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B12 Fraction May Lower Risk of Alzheimer's

by Nancy Walsh, Staff Writer, MedPage Today
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Serum levels of total homocysteine and the active fraction of vitamin B12 both appear to play a role in the development of Alzheimer's disease, a population-based study suggested.

The odds ratio for developing Alzheimer's disease after about seven years was increased, at 1.16 (95% CI 1.04 to 1.31) for each 1 µmol/L elevation in baseline homocysteine, according to Babak Hooshmand, MD, of Karolinska Institute in Stockholm, and colleagues.

In contrast, for each 1 pmol/L increase in the baseline level of the vitamin B12 fraction holotranscobalamin (holoTC), the odds ratio for later Alzheimer's disease was decreased, at 0.980 (95% CI 0.965 to 0.995), the investigators reported in the Oct. 19 issue of Neurology.

Elevated homocysteine levels have been linked with cardiovascular and cerebrovascular disease, but investigations into specific associations between dementia and homocysteine -- and factors that determine its serum level, such as folic acid and vitamin B12 -- have had conflicting or inconclusive results.

To assess the associations of homocysteine, holoTC, and folate with Alzheimer's disease risk, Hooshmand and colleagues analyzed data from a subsample of 271 participants in the Cardiovascular Risk Factors, Aging, and Dementia study in Finland.

Study participants were evaluated in 1998 for physical findings and information on sociodemographic characteristics and medical history. All were dementia-free at baseline.

Mean age of the entire cohort was 70.7 at that time point, and almost two-thirds were women.

Patients who had developed dementia were older at baseline, and typically had a lower body mass index and lower blood pressure.

Significant differences were seen in baseline levels of homocysteine and holoTC among those who later developed Alzheimer's disease:

- Total homocysteine, 14.9 µmol/L versus 12.6 µmol/L, P=0.01
- holoTC, 61.6 pmol/L versus 93.3 pmol/L, P=0.01

Baseline folate levels, however, did not differ between those who developed Alzheimer's disease and those who remained dementia-free.

what folate test?

The association between Alzheimer's disease and increased levels of baseline homocysteine remained after adjustment for multiple potential confounders, including age, sex, education, and smoking (OR 1.19, 95% CI 1.01 to 1.39).

Similarly, the reduced likelihood of dementia with higher baseline holoTC remained after adjustment for covariates (OR 0.977, 95% CI 0.958 to 0.997).

There was no association with folate in either adjustment.

When the investigators looked at the relation between Alzheimer's disease and all three variables, they found that the association with homocysteine was weakened slightly after adjustment for holoTC (OR 1.10, 95% CI 0.96 to 1.25).

Conversely, less effect was seen when the association of Alzheimer's disease and holoTC was adjusted for homocysteine (OR 0.984, 95% CI 0.968 to 1).

Further analysis identified an interaction between holoTC and age, with protective effects of increased level of the B12 fraction being more notable with older age (adjusted OR 0.994, 95% CI 0.989 to 0.998).

The investigators noted that, while the precise mechanisms underlying the

For instance, elevations of homocysteine "have been related to endothelial dysfunction, impaired nitric oxide activity, atherosclerosis, and subsequent increase in the risk of various cardiovascular and cerebrovascular events which may increase the risk of dementia and [Alzheimer's disease]," they wrote.

Homocysteine also might encourage the production of beta-amyloid in the brain, and holoTC might have significant effects on S-adenosylmethionine, a factor important in many brain functions.

Strengths of the study include its population-based design, fairly long follow-up, and adjustment for multiple potential confounders.

Limitations include the somewhat small sample size and the fact that hemoglobin and holoTC were measured only once. In addition, serum creatinine levels were not measured.

In an accompanying editorial, Sudha Seshadri, MD, of Boston University, described the study as "an important initial step" in clarifying the association between plasma holoTC and Alzheimer's disease.

But it is as yet unclear whether holoTC or homocysteine is the main player in the association. "Careful examination of the evidence is required to learn who is the perpetrator in the complex pathology of [Alzheimer's disease] and other dementias," Seshadri wrote.

Caution was also advised by Sam Gandy, MD, PhD, of Mount Sinai School of Medicine in New York City, who was not involved in the study.

"This is an interesting and potentially important study," Gandy said. But he added that "unfortunately, many physicians offer B12 injections indiscriminately for all sorts of ailments, and this report is likely to encourage that unfounded practice."

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The lead investigator and four co-authors reported no disclosures. Several other co-authors reported serving on advisory boards or receiving honoraria from a number of companies, including Elan Corporation, Janssen, Novartis, Pfizer, and Takeda. Some also reported research support from the Academy of Finland, the Swedish Research Council, and the European Union, and being on the advisory boards of a number of Alzheimer's disease publications including the *American Journal of Alzheimer's Disease & Other Dementias* and *Alzheimer's & Dementia*.

Editorialist Seshadri has received research support from the National Institutes of Health, is associate editor for the *Journal of Alzheimer's Disease*, and is on the editorial board of *Stroke*.

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