Blood Test for Alzheimer's Undergoing Final Evaluation

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CHICAGO — A simple blood test could soon allow clinicians to diagnose Alzheimer's disease accurately.

In an initial study of 88 patients, the test findings agreed with expert clinical diagnosis more than 90% of the time and had an overall accuracy of 97%. If the validation study confirms this, the test could be on the market by mid-fall, Dr. Louis Kirby said at the International Conference on Alzheimer's Disease.

An easy blood test that would diagnose early Alzheimer's could have enormous impact, said Dr. Kirby, whose company, Provista Life Sciences, owns the patent.

The test, to be marketed as LymPro, assumes that lymphocytes mirror a unique neuronal cell-cycle dysregulation seen in Alzheimer's patients, Dr. Kirby said at the meeting presented by the Alzheimer's Association. "Normally, neurons divide and mature, and then remain active for decades without dividing again. A great deal of relatively new research suggests that in Alzheimer's disease, neurons prepare to reenter the cell division process in an abnormal fashion."

Neurons that undergo this change proceed almost to mitosis but are then unable to redifferentiate. Researchers have concluded that the neurons then either die or produce Alzheimer's pathology (research summary—Biochim. Biophys. Acta 2007;1772:413-21).

Research also suggests that peripheral lymphocytes in Alzheimer's patients display a similar cell-cycle defect when exposed to a mitogenic stimulus, Dr. Kirby said. A 2001 study found that these lymphocytes were less able to express CD-69, a marker of white cell growth and proliferation, than lymphocytes from control patients. In fact, this study found that the expression of CD-69 inversely correlated with the level of dementia as measured by the Mini-Mental State Examination score (Neuroreport 2001;12:3969-72).

Dr. Thomas Arendt, of the University of Leipzig (Germany), was the lead investigator on many of these studies. He developed the LymPro test and has licensed the technology to Dr. Kirby's Arizona-based company.

Dr. Kirby's initial study included 88 patients: 32 with probable Alzheimer's disease, 26 with Parkinson's dementia, and 30 cognitively intact controls. All diagnoses were based on clinical testing and observation by dementia experts.

After applying a mitogenic stimulus to the peripheral lymphocytes in each blood sample, researchers could reliably differentiate between controls, Alzheimer's, and Parkinson's patients based on variations in the CD-69 levels, Dr. Kirby said. The test had 91% sensitivity and a 92% specificity, with an overall accuracy of nearly 97%.

And, Dr. Kirby said, since the blood test score correlated with the level of dementia on the Mini-Mental State Examination, "We have confidence that we should be able to dial back the diagnosis into the mild cognitive impairment stage, and—hopefully—even into the preclinical state." ■

Antibody May Dissolve Amyloid Brain Plaques

CHICAGO — An investigational monoclonal antibody may dissolve amyloid brain plaques in patients with Alzheimer's, though patients receiving it had no signs of improved cognition.

Dr. Eric Siemers, who presented the data from the trial, sponsored by Eli Lilly & Co., at the International Conference on Alzheimer's Disease, said the lack of cognitive improvements didn't trouble him. The 12-week period was probably too short to show any cognitive changes, said Dr. Siemers, medical director of Lilly's Alzheimer's Disease Research Team.

The vaccine (LY2062430) was safe for the Alzheimer's patients and healthy volunteers who received it, Dr. Siemers said. There were no infusion reactions or drug-related adverse events.

The study comprised 52 patients with mild-moderate Alzheimer's (mean Mini-Mental State Exam score 20) and 16 healthy volunteers. Patients were randomized to placebo or to one of four antibody infusions: 100 mg every 4 weeks, 100 mg every week, 400 mg every 4 weeks, or 400 mg every week. Volunteers got one 100-mg dose.

All patients underwent magnetic resonance imaging and blood and cerebrospinal fluid (CSF) sampling to determine the level of soluble amyloid β. A subgroup of 24 patients and 13 volunteers also underwent single-photon emission computed tomography (SPECT) to determine cortical amyloid plaque load. Cognitive status was assessed by the Alzheimer's Disease Assessment Scale–Cognition (ADAS-cog).

CSF and blood samples showed that the antibody affected levels of both $A\beta_{40}$ (a less-neurotoxic protein) and $A\beta_{42}$ (the toxic form in AD brain plaques) in a dose-dependent manner. Patients on the 400-mg/wk dose had a significant decrease in $A\beta_{40}$ but a significant increase in $A\beta_{42}$, suggesting the brain plaques were dissolving.

"Additionally, after treatment, we found correlation between β amyloid in the blood and the amount of amyloid plaque in the brain as determined by imaging, as well as the increase in blood and CSF of certain types of β amyloid found in plaques. These biomarker data suggest that the plaques in the brain may begin to dissolve after 12 weeks of treatment."

A phase III trial will begin in 2009. The meeting was sponsored by the Alzheimer's Association. ■

Methylphenidate Cut Patient Apathy, Eased Caregiver Distress in Small Prospective Trial

CHICAGO — Methylphenidate appears to improve the symptoms of apathy in patients with early Alzheimer's, benefiting both patients and caregivers, according to the results of a small prospective trial.

After taking the drug for 12 weeks, patients in the study showed significantly reduced frequency and severity of apathy, while their caregivers reported significantly reduced distress, Dr. Prasad Padala said at the International Conference on Alzheimer's Disease.

"Apathy is the most common behavioral and psychiatric symptom of dementia, occurring in up to 90% of patients, and it's one of the earliest symptoms to appear," said Dr. Padala of the University of Nebraska Medical Center, Omaha.

"Apathy also causes the caregivers a lot of stress, and it has a very high impact on functional status. Patients with apathy are three times more likely to be dependent on caregivers for their activities of daily living than are patients without apathy."

It's thought that dysregulation of both the dopaminergic and noradrenergic systems contribute to apathy, Dr. Padala said. Because of this presumed etiology, he and his colleagues decided to investigate the use of methylphenidate in the disorder. The drug works on both of these systems.

The study enrolled 20 patients (mean age 70 years) at the Veterans Affairs Medical Center in Omaha. All had early Alzheimer's disease, with a mean Mini-Mental State Examination score of 23. Every patient had a score of greater than 30 on the Apathy Evaluation Scale; on this 72-point scale, anything above 30 is considered significant apathy.

At baseline, patients were assessed with the Neuropsychiatric Inventory's apathy subscale, which scores apathy on a 1- to 4-point scale for frequency and on a 1- to 3-point scale for severity. The score is a product of the ratings for frequency and severity. Caregivers rate their distress on a 1-5 scale, with 5 being the greatest.

Patients were started on 5 mg methylphenidate twice daily, and titrated up to 10 mg twice daily. Follow-up visits were conducted at 4, 8, and 12 weeks. After 12 weeks of treatment, patients significantly improved in their total item score from baseline (5 vs. 1.6), as well as their frequency/severity score (9 vs. 2). Caregiver distress also improved significantly, decreasing from 3.25 to 1. Other neuropsychiatric measures improved significantly as well, including the score on the Apathy Evaluation Scale, the Instrumental Activities of Daily Living Scale, and the Clinical Global Impressions–Severity subscale.

"Caregivers noted substantial improvements in the patients, such as increased energy, spontaneity, motivation, and ambition," Dr. Padala said at the meeting sponsored by the Alzheimer's Association.

Two patients needed reductions in methylphenidate dosing: one because of loss of appetite and the other because of an increase in blood pressure. With this drug, as with many stimulants, an increase of 2-4 mm Hg in systolic blood pressure is not uncommon, Dr. Padala said. One patient developed a hacking cough that resolved spontaneously.

Dr. Padala is now conducting a 60-patient randomized, placebo-controlled trial.

He said he had no financial disclosures. ■

Continuous IVIG Stabilized Cognition

CHICAGO — Continuous infusions of immunoglobulin for 9 months stabilized cognition and function for Alzheimer's patients in a small placebo-controlled trial.

The 18-month-long phase II study included 24 patients with mild to moderate Alzheimer's. For the first 6 months, they were randomized either to placebo or to one of four intravenous immunoglobulin (IVIG) doses. For the remaining 12 months, all participants were switched to IVIG, but raters were still blinded to the dosing, said Dr. Norman Relkin, who presented the study's 9-month results at the International Conference on Alzheimer's Disease.

Patients who had received IVIG continuously for 9 months showed significantly better scores on measures of cognition and activities of daily living than did those taking placebo. When the IVIG arms were analyzed by dose, 0.4 g/kg of body weight every 2 weeks provided the best results in global functioning, cognition, and activities of daily living, Dr. Relkin said at the meeting, sponsored by the Alzheimer's Association.

Planning for a larger, phase III trial is underway; it is to be conducted at 35 academic centers in the United States.

Dr. Relkin of Cornell University, New York, coauthored another study that found that improvements in Alzheimer's patients treated with IVIG lasted only as long as the treatment continued. During the first 6 months of an 18-month trial, patients on IVIG gained a mean of nearly three points in the Alzheimer's Disease Assessment Scale for Cognition (ADAS-cog). In a 3-month washout, they lost almost all gain and did not recoup it when IVIG resumed over the next 9 months (doi:10.1016/j.neurobiolaging.2007.12.021).

The trial was cosponsored by Baxter International Inc. Dr. Relkin has financial ties to Baxter. ■