Key Summary of Published Article

A High-throughput Mass Spectrometry Assay for Quantifying Beta-amyloid 40 and 42 in Cerebrospinal Fluid

Background

- Alzheimer's disease (AD) is a chronic neurodegenerative disease. Early brain pathophysiology of AD involves aggregation of β-amyloid (Aβ) peptides, such as Aβ40 and Aβ42.[1]
- The Aβ42/Aβ40 ratio in cerebral spinal fluid (CSF) correlates with Aβ deposition inside cells.[2,3] Immunoassays are commonly used to measure CSF proteins but are subject to variability when quantifying.[4]
- **Objective:** The investigators of this study
  - developed and validated a high-throughput liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay to simultaneously measure Aβ40 and Aβ42 in CSF.
  - tested the ability of the Aβ42/Aβ40 ratio to distinguish diagnosed AD from non-AD dementia.
  - assessed the correlation between the Aβ42/Aβ40 ratio and the gene dose of the *APOE4* allele, another CSF biomarker of AD.

Methods

- Investigators at Quest Diagnostics developed a high-throughput LC-MS/MS assay to simultaneously measure Aβ40 and Aβ42; they assessed assay characteristics by standard laboratory methods.
- The ability of the Aβ42/Aβ40 ratio to distinguish AD was assessed using 170 clinical specimens from patients and 130 specimens from control individuals in the UC San Diego Shiley-Marcos AD Research Center (ADRC) Clinical Core Lumbar Puncture Study. Consensus clinical diagnoses included AD (n=102), mild cognitive impairment (MCI, n=37), and non-AD dementia (n=22).
- Differences in mean Aβ42/Aβ40 ratios across diagnosis groups were assessed by linear regression. The ability of the assay to distinguish patients with AD from healthy participants was evaluated by receiver operating characteristic curve analysis. Performance was compared to that of a 3-biomarker immunoassay.
- Correlation of the Aβ42/Aβ40 ratio with the gene dose of the *APOE4* allele, also measured by LC-MS/MS, was evaluated.

Results

- The reportable range of the assay was 100 to 25,000 pg/mL, the limit of quantification was 100 pg/mL, recovery was 93% to 111%, and intra- and inter-assay variation coefficients were <15% for Aβ40 and Aβ42.
- At an Aβ42/Aβ40 ratio cutoff of <0.16
  - clinical sensitivity was 78% and specificity was 91% for distinguishing AD from non-AD dementia.
  - clinical sensitivity was 78% and specificity was 81% for distinguishing patients with AD from healthy participants.
  - concordance with the 3-biomarker immunoassay was 71% after adjustment for chance agreement.
- The Aβ42/Aβ40 ratio decreased as the gene dose of the *APOE4* allele increased (P<0.001).

Conclusions

- The LC-MS/MS Aβ42/Aβ40 assay can help distinguish patients with AD from those with non-AD dementia and from healthy participants.
- The assay performed well relative to a 3-marker immunoassay, indicating it offers an acceptable alternative.

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