Imaging Detects Amyloid in Preclinical Alzheimer's

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

MADRID — PIB-PET imaging not only differentiated patients with mild cognitive impairment and Alzheimer's disease from normal controls, but it also identified amyloid pathology in subjects who did not yet express cognitive symptoms, according to findings from a small study.

The unexpected finding may have a huge effect on two of neurologists' dream goals: to identify patients destined to develop the disorder, and to initiate treatment that would avert or minimize its cognitive consequences, according to speakers at the 10th International Conference on Alzheimer's Disease and Related Disorders.

Dr. Steven T. DeKosky, chairman of the department of neurology at the University of Pittsburgh, used PIB-PET imaging (PET with Pittsburgh Compound B) and a radiotracer known as [18F]FDDNP to examine plaque deposition and the progression of amyloid plaques and neurofibrillary tangles in 59 subjects, of whom 14 had mild cognitive impairment (MCI), 14 had confirmed Alzheimer's disease, and 31 were age-matched controls. Both compounds bind to amyloid A, allowing scans to track the progression of plaques and neurofibrillary tangling in the brain.

The scan successfully separated Alzheimer's patients from controls with no overlap. The patients had about twice the amyloid deposition.

The differentiations between subjects with MCI and controls—as well as between MCI subjects and Alzheimer's patients—were not as clear-cut, however. "About 25% of our controls actually had some plaque binding, and 60% of our MCI subjects already had enough binding to put them in the Alzheimer's category," Dr. DeKosky said.

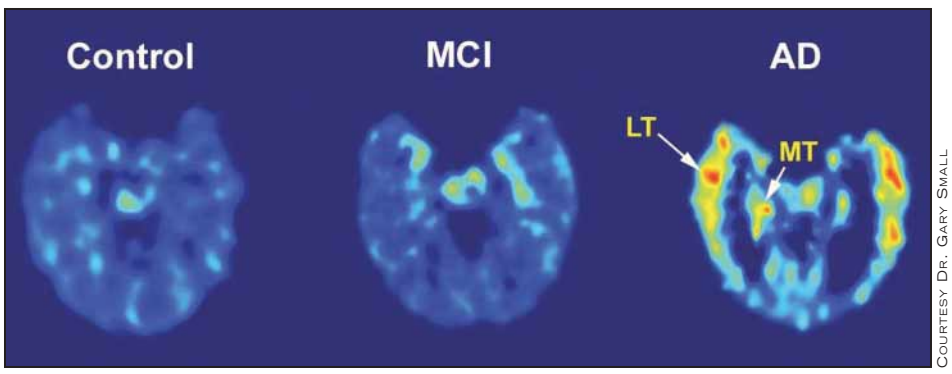
The scans clearly separated the groups, with no overlap between the controls and the Alzheimer's patients.

DR. SMALL

Interestingly, the amyloid burden in MCI subjects didn't necessarily correlate with cognitive function, Dr. DeKosky noted. "We had one MCI subject with very high binding but a very good Mini-Mental State [Examination] score, and one MCI subject who had very low binding, nearer to control levels, who had a very poor MMSE."

Dr. Gary Small, director of the memory and aging research center at the University of California, Los Angeles, used [18F]FDDNP not only to differentiate normal brains from those with MCI and Alzheimer's disease, but also to track the progression of the disorder.

His study involved 60 subjects (mean age 71 years): 20 controls, 20 with MCI, and 20 with Alzheimer's disease. All of the subjects received an [18F]FDDNP PET scan, and 12 had repeat scans 2 years later.



COURTESY DR. GARY SMALL

These PIB-PET images show FDDNP binding to amyloid plaques in normal, MCI, and Alzheimer's brains. Arrows show lateral temporal and mediotemporal lobes.

The scans clearly separated the groups with no overlap between the controls and the patients with Alzheimer's disease. But 60% of those with MCI had amyloid binding in the mediotemporal lobe that was of similar volume to that seen in Alzheimer's patients. "We also saw that some controls were beginning to show amyloid buildup in this area," Dr. Small said.

Follow-up scans were performed 2 years later on eight controls and four MCI subjects. Amyloid binding was stable in those who remained cognitively stable. But in those who declined cognitively—that is, going either from normal to MCI status, or from MCI to Alzheimer's disease—amyloid binding increased 5%-11% compared with their baseline scan.

The main difference between the compounds—as both are highly accurate in distinguishing the populations—seems to be the length of their activity, Dr. Small said: [18F]FDDNP has a 2-hour half-life, whereas the half-life of PIB is only 20 minutes.

The current lack of a sensitive and accurate diagnostic method greatly impedes both treatment and research, said Dr. Ronald Petersen, who moderated a press conference at the meeting, which was presented by the Alzheimer's Association.

"Tests that would track the progression of the disease would help us treat people earlier and greatly speed testing of new drugs in treatment trials," said Dr. Petersen, a spokesman for the association. " Imaging may be the solution, because it can help us look inside the brain and body to diagnose the disease, monitor progression, and track the effects of therapy," he said. ■

Overhaul Proposed for Alzheimer's Disease Diagnostic Criteria

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

MADRID — A set of newly proposed criteria could bring the diagnosis of Alzheimer's disease into the 21st century by shifting the focus from one based on loss of function toward one that incorporates measurable disease-induced biochemical and structural changes.

For a diagnosis of Alzheimer's disease (AD), the proposed criteria would require presence of an objective confirmed episodic memory disorder plus at least one of the following: a structural abnormality, probably atrophy of the mediotemporal lobe as seen on magnetic resonance imaging; a characteristic biochemical marker obtained from cerebrospinal fluid (CSF); or functional brain impairment as seen on positron emission tomography or single photon emission computed tomography.

The criteria were proposed by the International Working Group on Diagnostic Criteria for Mild Cognitive Impairment/ Alzheimer's Disease and were unveiled at the 10th International Conference for Alzheimer's Disease and Related Disorders.

Implementation will require years of testing across all stages of the disease. But the proposed criteria eventually could be a reliable way of distinguishing patients with AD from those with mild cognitive impairment (MCI) and other memory disorders, said Dr. Howard Feldman of the University of British Columbia's Clinic for Alzheimer's Disease and Related Disorders, Vancouver.

"We now diagnose dementia largely based on functional impairments," Dr. Feldman said. "One of the flaws with this is that it's not clear that function has a real neurobiological correlate, and it's difficult to put everyone on the same plane functionally."

However, recent advances regarding the clinical, structural, pathologic, and biochemical hallmarks of dementia can serve as the basis for a much more targeted diagnostic method, he said. "It's time to package these into a new set of criteria that work in mild, moderate, and advanced stages of the disease as well as in the prodromal stage." The cornerstone of the proposed criteria is the requirement for an episodic memory disorder, which must be gradual, progressive, and of at least 6 months' duration.

Tests of delayed recall are the best at distinguishing cognitively normal patients from those with MCI who will progress to AD, Dr. Feldman said. "It's imperative that we have a test that will allow for controlled encoding, a very important dimension of the impaired episodic memory in Alzheimer's." These types of tests, including the delayed recall and double memory tests, differentiate between the memory storage or encoding problems, which are characteristic of AD, and problems involving memory retrieval.

The medial temporal structural assessment could either be done qualitatively, on the hippocampus, choroidal fissure, or temporal horn, or quantitatively on hippocampus, entorhinal cortex, or parahippocampal gyrus. "Studies suggest good sensitivity and specificity for AD and normal patients, and good discrimination of those who will progress from MCI."

The proposed biochemical criterion would involve CSF measures of amyloid β1-42, total tau, or phospho tau. Finally, the functional brain scanning criterion on PET would show diminished glucose metabolism in the bilateral temporoparietal regions and posterior cingulate.

More research will be necessary to further hone each criterion, Dr. Feldman said. "We need to deal with the extent of abnormality each one would measure, and find cutoff points and specific instruments for each." ■

Funding for Imaging Studies in Dementia

The Alzheimer's Disease Neuroimaging Initiative—a 5-year study looking at imaging technology to improve early diagnosis and gauge the effectiveness of treatments—got a $2.1 million boost last month from the Alzheimer's Association.

Officials at the association had previously granted $1 million to help fund this $60 million public-private initiative launched by the National Institute on Aging in 2004.

The project is aimed at testing whether serial magnetic resonance imaging, positron emission tomography, biologic markers, and clinical and neuropsychological assessments can be used together to measure the progression of mild Alzheimer's disease and mild cognitive impairment.

Researchers also will evaluate the use of PET scans with Pittsburgh Compound B (PIB). "PET/PIB technology will be a valuable addition to the study," Dr. Samuel Gandy, chair of the Alzheimer's Association's Medical and Scientific Advisory Council, said in a statement. Patients are currently being recruited for the study. For more information, check www.nia.nih.gov/Alzheimers/ResearchInformation/ClinicalTrials/ADNI.htm.

—Mary Ellen Schneider