High CSF tau is related to reduced hippocampal volume and subjective cognitive decline in healthy elderly with amyloid pathology

Alexa Pichet Binette, Jacob W Vogel, Vladimir Fonov, Jennifer Tremblay-Mercier, Cécile Madjar, John Breitner, Louis Collins, Judes Poirier, Sylvia Villeneuve, PREVENT-AD Research Group

**BACKGROUND AND OBJECTIVES**

In preclinical stages of Alzheimer’s disease (AD), questions remain about relationships between cerebrospinal fluid (CSF) amyloid beta (Aβ) and tau proteins, and other markers of AD pathogenesis. In the PREVENT-AD cohort of cognitively normal older adults with a parental history of AD-like dementia, we assessed CSF Aβ and tau in relation to brain integrity and cognitive function.

**METHODS**

**Cohort**
Cognitively normal older adults with a family history of AD

<table>
<thead>
<tr>
<th>n=105</th>
<th>Age (years)</th>
<th>Male (%)</th>
<th>Education (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>63.5</td>
<td>29</td>
<td>15±3</td>
<td></td>
</tr>
</tbody>
</table>

**CSF Measurements**
Amyloid-beta 42 and 40 (Aβ 42 and Aβ 40), phosphorylated tau (P-tau)

**Neuroimaging**
Hippocampal volume adjusted for total intracranial volume

**Cognition**
- Repeatable Battery for Assessment of Neuropsychological Status (RBANS) total score
- Subjective cognitive decline: Self-reported change in memory compared to 20 years ago

**Statistical analyses**
General linear models with age as a covariate

**RELATIONSHIPS BETWEEN HIPPOCAMPAL VOLUME AND CSF MARKERS**

There was an interaction between P-tau and amyloid on the hippocampal volume: Individuals with high amyloid pathology (low CSF Aβ 40) present a lower hippocampal volume with higher P-tau level.

**SUBJECTIVE COGNITIVE DECLINE**
How do you feel about your memory compared to 20 years ago?

<table>
<thead>
<tr>
<th>Better</th>
<th>Identical</th>
<th>A bit worse</th>
<th>Much worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>3%</td>
<td>32%</td>
<td>58%</td>
<td>7%</td>
</tr>
</tbody>
</table>

**Binary logistic regression**
High amyloid pathology is associated (p=0.05) with reporting worsening of one's memory compared to 20 years ago.

**OBJECTIVE COGNITIVE SCORE**

There was no interaction between Aβ groups and P-tau on cognitive performance, although total RBANS score declines with elevated P-tau at trend level.

**CONCLUSIONS**

There are already detectable relations between CSF biomarkers, hippocampal volume and subjective cognitive decline in cognitively normal, asymptomatic elderly, driven mainly by individuals with high P-tau and low Aβ1-42 levels.

**FUTURE WORK**
Recent literature suggests that the ratio of CSF Aβ42/Aβ40 might be more sensitive to AD pathology (Janelidze et al., Annals Clin Transl Neurol, 2016) and predict better amyloid accumulation in the brain over to years (Racine et al., Alzheimer’s and Dementia, 2016) than Aβ42 alone. We are starting to investigate the effects of using such a ratio in our analyses.

Specifically, we looked at the difference between the relationships of amyloid and P-tau, using either CSF Aβ42 or Aβ42/Aβ40.

The association between levels of Aβ and P-tau was clearly dependent on APOE-ε4 status (interaction p<0.001). In ε4 carriers, we observed an expected relationship of higher Aβ pathology (lower CSF values) with higher P-tau, but the inverse was found in non-carriers.

When using the ratio Aβ42/Aβ40, the previous interaction is not significant anymore, but we still observed the same relationship in ε4 carriers.