

Scans May Predict AD Before Signs Appear

Technique has potential to fast-forward the search for preventive measures that could stall Alzheimer's.

BY KERRI WACHTER
Senior Writer

WASHINGTON — Hippocampal metabolic reductions seen on PET scans in people with no clinical signs of cognitive impairment may be able to predict who will go on to develop Alzheimer's disease and mild cognitive impairment, according to data presented at an international conference sponsored by the Alzheimer's Association.

Pending further investigation, the technique holds the potential to fast-forward the search for preventive measures—such as new medications—that could hold the disease at bay before it becomes clinically evident.

In a study of 53 people that spanned 24 years, those who eventually progressed from normal cognition at baseline to develop Alzheimer's disease (AD) showed 23% less hippocampal glucose metabolism on baseline fluorodeoxyglucose (FDG) PET scans, compared with a cognitively stable control group. Those who progressed from normal cognition to develop mild cognitive impairment (MCI) showed 11% less hippocampal glucose metabolism, compared with the control group, said Lisa Mosconi, Ph.D., of New York University.

Reduced hippocampal metabolism at baseline predicted progression to AD with 83% sensitivity and 86% specificity—a total accuracy of 85%. Progression to MCI was predicted with 74% sensitivity and 68% specificity—a total accuracy of 71%.

"These numbers are interesting when you consider that the signs of Alzheimer's disease were observed an average of 9 years after baseline, and the signs of MCI were seen 11 years after baseline," said Dr. Mosconi.

Dr. Mosconi and her colleagues followed 53 normal elderly volunteers for 10-24 years. Participants were at least 50 years old at baseline, had at least 12 years of education, and scored at least 28 on the Mini-Mental State Examination (MMSE) and no greater than 2 on the Global Deterioration Scale.

Every 2 years, the volunteers underwent complete clinical, neuropsychologic evaluations. Throughout the study, all participants also underwent at least two PET scans—30 underwent three scans—at least 3 years apart. All images were acquired with the same scanner.

Over the course of the study, 28 participants remained cognitively normal, 19 eventually developed MCI, and 6 developed AD.

Diagnosis of MCI and AD was made by

standard neuropsychologic evaluation.

The three groups (stable normal, normal to MCI, and normal to AD) were similar in terms of gender, education, and MMSE scores. However, the stable normal group was several years younger on average, so the researchers corrected the data for age.

The participants who eventually developed AD lost an average of 4% of their hippocampal glucose metabolism capacity per year, those who developed MCI lost 2%, and the control group lost 1%. The difference between those with AD and the

control group was statistically significant, but the difference between those with MCI and the control group was not.

The diagnoses of two of the patients who progressed from normal cognition to AD were confirmed by post-mortem examination—the most definitive means of diagnosing the disorder. At this examination, hippocampal and cortical volume reductions were observed that were consistent with AD pathology. At baseline, these

two patients had 35% and 15% reduced hippocampal metabolism, respectively, at baseline, compared with the control group.

The PET scans were analyzed using HipMask, a software program developed at the university. To develop this program, the researchers drew hippocampal regions of interest on MRI scans of some study patients (ranging in cognition from normal to AD). The MRI scans (and regions of interest) for each patient were then spatially normalized to the shape of an anatomical brain reference image, which is a custom-made template. The resulting images were then overlaid to produce an image containing only areas of the hippocampus where all of the images overlapped—the HipMask.

"The HipMask is a hippocampal masking image that includes only those portions of the hippocampus where the overlap of the subjects is maximized after size normalization procedures," said Dr. Mosconi. The HipMask was verified against individual MRI scans. On average, 96% of the HipMask represented true hippocampal tissue.

The HipMask was then applied to PET scans—performed within 3 months of the MRIs—to derive estimates of the hippocampal glucose metabolism—a measure of brain activity.

The results also were validated against the standard region-of-interest technique. There was very good correspondence between the HipMask results and the standard technique in all clinical groups, said Dr. Mosconi. ■

The participants' reduced hippocampal metabolism at baseline predicted progression to AD with 83% sensitivity and 86% specificity.

Middle-Aged Obesity Linked To Greater Risk of Dementia

People who are obese or overweight at middle age are at significantly greater risk for dementia in later life than normal-weight people, reported Rachel A. Whitmer, Ph.D., of the division of research, Kaiser Permanente, Oakland, Calif.

The investigators prospectively followed 10,276 people enrolled in the Kaiser Permanente medical program of northern California who were 40-45 years old between 1964 and 1973. At midlife, 10% were obese (BMI of 30 kg/m² or greater), 36% overweight (BMI 25-29.9 kg/m²), and 53% normal weight (BMI 18.6-24.9 kg/m²).

From January 1994 to April 2003, people who were obese at midlife had a 74%

greater risk of dementia, compared with people who had been of normal weight, while overweight people had a 35% greater risk.

In women, the corresponding increases were 107% for obesity and 55% for overweight; no significant differences were found in men.

People in the highest quintile of subscapular skinfold at midlife had a 72% increased risk of dementia, while people in the highest quintile of tricep skinfold had a 59% increased risk of dementia, compared with people in the lowest fifth of the two measures, Dr. Whitmer reported in the April 29 online edition of the British Medical Journal.

—Kevin Foley

Low Plasma β -Amyloid Levels May Be a Marker for Cognitive Decline

WASHINGTON — Plasma levels of β -amyloid may be low in elderly patients at risk for mild cognitive impairment or even Alzheimer's disease in the near term, according to research presented at an international conference sponsored by the Alzheimer's Association.

β -Amyloid is secreted as a 40-amino acid species (A β 40) and a 42-amino acid species (A β 42), both of which are found in the blood and cerebrospinal fluid (CSF). While A β 40 is the most prevalent species, A β 42 forms the plaques that are one of the pathological hallmarks of Alzheimer's disease (AD).

"Our results in this study indicate that the ratio of these two proteins [A β 42:A β 40] is a good biomarker for identifying those normal elderly subjects, who will develop Alzheimer's disease and mild cognitive impairment in the next 3-5 years," said Neill Graff-Radford, M.D., a professor of neurology at the Mayo Clinic in Jacksonville, Fla.

The researchers followed 565 cognitively normal individuals (median age 78 years; 62% female) yearly using the Mattis Dementia Rating Scale (DRS). Patients were followed for 2-12 years (median 3.7 years) after baseline plasma A β 42 and A β 40 levels were measured.

Over the course of the study, 54 individuals converted to AD or amnesic mild cognitive impairment (MCI), as diagnosed using the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Association and Mayo criteria.

The researchers compared baseline A β 42:A β 40 ratios in subjects who developed either AD or MCI with those who did not, after adjusting for age and *apoE* genotype—two risk factors for AD. They found that subjects with A β 42:A β 40 ra-

tios in the lowest quartile had three times the risk of developing MCI or AD, compared with those in the highest quartile.

Subjects with the lowest ratios of A β 42:A β 40 also were significantly more likely to show declined on DRS, even after adjustment for age and apolipoprotein E genotype.

Those with ratios in the lowest quartile developed AD or MCI earlier than those in the other groups, too. Participants in the lowest quartile started developing AD or MCI around 2 years' follow-up, while those with ratios in the next lowest quartile began around 4 years, and those in the upper half began at 6-8 years.

In those older than 80 years and with ratios in the lower half, 20% developed AD in 5 years, compared with 5% of those in the upper half.

"We have pretty convincing evidence and many of us believe that A β 42 is a very important therapeutic target," Dr. Graff-Radford said. High plasma levels of A β 42 have been associated with the early-onset genet-

ic form of AD, Down syndrome, the aging process, and with being a relative of someone with AD. However, low A β 42 levels have been found in the cerebrospinal fluid of patients with MCI or AD. Data from animal models suggest that low plasma and CSF levels may be a consequence of A β 42 deposition in the brain.

A biomarker for the disease could spur research into drugs and other preventive measures.

"To develop preventive therapies for Alzheimer's ... it's essential to have biomarkers related to Alzheimer's that identify the people at risk before they get the disease—kind of like a cholesterol test," Dr. Graff-Radford said.

—Kerri Wachter

'To develop preventive therapies for Alzheimer's ... it's essential to have biomarkers related to Alzheimer's that identify the people at risk.'