Editorial

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

J. M. K. Murthy

Department of Neurology, The Institute of Neurological Sciences, CARE Hospital, Hyderabad, India

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.[1] In recent years, attention has been focused on the identification and validation of novel biochemical factors that increase risk for stroke.[2] Homocysteine (Hcy) is one such novel candidate risk factor.[3]

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.[3–7] In this issue of the journal, Modi et al.[8] in a case–control study have also shown hyper-Hcy as an important 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.[9] 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.[10] 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 stoke.[11] 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 B_{12} deficiency.[12] In a case–control study in South India, *MTHFR* C677T gene mutation was found to be strongly associated with arterial stroke.[13] 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.[14]

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 Hcy-derived moieties (Hcy, homocystine, and Hcy-cysteine mixed disulfides) that exists in equilibrium *in vivo*.[15] Although the definition of hyper-Hcy has not been standardized across epidemiological studies, fasting plasma levels of Hcy between 5 and 15 mmol/l are generally considered normal.[4,16,17] As metabolism of Hcy occurs through one of two vitamin-dependent pathways, low levels of dietary folate, vitamins B_{12} and B_6 are associated with elevated plasma Hcy. Other factors that may be associated with elevations in Hcy 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.[18] Alcohol, smoking, and physical inactivity also may alter Hcy levels.[3] Folic acid, together with vitamins B_{12} and B_6 has been shown to be effective in reducing elevated plasma Hcy levels.[19] Vitamins in stroke prevention (VISP)[20] trial compared high-dose vitamins (folic acid 2.5 mg, vitamin B_{12} 0.4 mg, and vitamin B_6 25 mg) with low-dose vitamins (folic acid 0.02 mg, vitamin B_{12} 0.006 mg, and vitamin B_6 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 mmol/l was achieved:

J. M. K. Murthy
Department of Neurology, The Institute of Neurological Sciences, CARE Hospital, Hyderabad – 500 001, India, E-mail: jmkmurthy@satyam.net.in

13 mmol/l in the low-dose group *vs* 11 mmol/l in the high-dose group. After 2 years of follow up the cumulative incidence of recurrent cerebral infarction was 8.4% in high-dose vitamins group *vs* 8.1% in low-dose vitamins group (RR 1.0; 95% CI 08–1.3; P=0.80). The cumulative incidence of death was 5.4% in high-dose vitamins group *vs* 6.3% in the low-dose group (RR 0.9; 95% CI 0.7–1.1). However, VISP trial did not reliably exclude a modest but important reduction in the relative risk of stroke of <20% and perhaps an even greater reduction with greater reduction in tHcy. The lower than anticipated rates of recurrent strokes in both treatment groups and the short duration of follow up also limited the statistical power of the VISP trial to reliably identify or exclude a modest but important benefit of B-vitamin therapy.[21] The VITAmins TO Prevent Stroke (VITATOPS[22] trial is underway.

At present, there is insufficient data to recommend routine screening and treatment of high-tHcy with B-vitamins to prevent atherosclerotic vascular disease.[21] However, in India with high proportion of vegetarian population, no population-wide folic acid grain fortification program, and high prevalence of both folate and vitamin B_{12} 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 B_{12} or folate. Cobalamine dificiency was five times more than folate defieciency.[23] Levels of methylmalonic acid and Hcy are better indicators of true tissue difficiency of these two vitamins than serum levels alone.[24] Thus it will be appropriate to correlate levles of methylmalonic acid and Hcy with vitamin B_{12} and folate levels.

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