Biomarker Could Track Alzheimer's Progression

BY JAMES BUTCHER
Contributing Writer

SALZBURG, AUSTRIA — The investigational Pittsburgh B compound that binds to cerebral β-amyloid and is visible on positron emission tomography maintains its promise as a way to distinguish the elderly patients presenting with memory problems who will go on to develop Alzheimer's disease from those who won't progress.

A series of presentations at an international conference on Alzheimer's and Parkinson's diseases suggested that the ligand Pittsburgh B (PIB) compound, although still at the research stage, may also prove to be an invaluable biomarker to track disease modification in clinical trials.

Kerryn Pike, a research officer at Austin Health, Melbourne, presented the results of a study that examined the relationship between amyloid burden and cognitive function.

The researchers studied 108 individuals with varying degrees of cognitive impairment: 38 of the participants were healthy aging controls (mean Mini Mental State Examination [MMSE], 29.1), 34 had mild cognitive impairment (mean MMSE, 26.3), and 36 had mild Alzheimer's disease (mean MMSE, 22.1).

The average age of the participants was 72 years, and there was no significant difference in age among the three groups.

All the individuals were given neuropsychological tests, including the MMSE, California verbal learning test second edition, Rey complex figure test, digit span, verbal fluency, Boston naming test, and digit symbol coding tests.

The researchers calculated a composite episodic memory score and a composite nonmemory cognition score from these neuropsychological tests for each participant.

The participants also had a PET scan after being given an intravenous dose of the radiotracer ^{11}C-PIB. A "positive" PIB test was noted in 26% of the 38 healthy aging controls, 59% of the 34 patients with mild cognitive impairment (MCI), and 97% of the 36 patients with Alzheimer's disease (AD), suggesting that they had amyloid deposited in their brains. "About a quarter of healthy elderly are known to have amyloid plaques at autopsy," noted Ms. Pike.

Two of the MCI patients have gone on to develop AD, and the researchers plan to follow up the cohort over the coming years.

Individuals with MCI who had a positive PIB test did much worse in the neuropsychological memory tests than did participants with MCI who were negative for amyloid deposition (–2.95 standard deviations from control values vs. –1.1 standard deviations). "This suggests to us that amyloid deposition is a very early pathological process that affects memory specifically," said Ms. Pike.

Indeed, those people with mild cognitive impairment who were PIB positive did almost as badly in the memory tests as did the patients with Alzheimer's disease (–3.22 standard deviations from control values). The researchers found a correlation of 0.72 between amyloid load and memory score.

In addition, participants with MCI who were PIB positive were significantly older than the PIB-negative participants (73.6 years vs. 66.1 years) and the 6 nonamnestic MCI participants were significantly younger than the 28 amnestic MCI participants (mean 63.7 years vs. 71.9 years).

"All our nonamnestic MCI participants were PIB negative, and this suggests to us that they have different underlying pathology such as frontotemporal dementia, which doesn't have amyloid plaques," said Ms. Pike.

In a separate presentation, Dr. David Brooks, professor of neurology at Imperial College School of Medicine, London, presented data from a case series of 13 patients with dementia with Lewy bodies (DLB) and 13 patients with Parkinson's disease dementia (PDD) who were imaged using PIB.

The patients with DLB had a mean MMSE of 21, compared with 20 in the patients with PDD. The mean Unified Parkinson's Disease Rating Scale score was 31 in the patients with DLB and 35 in the patients with PDD.

Amyloid levels were raised in 11 of the 13 patients with DLB, although those levels were not as high as those seen previously in patients with AD. By contrast, only 2 of the 13 patients with PDD showed an increased amyloid burden, suggesting that PIB could potentially be used in the differential diagnosis of PDD and DLB. ■

Evidence-Based Medicine Does Not Support Cholinesterase Inhibitor Use

BY DOUG BRUNK
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CARMEL, CALIF. — The evidence for using cholinesterase inhibitors in patients diagnosed with Alzheimer's disease "is pretty darned poor," Dr. Laura Mosqueda said at the Western regional meeting of the American Federation for Medical Research.

She based her remarks on two recent meta-analyses of the topic. The first was a systematic review of randomized clinical trials of the cholinesterase inhibitors donepezil, rivastigmine, and galantamine.

In a search of the Medline, Embase, and Cochrane databases, researchers led by Dr. Hanna Kaduszkiewicz of Hamburg, Germany, evaluated 412 references published between 1989 and 2004 (BMJ 2005;331:321-7). Of these, 22 were included in the study.

In the 14 trials that used the Alzheimer's disease assessment scale–cognitive subscale, the mean difference between treatment and placebo groups ranged from 1.5 points to 3.9 points, which is a modest effect at best, said Dr. Mosqueda, director of geriatrics and a professor of family medicine at the University of California, Irvine.

In the 12 trials that used the Clinician's Interview-Based Impression of Change scale with caregiver input, the mean differences ranged from 0.26 to 0.54, "which is below what you're even allowed to score on the test," she said, explaining that the rater is allowed to use only whole integers.

The incidence of adverse effects from the medications was 20% among those in the treatment group and 7% among those who took placebo. The most common adverse events were nausea, vomiting, diarrhea, and weight loss.

"How many times have we had somebody who comes in with Alzheimer's disease, they're losing weight and going through a major work-up, only to realize that they're on donepezil, and that this may be the cause of the weight loss?" Dr. Mosqueda asked.

Sometimes you can spend your time prescribing instead of talking about issues related to AD.

DR. MOSQUEDA

She also highlighted a more recent Cochrane Review that was led by Dr. Jacqueline Birks of the University of Oxford (England). It was a meta-analysis of studies that also involved the cholinesterase inhibitors donepezil, rivastigmine, and galantamine (Cochrane Database Syst. Rev. 2006; DOI: 10.1002/14651858.CD005593).

It concluded that although these three cholinesterase inhibitors are modestly efficacious for mild to moderate Alzheimer's disease, there are no differences among them in terms of efficacy, even though the three drugs work in slightly different ways.

Despite the paucity of data showing efficacy, one factor that motivates physicians to prescribe cholinesterase inhibitors for Alzheimer's patients is the sense that they "really want to do something" for patients and their families, Dr. Mosqueda said.

"It's much faster to write that prescription than to sit down, review the evidence, and go over the pros and cons with the patient and family. That takes time to do, but I think it's so important for people to understand, so that they can make an informed decision."

Medication cost is a downside for some patients who have to pay out of pocket for cholinesterase inhibitors. Dr. Mosqueda noted that for families faced with making a financial decision between paying for a cholinesterase inhibitor prescription and enrolling their loved one in an adult day care program, "that adult day care program is much more efficacious. Other, more important issues may not be addressed [with the medication alone]. Sometimes you can spend your time prescribing medicines instead of talking about other issues related to Alzheimer's disease."

She concluded by saying that cholinesterase inhibitors "are nice, but all of us need comfort, identity, joy, and a big dose of love. That goes a long way when we're caring for people who have Alzheimer's disease and their families. Cholinesterase inhibitors may or may not be an adjunct to that." ■

Herpes Simplex May Play a Role in Some Alzheimer's Cases

SALZBURG, AUSTRIA — Herpes simplex virus-type 1 may be the root cause of some cases of Alzheimer's disease, according to research presented at an international conference on Alzheimer's and Parkinson's diseases.

Dr. Matthew Wozniak and Dr. Ruth Itzhaki of the University of Manchester (England) found that human neural cells infected with HSV-1 had contained far more amyloid β than had uninfected cells. "We've examined both neuronal and glial cells, and the increase occurs in both cell types," said Dr Wozniak.

HSV-1 causes several diseases, including cold sores and herpes simplex encephalitis. Most humans are infected, usually in infancy, and in some the virus is woken from its dormant phase in times of stress.

Previously, researchers from Dr. Itzhaki's laboratory demonstrated that HSV-1 DNA is present in brain tissue and that antibodies to the virus can be found in the cerebral spinal fluid in a high proportion of patients with Alzheimer's disease (AD) and elderly patients who do not show signs of the disease (J. Med. Virol. 2005;75:300-6). The study included 27 AD patients and 13 age-matched controls. Importantly, these same markers are generally absent in the brains of younger people.

Subsequently, the researchers increased the study population to 61 AD patients and 48 age-matched controls (Lancet 1997;349:241-4). They found that HSV-1 DNA in the brain and possession of an apolipoprotein E-α4 allele is a strong risk factor for AD (odds ratio 12).

More recently, the researchers demonstrated that HSV-1 infection decreases the concentration of full length amyloid precursor protein, Dr. Wozniak explained.

"A role for HSV-1 in AD points to the use of antiviral agents as a treatment for the symptoms of the disease," he suggested.

—James Butcher

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