Editorial
Neurological implications of hyperhomocysteinemia in patients with atherothrombotic disease

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Elevated homocysteine levels were first implicated in the pathology of atherosclerosis in the pioneering manuscript of McCully[1] over 30 years ago. Over the last decade, there has been a rapidly growing interest in homocysteine, a sulfur-containing amino acid that plays a central role in the metabolic pathways of thiol compounds. Such an interest is primarily because of the realization that hyperhomocysteinemia is an important risk factor for vascular disease independent of the other long-recognized factors such as hyperlipidemia, hypertension, diabetes mellitus, and smoking. An association between elevated homocysteine levels and atherosclerotic vascular disease is also biologically plausible, and experimental studies have shown elevated homocysteine to be both atherogenic and thrombogenic. A meta-analysis of the observational studies demonstrates that after adjustment for known cardiovascular risk factors and for the regression dilution bias in prospective studies, a 25% lower homocysteine level [about 3 μmol/l (0.41 mg/l)] was associated with an 11% lower coronary heart disease (CHD) risk and with a 19% lower stroke risk[2]. Since elevated homocysteine levels can often be normalized by dietary supplementation of folic acid (folate), pyridoxine hydrochloride (vitamin B_6) and cyanocobalamin (vitamin B_{12}), the attractive hypothesis that this inexpensive and well-tolerated therapy may be effective in decreasing the incidence of vascular disease has been forwarded. Indeed, reducing plasma homocysteine by means of multivitamin therapy produces favorable effects on the surrogate markers of vascular disease such as the endothelial function[3,4].

In order to assess the predictive role of the serum levels of homocysteine in patients with preexisting atherothrombotic disease, we have performed a prospective nested case-control study of homocysteine concentrations in patients with chronic CHD who participated in the Bezafibrate Infarction Prevention (BIP) study[5]. The BIP study was a secondary prevention randomized clinical trial of lipid modification among 3090 men and women with CHD, conducted in 18 medical centers in Israel. A 1-unit change in the log-transformed concentrations (because concentrations are positively skewed) of homocysteine was associated with a more than 3-fold risk of developing an incident ischemic stroke (odds ratio-OR 3.3; 95% confidence interval-CI 1.2 to 10.2), which practically did not change after adjusting for the conventional risk factors (OR 3.4; 95% CI 1.1 to 12.3). The relative odds adjusted for the traditional risk factors and potential confounding variables produced a graded association with higher homocysteine concentrations, with relative odds of 4.6 (95% CI 1.3 to 18.9) for concentrations in the upper quartile of homocysteine levels compared to the lowest quartile. The current cohort included patients with preexisting stable CHD associated with higher homocysteine concentrations. This notwithstanding, we found that the homocysteine concentration was a powerful predictor of incident ischemic stroke over the long-term follow-up.

It is well recognized that ischemic stroke is pathologically and etiologically heterogeneous and that the risk factors for one etiologic subtype may not be risk factors for other subtypes of stroke[6-12]. Recent studies have shown that acute hyperhomocysteinemia causes endothelial dysfunction, which might affect the cerebrovascular reactivity and promote the development of atheromas[8,9]. Increased homocysteine concentrations are associated with carotid artery wall thickening and stenosis[10] and also with ischemic events in patients with significant carotid stenosis[11]. It was also demonstrated that supplementing hyperhomocysteinemic patients with B vitamins could effectively prevent the progression of carotid artery atherosclerosis[13]. Eikelboom et al.[12] have found, in a case-control study, that hyperhomocysteinemia is associated in particular with stroke due to large-vessel atherosclerosis, and recently high homocysteine concentrations were shown to convey an independent risk for left atrial thrombus formation in patients with stroke caused by nonvalvular atrial fibrillation, supporting the thrombogenic role of high homocysteine levels in conditions associated with blood stasis[7].

Hyperhomocysteinemia as a risk factor may have profound public health implications for neurological disease in adults, beyond its association with ischemic stroke. Recent epidemiological and experimental studies have linked increased homocysteine levels with several neurodegenerative conditions including cognitive decline, vascular dementia, Alzheimer's disease, and the complications of Parkinson's disease[14-19]. Moreover, genetic and clinical data suggest associations between folate and homocysteine and some psychiatric disorders[20,21].

Patients with CHD are at an increased risk of ischemic stroke[22,23], the leading cause of severe neurological disability among adults. It is now recognized that subjects with cardiovascular risk factors and a history of stroke also have an increased risk, not only of vascular dementia, but also of Alzheimer's disease[24]. The relationship between homocysteine and cognition has been recently evaluated in several large studies. The most convincing support for elevated homocysteine levels as a risk factor for cognitive impairment and Alzheimer's disease comes from a longitudinal study that suggested that high plasma homocysteine at baseline almost doubled the risk of developing Alzheimer's disease over an 8-year follow-up period[14,15]. In the Rotterdam Scan Study, a population-based study including over 1000 subjects aged 60 to 90 years, higher homocysteine levels were associated with more atrophy of the hippocampus and cortical regions in the elderly who were at risk of developing Alzheimer's disease[25]. Homocysteine levels were also associated with silent brain infarcts and white matter lesions independent of each other and of other cardiovascular risk factors[26], and were associated with a decreased cognitive performance, in particular, a reduced psychomotor speed[16]. Increased concentrations of homocysteic acid, an N-methyl-D-aspartate receptor agonist and a metabolite of homocysteine, may result in excitotoxic damage to neurons. Further, homocysteine was found to promote copper-mediated and amyloid peptide-mediated toxic effects in neuronal cell cultures and to induce apoptosis in hippocampal neurons in rats.

The results from prospective studies assessing the relationship between homocysteine concentrations and the risk of cerebrovascular disease substantially differed from those of case-control studies and, on the whole, lower OR were found to be associated with homocysteine concentration[27]. Levels of homocysteine increase after an acute vascular event such as myocardial infarction or stroke[28-31]. The abundance of theories attempting to explain the vascular activity of elevated homocysteine levels emphasizes the lack of a consensus and the complexity of the issue. An alternative view on homocysteine was hypothesized by Dudman[32], who suggested that the overwhelming epidemiologic support for hyperhomocysteinemia and vascular events is not due to a direct atherogenic or thrombogenic effect of this molecule. Rather, according to this view, an increased homocysteine concentration is none other than a marker of tissue damage and repair. Our current work demonstrates that moderate hyperhomocysteinemia in patients with preexisting atherothrombotic disease is a powerful prognostic marker for the development of stroke. Recently, in a longitudinal study of over 1000 stroke patients, elevated homocysteine levels were also found by Boysen et al.[33] to be an independent risk factor for recurrent strokes. In this study, serum homocysteine levels were significantly higher in patients who presented with a recurrent stroke during the 15-month follow-up period than in those without recurrence. Further, at the index event, serum homocysteine levels were significantly higher in patients with ischemic cerebrovascular events than in those with intracerebral hemorrhage.

Several striking examples have raised the possibility of divergent conclusions between observational studies and later pivotal randomized clinical trials. Only randomized controlled studies that are currently underway can prove whether vitamin supplementation in patients with hyperhomocysteinemia is indeed also efficacious in reducing the incidence of clinical endpoints[34]. In the meantime, the treatment of hyperhomocysteinemia, that is well-tolerated and inexpensive, should be considered as a rational approach just as other therapeutic regimens addressed against other biochemical markers of disease vulnerability.

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