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Hyperhomocysteinemia, MTHFR, and Risk of Vascular Disease

To the Editor:

In contrast to data derived from many epidemiological studies,¹ Brattström et al² conclude that mild hyperhomocysteinemia is not causally related to the pathogenesis of vascular disease. Their conclusion is based on a meta-analysis of 23 studies in which they observed no significant increased risk of vascular disease among subjects with the TT genotype for the MTHFR C677T polymorphism (a common mutation that raises total homocysteine [tHcy] in plasma) compared with those with the CC genotype.

In our opinion, the authors have overlooked several crucial aspects:

1. They calculated that subjects with the MTHFR TT genotype have plasma tHcy concentrations 2.6 $\mu\text{mol/L}$ higher than those with the CC genotype. Presuming that an increase in plasma tHcy of 1 $\mu\text{mol/L}$ is associated with approximately a 10% increase in risk of vascular disease,¹ the expected odds ratio (OR) for the TT genotype compared with the CC genotype is 1.26. This is well within the 95% CI Brattström et al calculated (OR 1.12 [95% CI 0.92 to 1.37]). Therefore, their study does not prove or disprove whether TT genotype is associated with increased risk of vascular disease.

2. MTHFR regulates availability of 1-carbon units of folate not only for remethylation of homocysteine, but also for synthesis of thymidine and purines. Reduced MTHFR activity will hamper homocysteine remethylation but lead to higher availability of folate for DNA synthesis.^{3,4} The latter may be beneficial during cell division, eg, during repair of endothelial damage. Indeed, endothelial cells with the TT genotype in culture grow faster than those with the other MTHFR genotypes (H.J. Blom and E.F. van der Molen, unpublished observation, 1998).

3. It is not unlikely that the TT genotype emerges as a risk factor for vascular disease mainly in populations with low-normal folate intake, considering that it results in moderate hyperhomocysteinemia mainly in subjects with suboptimal folate status.⁵ In fact, from the data presented by Brattström et al,² it appears that this polymorphism is directly associated with vascular disease more often in European than North American studies. This may be explained in part by the fact that use of multivitamin supplements and fortification of grain products with folic acid is much more common in the United States/Canada than in Europe.

We are currently gathering original data of observational studies on the relationship between this polymorphism and risk of coronary heart disease (CHD). We will study whether the TT genotype is associated with a beneficial CHD risk profile, eg, low blood pressure. Preliminary results are expected in the summer of 2000.

Within 2 to 4 years, clinical trials of tHcy lowering by supplementation with folic acid (and vitamins B₆ and B₁₂) will be completed. Conceivably, these trials cannot prove a causal role of elevated plasma tHcy, as there is still a possibility that low vitamin status itself is the primary cause of vascular disease and elevation of plasma tHcy levels just a marker of low vitamin status. The premature conclusions drawn by Brattström et al could direct public health attention away from the possibly important role of folate and the other B vitamins.

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