Vitamins, homocysteine, and cognition1,2

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Poor cognition recently joined the list of ills associated with hyperhomocysteinemia. This is an area of rapidly increasing investigation, as can be shown by Internet searches for “cognition and homocysteine,” which identify 26 publications for 2002 and 2003 alone. In this issue of the Journal, Miller et al (1) report on a study at the University of California, Davis, of a large Mexican American cohort that confirms the association of hyperhomocysteinemia and impaired cognitive performance previously found in other large investigations (2–6). Their study also illustrates the challenges inherent in investigations of syndromes as multifactorial as impaired cognition and hyperhomocysteinemia.

There are plausible reasons for a causal relation because elevated homocysteine is a marker indicating deficiency of vitamin B-12, folate, or both; it also is a well-documented risk factor for vascular disease, which is related to both vascular dementia and Alzheimer disease. Vitamin B-12 is required for a healthy central nervous system, and up to 10% of patients with pernicious anemia have prominent mental symptoms, including memory loss (7). In addition, both vitamin B-12 and folate are necessary to ensure adequate methylation by S-adenosylmethionine in the synthesis of neurotransmitters, myelin, and phosphatidylcholine, as well as other compounds important to the nervous system. For further complexity, hyperhomocysteinemia is very prevalent in chronic renal insufficiency and is a marker for smoking, type 2 diabetes with hypertension and nephropathy, and poor diet. Thus, although elevated homocysteine is often treated as a uniform variable in studies related to cognition, it is likely that the different causes might have differing detrimental effects, and treatment that lowers homocysteine might be more beneficial for some conditions than for others. For instance, mental symptoms cleared significantly and rapidly in patients with severe vitamin B-12 deficiency (7). A small but intriguing treatment study recently showed that vitamin B-12 replacement improved cognitive performance and abnormalities on electroencephalogram in vitamin B-12–deficient seniors (8). Vascular dementia and the plaques and neurofibrillary tangles of Alzheimer disease would seem to be irreversible, however, and lowering homocysteine before the onset of disease would be necessary to show a treatment benefit.

The Sacramento Area Latino Study on Aging (SALSA) investigators described the magnitude of the effect of homocysteine in predicting impaired cognition in this study as “modest” (5%), which was less than that found in some other recent investigations (2, 3). However, SALSA was performed after the implementation of folate fortification of food in the United States, as the authors point out in the discussion. It is extremely likely that the folate status of this population had improved because of this fortification, because the mean red blood cell folate concentration was above the 95th percentile for the third National Health and Nutrition Examination Survey (NHANES III) in elderly Mexican Americans (9). The median total homocysteine concentration was 9.8 μmol/L, which is considerably lower than values found in other senior cohorts (2–6). Thus, homocysteine as a marker predicting long-term folate status had probably lost utility in this population, and the effects of folate deficiency on cognition could have been obscured. Although the median homocysteine concentration was low, hyperhomocysteinemia was still present in 17% of subjects and correlated inversely with vitamin B-12 status. Elevated methylmalonic acid concentrations (a sensitive marker of vitamin B-12 status) were found in 82% of the hyperhomocysteinemic subjects in another elderly cohort studied after fortification, and the prevalence of vitamin B-12 deficiency was 23% and was correlated with poor cognition (10). It is probable that many or most of the SALSA subjects in the highest homocysteine quintile have vitamin B-12 deficiency. This investigation would have been strengthened by measurement of methylmalonic acid, because the authors would have been able to more precisely define the role of vitamin B-12 deficiency in impaired cognition, now that folate deficiency has largely been removed as a variable.

Two of the strengths of SALSA were that the neuropsychological tests chosen were appropriate for “cross-cultural and multilingual neuropsychological assessment of older persons” (1) and that a sensitive Modified Mini-Mental State Examination with an expanded scale of 0–100 was used to determine global cognitive ability. The subjects lived in one region and were of similar ethnic backgrounds, but despite these safeguards to ensure that the cognition testing would be sensitive and uniform, the investigators still found that education was one of the strongest predictors of cognitive function. For instance, there was a 10-point difference between the scores of subjects with 0–5 y of education and those of subjects with > 12 y of education (1). In some other cohorts, educational attainment might be a marker of inborn intellectual ability, but, because 39% of these subjects were in the lowest educational group, that relation is not plausible. It seems likely that these tests of cognition reflect skills learned in school, and, in this poorly educated group, such measurements may not truly reflect intellectual abilities or signs of dementia. Future studies of biochemical markers and cognition should be large enough to stratify subjects carefully for education status and language abilities.

How is the clinician to use the data described in this investigation (1) and in other studies (2–8) showing links of poor cognition to hyperhomocysteinemia? Because folate status has improved in the United States during the past 5 y, with the result

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that total homocysteine values decreased, it may be possible to show a decline in the incidence of vascular dementia, strokes and other cardiovascular events, or even Alzheimer disease over the next decade. Therefore, one option is to wait for the results of prospective treatment studies and epidemiologic evidence before recommending widespread homocysteine-lowering treatment. This approach ignores the 10–20% of seniors with metabolic evidence of vitamin B-12 deficiency who may benefit greatly from replacement (7, 8, 10). If vitamin B-12 deficiency is suspected in a subject with hyperhomocysteinemia, it would be prudent to treat that person with a high dose of oral or parenteral vitamin B-12, because vitamin B-12 deficiency is a known cause of central nervous system demyelination. Another important point is that over-the-counter vitamin therapy is in widespread use in the United States, and it clearly improves folate and vitamin B-6 status. In contrast, high-dose oral vitamin B-12 supplements are required for the normalization of elevated methylmalonic acid concentrations (10). Public education about the necessity for higher doses of oral vitamin B-12 than those found in the usual multivitamin preparations may be of value to persons who want to ensure normal vitamin B-12 status.

REFERENCES