Cerebrospinal Fluid Biomarkers in Autopsy-Confirmed Alzheimer Disease and Frontotemporal Lobar Degeneration

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Study Question
Are fully automated Elecsys CSF immunoassays for β-amyloid (Aβ) and tau biomarkers, and an ultrasensitive Simoa assay for neurofilament light chain (NFL) levels associated with neuropathologic changes of Alzheimer disease (AD) and frontotemporal lobar degeneration (FTLD)?

What Is Known and What This Paper Adds
Clinical presentations have varying correlations with neuropathology in AD and FTLD. Biomarkers are therefore needed to assist in diagnosis and to accelerate drug development. This study provides Class II evidence that distinct CSF biomarker patterns of P-tau, T-tau, Aβ42, Aβ40, and NFL are associated with AD and FTLD neuropathology.

Methods
This analysis uses data from 101 patients with neurodegenerative diseases recruited from the University of California San Francisco Memory and Aging Center's Alzheimer's Disease Research Center. All participants had lumbar puncture for CSF sampling, a mean of 2.9 years prior to death. CSF samples were analyzed for Aβ40, Aβ42, total tau (T-tau), tau phosphorylated at amino acid residue 181 (P-tau), P-tau/Aβ42, and Aβ42/Aβ40 ratios using fully automated Elecsys CSF immunoassays; and NFL using an ultrasensitive Simoa assay. All patients had autopsy analysis. Neuropathology measures included Thal phases, Braak stages, CERAD scores, Alzheimer's disease Neuropathologic Change (ADNC), and primary and contributory pathologic diagnoses.

Results and Study Limitations
CSF biomarkers were associated with neuropathologic measures of Aβ (Thal, CERAD), tau (Braak) and overall AD neuropathologic change (ADNC) (p < 0.001). Patients with intermediate-high ADNC scores had significantly lower Aβ42 and Aβ42/Aβ40 and higher T-tau, P-tau/Aβ42 and P-tau/T-tau levels than ADNC none-low patients (p ≤ 0.001). The CSF P-tau/Aβ42 and Aβ42/Aβ40 ratios had high sensitivity (0.86–0.89), specificity (0.92–0.96) and overall diagnostic performance for intermediate-high ADNC (area under the curve [AUC] range: 0.95–0.96) Distinct variations in biomarker patterns were noted across different FTLD subtypes; with increased NFL and reduced P-tau/T-tau in FTLD-TDP, and reduced T-tau in progressive supranuclear palsy. A limitation of the study was the small sample size of the pathologic sub-groups.

Study Funding and Competing Interests
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