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CSF Synaptic Biomarkers in the Preclinical Stage of Alzheimer Disease and Their Association With MRI and PET

A Cross-sectional Study

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Study Question

Are CSF synaptic biomarkers altered in the early preclinical stage of Alzheimer disease (AD)?

What Is Known and What This Paper Adds

While synaptic dysfunction and alterations in the levels of associated CSF biomarkers are a known feature in symptomatic patients with AD, evidence on their levels in early preclinical stages of the disease are limited. This study reveals an increase in CSF synaptic biomarkers in preclinical AD and potential associations with other known risk factors. The current study sheds light on the elevated status of CSF biomarkers in early AD that also correlate with Aβ and tau pathologies.

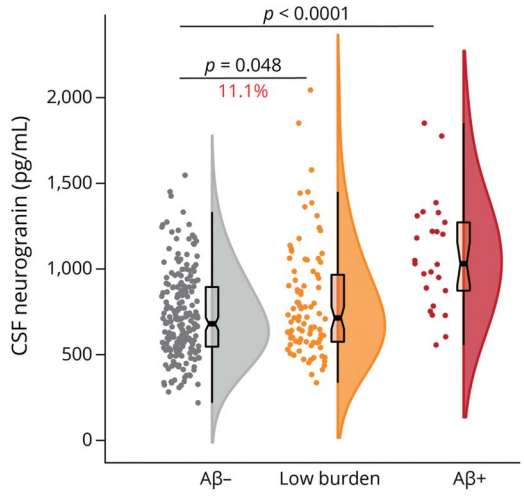
Methods

The ALFA (Alzheimer's and Families) study enrolled middle-aged, cognitively unimpaired individuals enriched for family history of AD (47.4%) and *APOE*-ε4 carriership (32.5%). Data from this nested analysis came from 397 people enrolled in the ALFA + cohort who participated based on their specific AD risk profile, determined by participants' AD parental history and *APOE* status, verbal episodic memory score, and CAIDE score. A detailed phenotyping was performed in ALFA + participants, including measurement of CSF biomarkers, a structural MRI, and fluorodeoxyglucose and Aβ PET imaging. CSF biomarkers were measured using immunoassays (Aβ40, Aβ42, GAP-43, neurogranin, neurofilament light chain/NfL, p-tau, and t-tau) and immunoprecipitation mass spectrometry (SNAP-25 and synaptotagmin-1). To study very early changes in the continuum, the following 3 groups were defined based on both CSF and PET Aβ status: (i) CSF/PET Aβ-negative (negative CSF Aβ42/40 and Aβ PET < 30 Centiloids), (ii) group with low burden of Aβ pathology (positive CSF Aβ42/40 but Aβ PET < 30 Centiloids), and (iii) CSF/PET Aβ-positive (positive CSF Aβ42/40 and Aβ PET ≥ 30 Centiloids).

Results and Study Limitations

All measured CSF biomarkers increased with age. CSF neurogranin was higher in females, and CSF SNAP-25 was higher in *APOE*-ε4 carriers. CSF biomarker levels were associated with Aβ load. Furthermore, CSF neurogranin, SNAP-25, GAP-43, and synaptotagmin-1 were significantly increased in participants with a low burden of Aβ, suggesting an association with early AD pathogenesis. Similarly, increased biomarker levels were associated with increased CSF p-tau, which was independent of Aβ. On analyzing the association of CSF biomarkers with neurodegeneration markers, CSF neurogranin and GAP-43 were significantly associated with changes in brain metabolism and cortical thickness. A limitation of the study is that not all synaptic biomarkers were included. Also, changes over time have not been predicted.

Figure CSF Synaptic Biomarkers Were Compared Between Groups



CSF/PET Aβ-negative group (gray), low burden group (yellow), and CSF/PET Aβ-positive group (red).

Registration, Study Funding, and Competing Interests

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The corresponding author(s) of the full-length article and the journal editors edited and approved the final version.

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