

**Predictive Performance of CSF Biomarkers for Conversion from
Mild Cognitive Impairment to Alzheimer's Disease**

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Background

Qualification of imaging and biochemical biomarkers for use in detection of Alzheimer's Disease (AD) pathology is of increasing interest in academic, pharmaceutical, and regulatory disciplines. There are accumulating data that support the hypothesis that early detection (risk for AD) of disease pathology is possible at the pre-dementia stage of the disease, prior to the onset of dementia when the clinical diagnosis is less certain. Here we summarize our experience in the qualification of CSF Amyloid beta42 (Abeta42), total tau (t-tau) and tau phosphorylated in the 181 threonine position (p-tau181).

Methods

We utilized an immunoassay platform and reagents (xMAP multiplex Luminex and Innogenetics research use only bead-based capture antibodies and reagents, AlzBio3, Ghent, Belgium) in this study. For analytical qualification we performed an interlaboratory quality assessment study and documented reproducibility during a total of 38 analytical runs: %CV values of 5.7%, 5.6% and 11.5% test-retest performance for ADNI subject CSF Abeta42, t-tau and p-tau181, respectively. For clinical qualification of this analytical system, we first established threshold CSF biomarker concentrations for AD detection using pre-mortem CSF samples collected from subjects diagnosed with AD at autopsy and an age-matched cognitively normal control (CN) group (all samples provided by the UPenn Alzheimer's Disease Clinical Core). We employed Receiver Operating Characteristic curve analyses to determine threshold "cut-point" concentrations that effectively discriminated between AD and CN subjects and then applied the same analytical methodology for biomarker concentrations in CSF collected from 410 subjects enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI) at baseline. For assessments of the predictive performance of CSF biomarkers, biomarker ratios and a logistic regression model that included Abeta42, t-tau and APOE genotype (LRTAA) we applied survival analysis techniques.

Results

Utilizing these ADNI data and the non-ADNI subject-based disease detection cutpoints we confirmed the expected significantly decreased CSF Abeta and increased tau concentrations in 100 AD subjects compared to the 114 CN subjects and intermediate abnormalities of these biomarkers in the 196 ADNI subjects who provided CSF at entry into the study. For the 37 MCI subjects who converted to a clinical diagnosis of AD within 12 months of entry into the study the incidence of an AD-like biomarker profile was 86.5%, 89% and 86.5%, respectively, for Abeta42 alone, t-tau/Abeta42 and LRTAA, using the autopsy-confirmed cutpoints. Using Kaplan-Myer survival analyses each of these three biomarker measures provided conversion prediction based on the established cutpoints (respective p values of 0.0005, <0.0001 and 0.0001, respectively). We are further evaluating the predictive performance of these biomarkers by applying the same immunoassay methodology to an earlier stage of MCI subjects in the ADNI GO and ADNI 2 study and will discuss this new data.

Discussion

These study data provide, in a large multicenter investigation, support for the hypothesis that CSF biomarkers can provide a basis for establishing in MCI subjects the risk for conversion to a clinical diagnosis of probable AD. Such information may be useful to establish risk-based cohorts in future treatment trials. Essential to the use of CSF biomarker measurements in this context is use of highly standardized analytical methodology and associated pre-analytical factors. Further characterization of the clinical utility of CSF biomarkers over longer periods of followup in the ADNI MCI subjects is underway including evaluations of combinations with imaging biomarkers. In addition, it is very well appreciated that AD as in other diseases, the presence of pathology, in addition to the classical amyloid beta plaques and hyperphosphorylated plaques, is an important feature of the disease to take into account in assessment of the utility of CSF biomarkers and recent efforts along these lines will be described.