Protein Levels Correlated With AD Progression

BY MARY ANN MOON

FROM THE ARCHIVES OF GENERAL PSYCHIATRY

Elevated plasma levels of a protein called clusterin appear to correlate with the degree of brain atrophy, the severity of symptoms, and the speed of the clinical progression of Alzheimer's disease, a report shows.

Moreover, clusterin levels appear to rise well before symptom onset or amyloid-beta deposition is noted in the seemingly healthy brains of older patients who go on to develop Alzheimer's disease.

Raised plasma clusterin concentrations were seen 10 years before amyloid-beta deposition, suggesting that clusterin plays an etiopathological role, and is not simply a reaction to other pathology in Alzheimer's disease (AD), according to Dr. Madhav Thambisetty, who was at the King's College Institute of Psychiatry, London, when he conducted the study with his associates. He is now with the Laboratory of Personality and Cognition in the Intramural Research Program at the National Institute of Aging, Bethesda, Md.

The findings do not endorse plasma clusterin level as a stand-alone biomarker for AD. "There may well be other proteins in plasma related to the disease process, and indeed our previous studies and those of others suggest this is the case," they said.

Previous research has suggested that clusterin is one of several extracellular "chaperones" that regulate amyloid formulation and clearance. However, studies comparing clusterin levels in cerebrospinal fluid between AD patients and control subjects have produced inconclusive results.

In their study, Dr. Thambisetty and his colleagues used plasma proteomics and neuroimaging to identify proteins that might be associated with AD.

They identified 13 spots on gel electrophoresis that correlated with hippocampal atrophy in a sample of 44 patients who had mild cognitive impairment or mild to moderate AD, then performed the same analysis in a separate sample of 51 AD patients who clearly had either slow-progressing or fast-progressing AD. Only one protein – clusterin – was common to both groups in this discovery-phase study.

The researchers then confirmed the link between clusterin and AD in a validation cohort of 689 subjects from two European studies: 464 patients with AD, 115 with mild cognitive impairment, and 110 healthy controls. This time, they correlated clusterin levels with MR imaging that showed atrophy of the entorhinal cortex, a component of the medial temporal lobe that shows early pathological changes in AD.

Plasma clusterin also negatively correlated with cognitive scores on the Mini-Mental State Examination in a subset of 576 subjects, indicating a correlation between rising clusterin and declining cognition.

Further, higher clusterin levels were noted in patients with rapid progression of AD than in those with slower progression of AD. The association was observed in 344 patients who had shown accelerated cognitive decline before their blood samples were obtained and in 237 subjects whose cognitive decline accelerated after their blood samples were obtained.

Thus, the association was evident retrospectively and prospectively, relative to the time of blood sampling.

Data from a U.S. longitudinal study of aging were used to test the hypothesis that plasma clusterin level is a marker of future AD pathology in apparently healthy older adults. The researchers found that high clusterin levels predicted AD-associated changes on PET imaging as long as 10 years before those changes were evident. ■

VITALS

Major Finding: High clusterin levels were noted in 344 patients who had accelerated cognitive decline as well as in 237 subjects whose cognitive decline accelerated after their blood samples were obtained.

Data Source: Data from European centers participating in the AddNeuroMed study and the Baltimore Longitudinal Study of Aging.

Disclosures: The study was funded by the Alzheimer's Research Trust, and several other organizations. Intellectual property has been registered on the use of plasma proteins, including clusterin, for use as biomarkers for AD by King's College London and Proteome Sciences, with Dr. Thambisetty and an associate named as coinventors.

Dietary Pattern Linked to Risk for Alzheimer's Disease

BY MARY ANN MOON

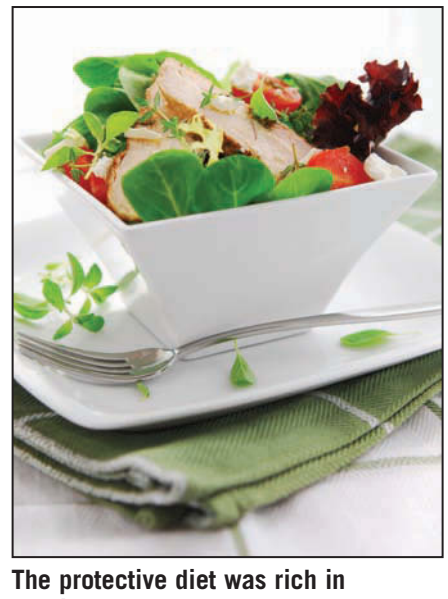
FROM THE ARCHIVES OF NEUROLOGY

A diet rich in certain foods such as nuts, fish, and vegetables and low in high-fat dairy foods and red meat appears exert a preventive effect on the development of Alzheimer's disease, a study shows.

"Our findings provide support for further exploration of food-combination–based dietary behavior for the prevention of this important public health problem," wrote Yian Gu, Ph.D., of the Taub Institute for Research in Alzheimer's Disease and the Aging Brain at Columbia University, New York, and associates.

The researchers sought to assess food combinations rather than individual nutrients in relation to Alzheimer's risk, so they studied dietary data obtained by food frequency questionnaires in two multiethnic cohorts: elderly subjects participating in the 1992 and the 1999 Washington Heights–Inwood Columbia Aging Project (WHICAP). Their study included 2,148 individuals who underwent serial batteries of neuropsychological tests, assessments of social and occupational function, and specific testing for cognitive deficits and dementia.

During an average follow-up of about 4 years, 253 of these subjects developed Alzheimer's disease. Subjects were diagnosed for dementia using the criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association.



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The protective diet was rich in cruciferous and dark green vegetables.

The investigators calculated dietary patterns based on variations in the content of seven key nutrients that have been most consistently related to dementia risk in the literature. Only one dietary pattern was found to be strongly associated with AD prevention: a diet rich in omega-3 polyunsaturated fatty acids, omega-6 polyunsaturated fatty acids, vitamin E, and folate and poor in saturated fatty acids and vitamin B_{12}. ■

Disclosures: This study was funded by the National Institute on Aging.
No financial conflicts of interest were reported.

APOE Genotype Associated With Phenotypic Differences in AD

BY ELIZABETH MECHCATIE

FROM THE PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE U.S.A.

Cognition and neuroanatomy differed between carriers and noncarriers of the e4 allele of the apolipoprotein E gene in a study that compared the phenotypic expression of the allele in people with mild Alzheimer's disease.

"We found the presence or absence of the APOE e4 allele influences the cognitive and anatomic phenotypic expression of AD in a dissociable manner," concluded Dr. David A. Wolk of the University of Pennsylvania, Philadelphia, and his coauthors in the Alzheimer's Disease Neuroimaging Initiative.

The results "have important implications for the early detection and monitoring of AD, because APOE carrier status seems to exert a strong influence on the cognitive and anatomic expression of the disease" (Proc. Natl. Acad. Sci. U.S.A. 2010 May 17 [doi: 10.1073/pnas.1001412107]).

The e4 allele is "the major genetic risk factor" for AD and is one of the three major alleles of the APOE gene, which codes for a lipid transport protein. Previously available data on the association between APOE allele carrier status and phenotypic differences have varied or have been inconsistent, according to the investigators.

To address concerns over possible misdiagnoses, Dr. Wolk included cerebrospinal fluid testing data to improve the accuracy of the diagnosis of Alzheimer's disease in the study's 67 e4 carriers and 24 noncarriers.

The APOE e4 carriers had significantly greater impairments in delayed recall as well as recognition memory and memory retention. In comparison, noncarriers showed significantly greater impairments in tests of working memory, executive control, and lexical access.

In a statement from the university, Dr. Wolk's co-author, Dr. Bradford Dickerson of Massachusetts General Hospital, Boston, referred to recent studies describing differences in the way in which Alzheimer's patients responded to drugs, based on whether they had the APOE e4 allele or not. "Rather than restricting trials exclusively to patients with or without APOE e4, the results suggest that different behavioral and brain measures might be a useful approach to consider in evaluating investigational drugs," he said. ■

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