Cerebrospinal fluid and PET measures of tau pathology reflect different states of AD pathophysiological progression

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Background

Alzheimer’s disease (AD) is characterized by a decades-long period of pathophysiological changes leading to the onset of dementia. At the dementia stage, the brain is likely to be too seriously affected for any intervention to meaningfully alter the disease process. As a result, some in the research field have suggested to shift from a cognitive-based to a biological-based definition of the disease. Criteria for disease definition include measures of pathological hallmarks (amyloid-β [Aβ] and tau) and neurodegeneration.

Owing to the availability of cerebrospinal fluid (CSF) and imaging markers, either magnetic resonance imaging (MRI) or positron emission tomography (PET), of disease process, modalities are often used interchangeably. However, investigations of CSF and PET measures of AD pathology suggest that these two modalities provide both overlapping and complementary information. Some investigators have suggested that CSF Aβ abnormality may occur earlier than PET.

With the availability of novel PET tracers we can now investigate whether CSF (P-tau) and PET (Floetopirin) measures of tau pathology are indicative of different pathophysiological stages.

Participants and Methods

248 ADNI participants with at least:
- One FTP-PET scan
- One amyloid scan
- One CSF sample

117 ADNI participants (62 healthy, 55 with MCI) with a FTP-PET scan and a CSF biomarker assessment within a 24-month period

Threshold derivation: ROC analyses

P-tau ROC: 0.50 (95% CI: 0.40 - 0.60)
- Tau = 0.52

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Sample characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>CSF/PET-</th>
<th>CSF+/PET-</th>
<th>CSF+/PET+</th>
<th>CSF-PET+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>74.53</td>
<td>78.84</td>
<td>77.50</td>
<td>77.36</td>
</tr>
<tr>
<td>Sex</td>
<td>33 (47%)</td>
<td>8 (47%)</td>
<td>4 (50%)</td>
<td>15 (57.1%)</td>
</tr>
<tr>
<td>MMSE</td>
<td>34.49 (1.49)</td>
<td>31.22 (4.08)</td>
<td>13 (69.0%)</td>
<td>12 (66.7%)</td>
</tr>
<tr>
<td>Education</td>
<td>18.42</td>
<td>18.79</td>
<td>18.60</td>
<td>18.75</td>
</tr>
<tr>
<td>APOE ε2 carriers (%)</td>
<td>1 (6%)</td>
<td>6 (27%)</td>
<td>5 (22%)</td>
<td>13 (60.7%)</td>
</tr>
<tr>
<td>Memory composite</td>
<td>1.05 (0.72)</td>
<td>1.07 (0.32)</td>
<td>1.31 (0.63)</td>
<td></td>
</tr>
<tr>
<td>Executive function composite</td>
<td>0.81 (0.45)</td>
<td>0.91 (0.50)</td>
<td>1.13 (0.55)</td>
<td></td>
</tr>
</tbody>
</table>

CSF PET classification:

- CSF+/PET-: CSF+ PET- (N=15)
- CSF-/PET+: CSF- PET+ (N=16)
- CSF+/PET+: CSF+ PET+ (N=15)
- CSF-/PET-: CSF- PET- (N=34)

Cross-sectional analysis:

Group comparison of:
- Key demographic variables
- Global PET amyloid (AV45, cerebellum normalized)
- FTP/PET Braak stage
- Cognition (executive function and memory)

Tau concordance status:

- CSF+/PET-: CSF- PET- (N=15)
- CSF-/PET+: CSF- PET+ (N=16)
- CSF+/PET+: CSF+ PET+ (N=15)
- CSF-/PET-: CSF- PET- (N=34)

Cognition: Cognitive impairment in CSF+/PET+ individuals only

CSF: CSF+ + PET+ persons have increased retrospective CSF P-tau accrual

Conclusions

Among 117 ADNI participants categorized according to their levels of tau pathology as measured by PET and CSF we found that:
- CSF–PET+ occurred less frequently than CSF+PET–, CSF–PET- or CSF+PET+
- Participants with at least one positive tau biomarker had increased Aβ pathology
- Only CSF+ showed retrospective change in CSF tau levels
- CSF+/PET+ participants were more likely to have worse cognitive performance
- CSF+/PET+ persons had consistent retrospective cognitive decline

Results are consistent with the notion that CSF P-tau is an early indicator of AD pathophysiological changes. Given the reduced inference from the CSF–PET+ group, it is unclear whether this stage is artifactual or represents an alternate pathogenetic route. Longitudinal CSF/PET studies will improve our understanding of this phenomenon.

References


Acknowledgments