Methylenetetrahydrofolate Reductase Gene and Coronary Artery Disease

To the Editor:

Brattström et al performed a meta-analysis of the results of 13 studies on plasma homocysteine concentrations in the 3 genotypes of the C677T mutation of the enzyme methylenetetrahydrofolate reductase (MTHFR) and of 23 case-control studies on this mutation in cardiovascular disease. They found that the TT (homozygous mutant) genotype was associated with mildly elevated plasma homocysteine concentrations but with a relative risk of vascular disease of only 1.12. They concluded that although the C677T mutation of MTHFR is a major cause of mild hyperhomocysteinemia, it is not a risk factor for cardiovascular disease.

We are greatly concerned by this meta-analysis, particularly by the inclusion of different populations. The impact of the C677T mutation on plasma homocysteine and its association with coronary artery disease (CAD) reflect a gene-environment interaction. However, Brattström et al pooled data from populations that differed in their ethnic origin, geographic location, and probably nutritional status. A review of the pooled studies on MTHFR polymorphism in CAD and of more recent works, including a preliminary report from our institution, shows that almost all the negative studies included populations of Anglo-Saxon origin, whereas all the positive studies included populations of other ethnic origins: Dutch, Irish, Japanese, and Israeli Jews. This suggests that the association between MTHFR polymorphism and CAD is population specific and cannot be subjected to meta-analysis.

Although it is not yet clear why the role of MTHFR C677T as a risk factor for CAD varies among populations, differences in plasma homocysteine levels in homoyzogotes may provide at least a partial answer. For example, in some populations, hyperhomocysteinemia is confined to those TT homozygotes with plasma folate levels in the lowest quartile, whereas in other populations it also occurs with higher folate levels. Other factors may also be important in this context, including differences in folate intake and in plasma folate, in itself a possible coronary risk factor, and in concomitant genetic disturbances in the clotting system. Moreover, there is strong evidence that the role of this mutation also varies within populations and among phenotypes. In our population, for example, the TT genotype was overrepresented in those with premature CAD. A similar association with premature CAD was found in 2 other positive case-control studies. Since early onset characterizes only a minority of CAD patients, the role of MTHFR polymorphism in this setting could have eluded authors who did not specifically address this issue.

Therefore, it is much too early for a verdict to be rendered on the role of MTHFR in CAD, and much more evidence is necessary.

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Response

In responding to the 3 points Drs Blom and Verhoef make about our article, we should emphasize that our aim was to examine in a meta-analysis all published data on the relationship between vascular disease and the TT genotype for the MTHFR C677T polymorphism. In the ~6000 vascular patients and similar number of controls, the prevalence of the TT genotype was between 11% and 12% in both groups. Of the 23 studies, only 4 showed a significantly higher TT genotype prevalence in vascular patients; 3 of these were among the 6 studies with the smallest numbers of patients. Given that the mutation is associated with a modest homocysteine elevation when folate levels are below median population levels, and extrapolating from these findings and from data in 13 studies in which homocysteine was also measured, we concluded in our Abstract that “our findings suggest that the mild hyperhomocysteinemia found frequently in vascular disease patients is not causally related to the pathogenesis of the vascular disease.” These 2 aspects of our article are relevant to the 3 points Drs Blom and Verhoef make.

We agree with their first comment that the expected OR with the TT genotype compared with the CC genotype falls within the CI we calculated (1.12; 95% CI 0.92 to 1.37) and that these findings neither support nor reject an association between mild homocysteine elevation associated with the TT genotype and vascular disease. But the data do show that the prevalence of the TT genotype in a large number of subjects with and without vascular disease is not different. This is strong evidence that the mutation itself is not associated with enhanced cardiovascular risk.

We also agree with the second point. There is always the possibility that the mutation itself could be beneficial and offset any potentially damaging effect of a modest homocysteine elevation. This point was included in the Discussion of our original submission but was omitted in the final version in response to an editorial request to shorten the manuscript.

We also agree with the third point. Those bearing the TT genotype have an increased requirement for folate, so that in general, the TT genotype is associated with homocysteine elevation only in those among the population who have circulating folate concentrations below median population levels. Multivitamin supplementation and fortification of grain products are certainly more common in North America than in Europe and Australia. However, 2 large studies from widely separated parts of Australia found an almost identical prevalence of the TT genotype in patients aged ≤65 years with coronary disease established angiographically and the same prevalence in appropriate numbers of controls.

In a few years, the outcome data from the 7 major trials of the effects of folate (with or without vitamin B12) in vascular disease patients that are ongoing worldwide will provide answers for the therapeutic relevance to cardiovascular risk of folate (with or without vitamin B12) in vascular disease patients. The results...
will answer questions Dr. Mager raises in his thoughtful letter and, in particular, whether or not the TT genotype is overrepresented in younger patients with coronary artery disease.

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