Hyperhomocysteinemia, ischemic stroke, and B-vitamin treatment: the jury is still out

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Ischemic stroke has a high prevalence and high burden of illness. Prevention remains the optimal strategy to reduce the burden of ischemic stroke at the population level. Established causal risk factors are estimated to account for one-half of vascular disease risk. In recent years, attention has been focused on the identification and validation of novel biochemical factors that increase risk for stroke. Homocysteine (Hcy) is one such novel candidate risk factor.

The available data are conflicting concerning the association between hyper-Hcy and ischemic stroke. Numerous case-control studies have shown an association between hyper-Hcy and stroke, but the evidence from prospective studies is not unequivocal. In this issue of the journal, Modi et al. in a case-control study have also shown hyper-Hcy as an independent risk factor for ischemic stroke.

A common polymorphism (677C → T) in the gene encoding the N5, N10-methylenetetrahydrofolate reductase (MTHFR) enzyme, which converts dietary folate to its active cofactor in Hcy catabolism, has been studied as a candidate genetic risk factor for stroke. Data is conflicting concerning ischemic stroke risk associated with MTHFR 677T allele. Results of meta-analysis suggest an association between mild-to-moderate hyper-Hcy and ischemic stroke. The MTHFR TT genotype may have a small influence in determining susceptibility to ischemic stroke. A graded increase in ischemic stroke risk with increasing MTHFR 677T allele dose was observed suggesting an influence of this polymorphism as a genetic stroke risk factor and supporting other evidence indicating a causal relationship between elevated Hcy and stroke. As T allele dose increases, this functional polymorphism causes a graded elevation in total Hcy in mild–moderate range, most pronounced in individuals with low-dietary folate consumption, which will have a greater impact in India with its vegetarian population. A hospital-based study in Western India suggests a high prevalence of both folate and vitamin B12 deficiency. In a case-control study in South India, MTHFR C677T gene mutation was found to be strongly associated with arterial stroke. In this study, tHcy levels were very high and the percentages of mutated alleles in patients with tHcy 16–50 µmol/l was 25.4% and in patients with tHcy > 50 µmol/l it was 38%. Mutated alleles were not detected in any patient with tHcy < 15 µmol/l.

The mechanisms proposed to link Hcy to vascular damage, stroke, and cardiovascular disease include impairment of endothelial functions, endothelial desquamation, oxidation of low-density lipids, increased monocyte adhesion to the vessel wall, impaired vascular response to nitric oxide, and thrombotic tendency mediated by activation of coagulation factors and platelet dysfunction.

Hcy is a sulfur-containing amino acid formed in vivo from methionine derived from dietary protein. The term Hcy describes the total circulating pool of free and protein-bound Hey-derived moieties (Hcy, homocystine, and Hcy-cysteine disulfides) that exists in equilibrium in vivo. Although the definition of hyper-Hcy has not been standardized across epidemiological studies, fasting plasma levels of Hey between 5 and 15 µmol/l are generally considered normal. As metabolism of Hey occurs through one of two vitamin-dependent pathways, low levels of dietary folate, vitamins B12 and B6 are associated with elevated plasma Hey. Other factors that may be associated with elevations in Hey include age (older than age 70), renal insufficiency, more than four cups of coffee per day, and drugs such as methotrexate, 6-azauridine, nicotinic acid, and bile acid sequestrants. Alcohol, smoking, and physical inactivity also may alter Hey levels. Folic acid, together with vitamins B12 and B6 has been shown to be effective in reducing elevated plasma Hey levels. Vitamins in stroke prevention (VISP) trial compared high-dose vitamins (folic acid 2.5 mg, vitamin B12 0.4 mg, and vitamin B6 25 mg) with low-dose vitamins (folic acid 0.02 mg, vitamin B12 0.006 mg, and vitamin B6 0.2 mg). Both the groups received the same daily dose of nine other vitamins according to the recommendation of the food and drug administration. An absolute difference in mean tHcy of 2 µmol/l was achieved.

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Blood levels of homocysteine was five times more than folate deficiency. Thus it will be appropriate to correlate levels of methylmalonic acid and Hcy with vitamin B12 deficiency, screening may be recommended in a select group of patients with cerebral ischemia with no identifiable risk factor for. A recent study in North India shows that 46.9% of the normal subjects studied had subnormal levels of vitamin B12 or folate. Cobalamine deficiency was five times more than folate deficiency. Levels of methylmalonic acid and Hcy are better indicators of true tissue efficiency of these two vitamins than serum levels alone. Thus it will be appropriate to correlate levels of methylmalonic acid and Hcy with vitamin B12 and folate levels.

References

7. Christen WG, Ajanì TA, Glynn RJ, Hennekens CH. Blood levels of homocysteine and increased risks of cardiovascular disease causal or casual? Arch Intern Med 2000;160;422-34.