

Control #: 09-HT-2689-ALZ

P4 - Wednesday Posters - Presentation #P4-361; Speaking Time: 7/15/2009 12:30-3:00 PM)

Biomarker Based Diagnosis Of Very Mild Alzheimer's Disease: A Multicenter Study

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Background: Biomarker-supported diagnosis of Alzheimer's disease has been proposed to enhance early clinical detection of AD (Dubois et al., Lancet Neurology, 2007).

Objective: To develop a hypothesis-driven multi-biomarker classification algorithm for the detection of very mild AD.

Methods: A total of 345 subjects including 81 patients with AD diagnosed according to the standard clinical NINCDS-ADRDA criteria, 163 amnesic mild cognitive impairment (MCI) patients and 101 elderly healthy controls (HC) were assessed in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Predictor variables included 1) cerebrospinal fluid (CSF)-concentration and ratios of total tau, p-tau¹⁸¹, and A β ¹⁻⁴² 2) MRI volumetric measures of the left and right hippocampus and entorhinal cortex, and 3) Rey Auditory Verbal Learning test (RAVLT) and ADAS subtest scores of memory. These measures were obtained only for research purposes at baseline. Multiple logistic regression analyses, validated by random-split resampling, were performed.

Results: 50 out of 163 amnesic MCI patients had converted to AD (MCI-AD) after a mean follow-up interval of 1.5 years. Significant neuropsychological predictors were ADAS delayed recall, and RAVLT total-immediate and 30-min.-delayed recall (classification accuracy = 89.9%) for the discrimination between MCI-AD and HC. In combination with these memory tests, unilateral hippocampus volume (left or right) improved differentiation between MCI-AD converters vs. HC most robustly, reaching a resampling validated sensitivity of 88.9% and the specificity of 96.76% (classification accuracy = 94.09%). The optimal cut-off value for the left hippocampus volume in this model was 2929 mm². Cross-validation of the model by application to the classification of HC against AD reached a classification accuracy of 95.69%. The ratio of CSF concentration of total tau/A β ¹⁻⁴² added independently to the prediction accuracy, although less robustly when compared to the hippocampus-only model. Similarly to the CSF-ratio of total tau/A β ¹⁻⁴², a recently in autopsy-confirmed AD and HC cases established AD-biomarker signature including CSF-tau, A β ¹⁻⁴², and ApoE genotype contributed marginally to the left hippocampus volume plus memory model, with the extended model reaching an overall classification accuracy of 95.6%.

Conclusion: A combination of hippocampus volume and episodic memory performance shows a robust and clinically significant diagnostic accuracy of AD at a very early stage.



Control #: 09-A-1275-ALZ

O3-01 - Neuroimaging: Prediction and Early Markers, Presentation #: O3-01-01;

Speaking Time: 7/14/2009, 3:00 - 3:15 PM

Comparing predictors of conversion: Data from the Alzheimer's Disease Neuroimaging Initiative

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Background: A variety of measures (genetic, cerebrospinal fluid (CSF), brain glucose metabolism, gray matter volume) have shown promise in predicting conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD). However, the difficulty of obtaining all measurements in the same subjects has prevented comparisons across candidate predictors. The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a large multisite study designed to improve detection of longitudinal decline in AD and MCI. Here, we compared the utility of baseline measurements for predicting cognitive decline in MCI and conversion from MCI to AD.

Methods: Candidate predictors of decline included hippocampal volume, relative rates of glucose metabolism in a prespecified composite region of interest (FDG-ROI) that included angular, temporal, and posterior cingulate areas; number of apolipoprotein E4 (ApoE4) alleles; and CSF measurement of Abeta42, total tau (t-Tau), and tau phosphorylated in the 181 threonine position (p-Tau181p). Independent and outcome measures were analyzed in continuous and dichotomous forms. Models with dichotomous outcomes assessed conversion from MCI to AD, whereas models with continuous outcomes assessed cognitive decline over 2 years. Analyses were carried out in MCI subjects using all available data (N = 66 to 196 depending on the measure) controlling for age, education, and sex.

Results: 26.1% of MCI patients converted from MCI to AD over 2 years. Low baseline FDG-ROI values predicted both conversion to AD and cognitive decline in all models ($p < 0.03$). In addition, low hippocampal volume, presence of ApoE4 alleles, and p-Tau181p predicted conversion or decline in some models. When all predictor variables were included in a model, only FDG-ROI values significantly predicted conversion ($p = 0.003$).

Conclusions: Low baseline FDG-ROI measurements in MCI subjects reliably predict both conversion to AD and cognitive decline over a 2 year period. Hippocampal volume, ApoE4 status, and CSF biomarkers also appear to play important predictive roles. The addition of more longitudinal data will help elucidate the independent and additive contributions of these baseline measurements to the prediction of disease progression.

Control #: 09-A-2356-ALZ

O3-01 - Neuroimaging: Prediction and Early Markers, Presentation #O3-01-08

Speaking Time: 7/14/2009, 4:45 - 5:00 PM

Hippocampal glucose metabolism predicts cognitive decline and correlates to disease progression in the ADNI population

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Background: Declines in regional cerebral metabolism (rCMglc) measured with Positron Emission Tomography (PET) imaging have been demonstrated to predict and correlate to the progression of Alzheimer's Disease (AD), and to differentiate between dementias. Recent studies have shown that the diagnostic accuracy is improved by including measurement of the hippocampus (HIP) (Mosconi et al, 2005, 2008). However, HIP rCMglc cannot be accurately and practically sampled in broad populations using conventional techniques. An automated method has been developed and demonstrated that achieves accurate, rapid sampling, and optimize sensitivity and specificity without compromise from spatial normalization, smoothing, spillover, and atrophy (Mosconi, 2005). By including HIP rCMglc, highly sensitive and specific differential diagnostic accuracies have been achieved (Mosconi, 2008).

Methods: We applied our automated sampling method to 250 subjects from the ADNI database (78 female, 172 male, age 59 - 88, average 76 years; 79 NL, 111 MCI, 60 AD at initial diagnosis). Using the automated sampling approach, rCMglc was measured in 32 regions of interest in the baseline FDG-PET scans of 250 ADNI subjects. Regions included left and right hippocampi (HIP), amygdala, posterior cingulate cortex, inferior parietal lobes, medial, lateral, and superior temporal lobes, normalized to the cerebellum and age-corrected. Subjects were stratified into 7 subgroups across normal (NL), MCI, and AD categories, based upon initial diagnosis and progressive CDR, GDS scale, and MMSE scores.

Results: We observed a significant correlation between rCMglc in several regions and the clinical progression from stable NL (NL-nonDecl, n=14) to NL with subsequent clinical decline (NL-Decl, n=74, subdivided by extent of decline), to subcategories of MCI (MCI-nonDecl, n=77 and MCI-Decl and mild-AD, n=37) and AD. HIP rCMglc was found to be the most sensitive predictor of decline and discriminator between disease stages. As compared to the stable NL, HIP CMRglc was reduced by 5% in NL-Decl, 12% in stable MCI, 14% in MCI-Decl ($P<0.05$), and 24% in AD ($P<0.001$).

Conclusions: These results demonstrate in a broad population the feasibility of achieving highly specific diagnostic accuracies by incorporating HIP rCMglc, and provide insight to the continuum of decline through which normalcy advances to late stage dementia.