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UNTIL TUESDAY, JULY 14, 2009, 8:30 a.m. (Vienna) / 2:30 a.m. ET (U.S.)

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BRAIN IMAGING (MRI/PET) AND MEASUREMENTS OF PROTEINS IN SPINAL FLUID MAY IMPROVE ALZHEIMER'S PREDICTION AND DIAGNOSIS

New Results from ADNI Data Bring Us Closer to Earlier Detection of Alzheimer's

Vienna, July 14, 2009 – Changes in the brain measured with MRI and PET scans, combined with memory tests and detection of risk proteins in body fluids, may lead to earlier and more accurate diagnosis of Alzheimer's, according to new research reported today at the Alzheimer's Association 2009 International Conference on Alzheimer's Disease (ICAD 2009) in Vienna.

The National Institute on Aging's (NIA) Alzheimer's Disease Neuroimaging Initiative (ADNI), data from which forms the basis of these three studies, is a \$60 million, 5-year, public-private partnership to test whether imaging technologies (such as MRI and PET), other biomarkers, and clinical and neuropsychological assessment can be combined to measure progression toward Alzheimer's. ADNI is the first study to examine a number of candidate Alzheimer's biomarkers in the same individuals. The study is expected to be a landmark for identifying Alzheimer's biomarkers, with data widely available to researchers. ADNI is primarily funded by NIA, part of the National Institutes of Health (NIH), with private sector support through the Foundation for NIH. The Alzheimer's Association is one of the ADNI sponsors.*

A biomarker is a substance or characteristic that can be objectively measured and evaluated as an indicator of normal body processes, disease processes, or the body's response(s) to therapy. For example, blood pressure is a biomarker that indicates risk of cardiovascular disease.

“With the continued aging of the population and the growing epidemic of Alzheimer's, early detection of the disease is crucial for risk assessment, testing new therapies, and eventual early intervention with better drugs, once they are developed,” said Ronald Petersen, PhD, MD, chair of the Alzheimer's Association Medical & Scientific Advisory Council.

“It is widely believed that Alzheimer's disease brain changes, including amyloid plaques and neurofibrillary tangles, begin many years before we see symptoms. It is critical to identify affected individuals while they are still relatively cognitively healthy so that future therapies can preserve healthy memory and thinking function. And, in order to develop those new therapies, we need to identify ‘at risk’ individuals now in order to steer them to clinical trials,” Petersen added.



Petersen is Professor of Neurology; Cora Kanow Professor of Alzheimer's Disease Research; and Director, Mayo Alzheimer's Disease Research Center, Mayo Clinic College of Medicine, Rochester, MN. He is one of the Principal Investigators of ADNI.

Memory Tests and Hippocampal Volume May Accurately Diagnose Early Alzheimer's

Researchers led by Michael Ewers, PhD, senior research fellow at Trinity College Institute of Neuroscience, Trinity College Dublin, Ireland, and Harald Hampel, MD, MSc, Chair of Psychiatry, Trinity College Dublin, identified 345 ADNI participants (81 with Alzheimer's, 163 with amnesic MCI; 101 elderly healthy controls) on whom there was available data including (a) cerebrospinal fluid (CSF) concentration and ratios of Alzheimer's related proteins: total tau, phosphorylated tau (p-tau181), and beta-amyloid (A β 1-42), (b) MRI volume measures of certain sections of the brain, including the left and right hippocampus, entorhinal cortex, and medial temporal lobe, and (c) scores on certain standard memory, learning and brain function tests, including the Rey Auditory Verbal Learning test (RAVL) and the Alzheimer's Disease Assessment Scale (ADAS).

From this data they used statistical methods to identify the best set of predictors that correctly identified (a) healthy people versus those with Alzheimer's, and (b) people with mild cognitive impairment (MCI) who progressed to Alzheimer's (of which there were 50 people in the study who converted over the next year and a half).

"The clinical symptoms of MCI alone are not enough to allow for early diagnosis of Alzheimer's," Ewers said. "In fact, a substantial proportion of people with MCI may revert back to normal or may not develop Alzheimer's for years. Thus, the challenging task is to discern which of people with MCI have the Alzheimer's brain changes that may be responsible for their initial memory and thinking problems and their eventual progression to Alzheimer's, so that they can be targeted for Alzheimer's-specific treatments."

The researchers found that results of three subunits of the memory tests could be combined to reach a classification accuracy of 89.9% for distinguishing people who progressed from MCI to Alzheimer's versus healthy people. They found that by adding in results from MRI volume measurements of the left hippocampus – a brain region closely linked to memory and Alzheimer's – they could increase classification accuracy to 94%. When, as a means to validate the findings, the same set of tests and measures was applied to distinguish the healthy people from those with Alzheimer's, classification accuracy was 95.7%.

When the researchers also included measures of tau and beta amyloid in CSF and presence or absence of a known Alzheimer's risk genotype (ApoE-e4), they could correctly identify people with MCI who progressed to Alzheimer's within 1.5 years with 95.6% accuracy, but the model including only memory tests plus hippocampus was the most robust predictor set.

"Our results show that a relatively simple prediction model, including the combination of hippocampus volume measured by MRI with memory tests, may be able to accurately diagnose Alzheimer's at a very early stage in the disease," Ewers said. "We believe this is the first large-scale, multi-center study to use this variety of biomarker candidates in MCI and Alzheimer's. This diagnostic model needs to be validated in autopsy-confirmed Alzheimer's cases."

Poor Results on PET Brain Measurements and Memory Test Scores Increase Alzheimer's Risk 15 Times for People with MCI

Susan M. Landau, PhD, of the Helen Wills Neuroscience Institute at the University of California, Berkeley, and colleagues used data from 85 ADNI participants with MCI (ages 55–90) to compare the utility of a variety of baseline measurements for predicting decline in MCI and conversion from MCI to Alzheimer's over a two-year period.

Candidate predictors of decline included hippocampal volume measured with MRI; relative rates of glucose metabolism in certain, prespecified brain regions measured with FDG-PET scans; number of apolipoprotein E4 (ApoE4) alleles, which is an Alzheimer's risk gene; CSF measurement of Alzheimer's related proteins, including beta amyloid (A β 1-42), total tau (t-Tau), and tau phosphorylated in the 181 threonine position (p-tau181); and a test of memory recall ability (AVLT). Participants were evaluated at approximately 6 month intervals to determine whether decline to Alzheimer's had occurred. Approximately 17% (1 in 6) MCI patients converted to Alzheimer's disease per year in this study.

The researchers found that low baseline FDG-PET measurements and poor memory recall in people with MCI reliably predicted progression to Alzheimer's over the two year follow up period of the study.

“The novel finding of our analysis is that when we directly compared all the potential predictors to one another, we found that the amount of glucose metabolism, as measured by FDG-PET, and memory recall ability, measured by AVLT total recall, were the most predictive of conversion from MCI to Alzheimer's,” Landau said. “People who did poorly on those two measurements – that is, low glucose metabolism combined with poor memory performance – were 15 times more likely to convert to Alzheimer's compared to individuals who were normal on those measurements.”

“When the measurements are considered individually, p-tau (a CSF protein) and hippocampal volume also significantly predict conversion from MCI to Alzheimer's. Specifically, MCI patients in our study who were low on these measures had a 2 to 4 times higher risk of progressing to Alzheimer's,” Landau added.

Additionally, all measurements (ApoE4 status, hippocampal volume, FDG-PET, CSF biomarkers, and memory recall ability) played a role in predicting cognitive decline, regardless of whether the patients converted to Alzheimer's or not. P-tau181 had the strongest value in predicting subsequent cognitive decline.

According to the researchers, the selection of a biomarker, or set of biomarkers, will be critical in research to select participants who are most likely to experience Alzheimer's over time, and enable these individuals to participate meaningfully in clinical studies, such as those for Alzheimer's drug treatments.

PET Measurements of the Hippocampus May Improve Alzheimer's Diagnosis

According to Dawn Matthews, Chief Executive Officer and President of Abiant, Inc., and colleagues at New York University School of Medicine, declines in regional cerebral glucose metabolism (rCMglc) in the brain as measured with Positron Emission Tomography (PET)

imaging have been demonstrated to correlate to the progression of Alzheimer's, and to differentiate between dementias. Recent studies have shown that the accuracy of Alzheimer's diagnosis may be improved by including measurement of rCMglc in the hippocampus (HIP), a region of the brain that is critical to the formation of new memories. However, according to the researchers, HIP rCMglc cannot be accurately and practically sampled in broad populations using conventional techniques. This is because the hippocampus has an irregular shape and undergoes varying degrees of shrinkage during aging and when affected by disease, such as Alzheimer's. Conventional analysis techniques rely on the ability to align images of each patient's brain to a template brain map, and there is loss of sensitivity and precision due to the difficulty of aligning this irregular shape.

Lisa Mosconi, PhD, and colleagues in the Center for Brain Health at New York University (NYU) School of Medicine, directed by Mony de Leon, PhD, developed and tested an automated method that achieves accurate, rapid sampling of many brain regions, including the hippocampus. Matthews and her team collaborated with NYU to apply the automated method to 250 subjects from the ADNI database (78 female/172 male, age 59-88; 79 healthy, 111 MCI, 60 Alzheimer's). Using the automated approach, rCMglc was measured by PET in 32 brain regions. Participants were divided into seven subgroups across normal, MCI, and AD categories, based upon their initial diagnosis and results of subsequent memory and thinking tests up to 3 years after the scan.

The researchers observed a significant correlation between rCMglc in several brain regions and the progression from "stable normal" to "normal with subsequent clinical decline", to subcategories of MCI and Alzheimer's. They also found that HIP rCMglc was a sensitive predictor of decline and discriminator between disease stages. As compared to people considered "stable normal," HIP rCMglc was reduced by 5% in "normal with subsequent clinical decline", 12% in "stable MCI," 14% in "MCI with subsequent clinical decline" ($p < 0.05$), and 24% in Alzheimer's ($p < 0.001$).

"We found that glucose metabolism levels were highest in the healthy participants who did not decline to MCI, lower in healthy people who later declined, and progressively lower in people with MCI who remained MCI, lower in MCI patients who declined to AD, and lowest in those with Alzheimer's," Matthews said. "These results demonstrate the feasibility of achieving highly specific diagnosis by incorporating glucose metabolism measurements from the hippocampus."

About ICAD 2009

The 2009 Alzheimer's Association International Conference on Alzheimer's Disease (ICAD 2009) brings together more than 5,000 researchers from 60 countries to share groundbreaking research and information on the cause, diagnosis, treatment and prevention of Alzheimer's disease and related disorders. As a part of the Association's research program, ICAD 2009 serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community. ICAD 2009 will be held in Vienna, Austria at Messe Wien Exhibition and Congress Center from July 11-16.

About the Alzheimer's Association

The Alzheimer's Association is the leading voluntary health organization in Alzheimer care, support and research. Our mission is to eliminate Alzheimer's disease through the advancement of research, to provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's. For more information, visit www.alz.org.

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* A list of ADNI sponsors is here: http://www.adni-info.org/index.php?option=com_content&task=view&id=8&Itemid=30

- Michael Ewers, et al - Biomarker Based Diagnosis Of Very Mild Alzheimer's Disease: A Multicenter Study (Funders: Science Foundation Ireland (SFI), the Health Service Executive (HSE), the Health Research Board (HRB) of Ireland, National Institute on Aging, Foundation for the National Institutes of Health, National Institutes of Health, Evelyn F. McKnight Brain Institute of the University of Arizona, State of Arizona and Arizona Department of Health Services, Pfizer, Eisai, Janssen, Novartis, Lilly, Astra Zeneca, Sanofi, Canadian Institutes of health Research, Alzheimer Society of Canada, Michael Smith Health Research Foundation.)
- Susan Landau, et al - Comparing predictors of conversion: Data from the Alzheimer's Disease Neuroimaging Initiative (Funders: National Institute on Aging, ADNI Partnership)
- Dawn C. Matthews, et al - Hippocampal glucose metabolism predicts cognitive decline and correlates to disease progression in the ADNI population (Funder: Abiant, Inc.)

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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

Michael Ewers^{1,2}, Cathal Walsh³, John Q. Trojanowski⁴, Leslie M. Shaw⁵, Philip Sheltens⁶, Arun LW Bokde^{1,2}, Howard Feldman⁷, Gene E. Alexander⁸, Bruno Dubois⁹, Harald Hampel^{1,2}

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Disclosure Block: M. Ewers, None.

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.

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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.

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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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Disclosure Block: D.C. Matthews, Abiant, Employee; Abiant, Stock Shareholder (directly purchased); Abiant, Board Member/Officer; L. Mosconi, Abiant, Consultant; R. Andrews, Abiant, Employee; K. Rickert, Abiant, Employee; W.H. Tsui, None; Y. Li, None; R. Mistur, None; M.J. de Leon, None.

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.

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