Brain imaging and proteins in spinal fluid may improve Alzheimer's prediction and diagnosis

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 or 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 amnestic 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 (Aβ1-42), (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□□) 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 (Aβ1-42), 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