

Homocysteine, Cognition and Brain White Matter Hyperintensities

Jong-Ling Fuh

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Homocysteine is a sulfur-containing amino acid derived from methionine⁽¹⁾. It is converted by folate, vitamin B12 and B6 to cysteine, or can be recycled into methionine. Homocysteine levels in blood increase with age and with diminishing renal function, but are largely determined by dietary intake and levels of vitamins B12, B6, and folate⁽²⁾. In recent years, studies have shown that hyperhomocysteinemia might be a risk factor for vascular disease, brain atrophy, cognitive impairment, Alzheimer disease (AD), depression, and several neuropsychiatric diseases⁽³⁻⁶⁾.

In this issue, Tu and colleagues evaluated 92 AD patients, investigating the relationship between cognition change, plasma homocysteine level, and white matter hyperintensities (WMH)⁽⁷⁾. They found that homocysteine levels did not differ between AD patients and controls, and homocysteine levels did not correlate with cognitive scores. However, plasma homocysteine levels were associated with rapid cognitive decline and higher WMH in the trigone area on brain magnetic resonance imaging (MRI).

Previous studies relating homocysteine levels to dementia risk have shown inconsistent results⁽⁸⁻¹³⁾. However, a recent meta-analysis evaluated nine qualitatively good case-control studies, finding a pooled standardized mean difference in homocysteine levels of 1.04 (0.44-1.63), for 631 patients with AD and 703 controls

⁽⁴⁾. The findings strongly suggest that levels of homocysteine are higher in AD, most likely caused by lower folate, vitamin B12, and possibly vitamin B6 levels during disease. The study also analyzed three prospective cohort studies (2569 subjects), and found that hyperhomocysteinemia gave a pooled relative risk for AD of 2.5 (1.38-4.56)⁽⁴⁾. The reason that total plasma homocysteine levels did not differ between AD patients (12.9 ± 7.3) and age-matched controls (12.1 ± 4.4) in the Tu et al. study⁽⁷⁾ is not clear. In 17 case-control studies identified from Pubmed, Embase, Psychinfo and other websites⁽⁴⁾, all except one found much higher total plasma homocysteine levels in AD patients than observed in the Tu et al. study. Plasma homocysteine levels in the control groups in the Tu et al. study⁽⁷⁾ were in the middle range of the 17 case-control studies⁽⁴⁾. This suggests further study is warranted to investigate the relationship between homocysteine and AD in Taiwanese populations.

Although results are somewhat inconsistent^(14,15), most studies confirmed that hyperhomocysteinemia is a risk factor for atherosclerotic diseases and thromboembolic events^(16,17). Increasing evidence suggests that cerebral vascular pathology may be synergistic with AD pathology, leading to earlier onset of clinical dementia symptoms and more severe dementia than would have been produced by AD pathology alone^(18,19).

From the Department of Neurology, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan and National Yang-Ming University School of Medicine, Taipei, Taiwan.
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Correspondence to: Jong-Ling Fuh, MD. Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan, 112.
E-mail: jlfuh@vghtpe.gov.tw

Homocysteine levels also correlate with WMH and increased risk of small- and large-vessel disease⁽²⁰⁾. Nevertheless, several studies including the Tu et al. study⁽⁷⁾ and a very similar study⁽²¹⁾ support that WMH does not mediate the association between homocysteine and cognition⁽²²⁾.

The mechanisms by which homocysteine affect cognitive function remain controversial. Several studies suggested that hyperhomocysteinemia in persons with cognitive impairment or dementia are not causative, but reflect concomitant vascular disease⁽²³⁾. Some studies proposed that S-adenosylhomocysteine (SAH) is a better marker of AD development than homocysteine^(24,25). Methionine is activated to S-adenosylmethionine (SAM), which is required for numerous methylation reactions⁽⁶⁾. SAH is produced from SAM through release of the methyl group. Elevated SAH concentrations antagonistically reduce the SAM-dependent methylation capacity, impairing cell functions, increase DNA damage, and perturb myelin biosynthesis in the brain⁽⁶⁾. Popp and colleagues found that phosphorylated tau is more strongly associated with SAH than homocysteine⁽²⁴⁾. Another study supported SAH-induced, rather than homocysteine-induced cytotoxic changes in endothelial cells in culture⁽²⁶⁾. The importance of SAH in endothelial cell pathology also explains why, even with adequate lowering of homocysteine levels, no significant beneficial effects have been seen with combined folate and vitamin B12 treatment, with or without vitamin B6, in several clinical interventional trials on cardiovascular disorders⁽²⁷⁾.

Giving the continuing debate on the role of homocysteine in cardiovascular and neurodegenerative disorders, additional prospective studies on homocysteine are warranted.

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