Possible Biomarker for Preclinical AD Found

BY MARY ANN MOON
Contributing Writer

Cerebrospinal fluid levels of amyloid-beta 42 may be a biomarker for the early, asymptomatic phase of Alzheimer's disease—a long-awaited leap forward in the quest for preclinical diagnosis, reported Dr. Elaine R. Peskind of the University of Washington, Seattle, and her associates.

Adults who carry the apolipoprotein E4 allele but are cognitively normal show a marked decline in cerebrospinal fluid (CSF) levels of amyloid-beta 42 ($A_{\beta42}$), presumably because the protein is precipitating out of the CSF and being deposited in plaques within the brain parenchyma, Dr. Peskind and her colleagues noted.

This decline of $A_{\beta42}$ in cerebrospinal fluid appears to begin in early adulthood and to rapidly accelerate between the ages of 50 and 60 years in apo E4 carriers, long before clinical manifestations of Alzheimer's disease (AD) typically appear.

The finding bolsters the theory that $A_{\beta42}$ deposition in the brain is a key initiating factor in the pathogenesis of AD, the researchers said. The findings may also point the way to new therapies and preventive strategies (Arch. Neurol. 2006;63:936-9).

Dr. Peskind and her associates assessed both the apo E genotype and CSF concentrations of $A_{\beta42}$ in 184 healthy adults aged 21-88 years. The 94 men and 90 women had normal cognition and function. Those with the apo E allele not only had lower levels of $A_{\beta42}$, but their levels also declined in a linear fashion as age increased. CSF levels also dropped off precipitously between the ages of 50 and 60 years. In contrast, subjects who did not carry the apo E4 allele showed a slight rise in $A_{\beta42}$ levels until age 50 and then a slight and slow decline afterward.

Further research is needed, but researchers and clinicians should note that "therapeutic strategies aimed at prevention of AD may need to be applied in early midlife or even younger ages to have maximal effect on amyloid deposition," the researchers concluded.

In an editorial, Dr. Roger N. Rosenberg of the University of Texas Southwestern Medical Center, Dallas, said the findings suggest that treatment should target "soluble A_{β} and tau levels rather than insoluble plaques and tangles" (Arch. Neurol. 2006;63:926-8).

The "plaques and tangles that have captivated our visual attention for a century may not be the key targets for effective therapies after all," said Dr. Rosenberg. ■

New Dementia Risk Score Targets Modifiable Factors

BY BRUCE K. DIXON
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Advancing age, limited education, high cholesterol levels, high blood pressure, and obesity at midlife are significantly associated with the later development of dementia, according to findings from a 20-year follow-up study.

A new, simple dementia-risk prediction tool may allow for the earlier detection of the disease based on these midlife factors, Miia Kivipelto of the Karolinska Institute in Stockholm and colleagues reported in the Lancet Neurology (Epub ahead of print: doi 10.1016/S1474-4422(06)70537-3).

The detection technique highlights the role of vascular factors in the development of dementia "and could help to identify individuals who might benefit from intensive lifestyle consultations and pharmacological interventions," they said.

Data were derived from the population-based Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study, in which 1,409 patients were studied in midlife and reexamined 20 years later; 4% were diagnosed with dementia.

Future dementia was associated with age 47 or older, less than 10 years of education, systolic blood pressure over 140 mm Hg, high cholesterol levels greater than 6.5 mmol/L, and obesity (body mass index over 30). In a second model that factored in apolipoprotein ε4 status (carriers vs. noncarriers), age and education became more predictive and cholesterol less so.

Potential risk factors not examined in this study include a family history of dementia, serum triglyceride levels, concentrations of high- and low-density lipoproteins, waist-to-hip ratio, and diabetes (insulin resistance). "There is much evidence that diabetes is associated with an increased risk of dementia, and thus its inclusion in future risk scores is important," the investigators explained, adding that further research is needed to validate the dementia risk score. ■

ALTERNATIVE MEDICINE
AN EVIDENCE-BASED APPROACH

Huperzine A for Alzheimer's Disease

History of Use

Extracts of the club moss *Huperzia serrata* have been used for centuries in traditional Chinese medicine to treat conditions including inflammation, fever, and schizophrenia. Plants such as this one from the lycopod family existed as far back as 400 million years ago, according to fossil records. The plant's names in Chinese are qian ceng ta, "thousand-laid pagodas" (referring to its multileafed structure), and jin bu huan, "more valuable than gold" (Pharmacol. Biochem. Behav. 2003;75:675-86).

► *Extracts of the club moss* Huperzia serrata *have long been used in traditional Chinese medicine as a remedy for various ailments including inflammation and schizophrenia.*
► *Clinical trials in China have shown benefits in dementia, and a phase II study sponsored by the National Institutes of Health is currently investigating the compound for the treatment of Alzheimer's disease.*

The plant is approved for the treatment of Alzheimer's disease in China, and is sold as a dietary supplement in the United States. The process of extraction was made publicly available in 1986 but is not patented, so neither pharmaceutical nor supplement manufacturers have thus far been willing to invest in the clinical studies that would be needed for Food and Drug Administration approval.

Rationale for Use

Huperzine A is a potent, selective, reversible inhibitor of acetylcholinesterase. In vitro studies have shown that huperzine A's acetylcholinesterase-inhibiting activity exceeds that of tacrine and galantamine, and animal studies have found that the compound has greater bioavailability and crosses the blood-brain barrier more easily than tacrine or donepezil (Curr. Med. Chem. 2000;7:355-74).

It also is selective for brain acetylcholinesterase, rather than peripheral acetylcholinesterase, which limits its potential for cholinergic adverse effects. Other properties of huperzine A include protection against oxidative stress, which is thought to be involved in the progression of Alzheimer's disease, and regulation of apoptotic proteins.

In an animal model, it also showed protective effects against transient cerebral ischemia and reperfusion (Pharmacol. Biochem. Behav. 2006;83:603-11).

Furthermore, the compound helps prevent glutamate-induced neuronal cell death, a capacity that has led to its use not only in Alzheimer's disease but also as a prophylactic agent against organophosphate nerve gases such as soman (Neurotoxicology 2002;23:1-5).

The Chinese Experience

Most of the clinical studies involving huperzine A have taken place in China. In one randomized trial at the Zhejiang Supervision and Detection Station of Drug Abuse, Zhejiang Medical University, Hangzhou, China, 103 patients with DSM III-R diagnoses of Alzheimer's disease received 200 µg of huperzine or placebo orally twice daily for 8 weeks.

On multiple evaluations including the Wechsler memory scale, Mini-Mental State Examination (MMSE), and Hasegawa dementia scale, 29 (58%) of the huperzine-treated patients showed significant improvements in memory as well as in cognitive and behavioral functions, compared with 19 (36%) of placebo-treated patients (Zhongguo Yao Li Xue Bao 1995;16:391-5). The average improvement in the huperzine-treated group on the MMSE was 3 points, compared with an improvement of 0.4 points in the placebo group.

Diarrhea, anorexia, and hyperactivity each were reported in about 10% of patients receiving both active and placebo treatment.

Another study conducted in 15 centers in China randomized 202 patients with possible or probable Alzheimer's disease initially to receive 100 µg huperzine twice daily or placebo. Dosages were adjusted up to 200 µg twice daily according to patient response.

A total of 37.8% of patients in the huperzine group improved by 4 points or more on the MMSE, compared with 10.1% in the placebo group. Improvements of 10% in activities of daily living were seen in 32.7% of those on the active treatment, compared with 17.2% of those receiving placebo. Positive effects on symptoms of depression, delusions, and repetitive activities also were seen (Zhonghua Yi Xue Za Zhi 2002;82:941-4).

The NIH Trial

In the first trial outside of China, the National Institute on Aging currently is conducting a phase II clinical trial evaluating huperzine A in doses of 200 µg or 400 µg twice a day among patients with Alzheimer's disease. The aims of the study are to determine if huperzine improves cognitive function, global clinical status, activities of daily living, and behavior, and to evaluate the tolerability of the supplement. Additionally, the study is investigating the relationship between blood cholinesterase activity and cognitive function.

In an interview, principal investigator Dr. Paul Aisen said, "We think it's a very promising treatment for Alzheimer's disease. Based on our work so far and the Chinese literature, we hope this will be more effective and better tolerated than existing treatments. We're optimistic."

Dr. Aisen, professor of neurology and medicine and director of the memory disorders program at Georgetown University, Washington, said that he and his colleagues confirmed the compound's safety and its "excellent" cholinesterase inhibition in phase I tests. He added that laboratory tests have shown that huperzine exhibits N-methyl-d-aspartate antagonism similar to that shown by memantine, and that it appears to have some very promising neuroprotective activities.

The trial has enrolled 124 patients, with a goal of 150.

"My view is that with any treatment, no matter how promising, you have to do carefully controlled blinded studies, and that's what we're doing here," Dr. Aisen said. Clinicians and patients interested in the study can call 202-687-3355.

Participants must be aged 55 or older, have a diagnosis of mild to moderate Alzheimer's disease, and not be taking any of the drugs currently licensed for use in dementia.

—Nancy Walsh