>
<td>62.7 (6.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration or CSF (years, mean (SD))</td>
<td>5.1 (3.8)</td>
<td>7.4 (5.4)</td>
<td>4.2 (3.8)</td>
<td>4.7 (2.3)</td>
<td>3.5 (2.0)</td>
<td>2.2 (1.3)</td>
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</tr>
</tbody>
</table>

Results

CSF sTREM2 levels did not differ significantly between FTD and controls (mean (SD)=7.4 (3.2) vs. 6.8 (1.6) ng/ml, P=0.43), or between clinical subtypes of FTD:

CSF sTREM2 levels were higher in GRN mutation carriers than controls (9.7 (2.9) vs. 6.8 (1.6) ng/ml; P=0.028) and other mutation groups (P=0.01). Levels were also higher in individuals with a clinical diagnosis of FTD but AD like CSF (likely AD pathology) than those with FTD and non-AD like CSF (likely FTD) (F(2,3)=3.77, P=0.029):

CSF sTREM2 levels were positively associated with age in FTD (β=0.189, P=0.001) and in most clinical subgroups, particularly bvFTD (β=0.271, P=0.017):

CSF sTREM2 levels were negatively associated with disease duration (β= -0.235, P=0.025) particularly in those with non-AD like-CSF (β= -0.253, P=0.018):

CSF sTREM2 levels were positively associated with CSF T-tau, P-tau and Aβ42 in FTD and T-tau in controls:

CSF sTREM2 levels were positively associated with CSF T-tau and Aβ42 in FTD with non AD-like CSF, and with T-tau and P-tau in FTD with AD-like CSF:

Conclusions

CSF sTREM2 levels do not differ between FTD and controls overall, or between clinical subtypes of FTD. However, individuals with FTD due to GRN mutations or with FTD due to underlying AD pathology have higher sTREM2 levels, perhaps due to more intense microglial activation.

CSF sTREM2 levels increase with age in FTD, similar to previous studies of AD, but are lower at longer disease durations. Levels may decrease over time, or lower levels could reflect less intense disease.

CSF sTREM2 levels correlate with levels of CSF T-tau, a marker of neuronal injury, in FTD, irrespective of underlying pathology. CSF sTREM2 levels may be a biomarker of disease intensity, but this requires longitudinal confirmation.

Future work: CSF sTREM2 levels are being examined in a large familial FTD cohort with GRN, C9orf72 and MAPT mutations to establish if, and when, levels rise pre-symptomatically. This may aid prediction of disease onset and guide early treatment initiation in future clinical trials.

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