Underestimated risk for stroke patients

MTHFR 677 TT genotype and hyperhomocysteinaemia: an underestimated risk TANDEM for patients with stroke

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Synergy between hyperhomocysteinaemia and conventional risk factors for stroke

Hyperhomocysteinaemia (hyperH(e)) is still considered to be one of the less documented risk factors for stroke.¹ One of the most frequent causes of hyperH(e) is a single-nucleotide polymorphism in the gene methylenetetrahydrofolate reductase (MTHFR). The homozygotic TT genotype is found in approximately 10–12% of the population and is associated with a 25% higher homocysteine level in patients with than in those without this mutation.¹

The distribution of the MTHFR 677 TT genotype and hyperH(e) in young patients with stroke aged <45 years was compared with that in healthy controls in the paper by Pezzini *et al*² (see p 1150). The paper by Kloss *et al*³ compared the distribution of the MTHFR 677 TT genotype and hyperH(e) between patients with cervical artery dissections (CADs) and controls. Pezzini *et al* carried out a statistical analysis with a two-way and a three-way interaction and the classification and regression tree model to determine whether hyperH(e) was the consequence of a genetic background and not due to the confounding influence of established predisposing risk factors. Homocysteine levels were found to be higher in cases than in controls, and an increased risk was observed with the MTHFR 677 TT genotype (odds ratio 1.98; 95% confidence interval 1.04 to 3.78). In the paper by Kloss *et al*, the

frequency of the MTHFR 677 TT genotype was reported to be slightly higher in patients with CAD, without reaching significance ($p = 0.21$). However, the presence of the MTHFR 677 TT genotype was significant ($p = 0.032$) in the subgroup of patients with multiple dissection (three or more events).

Both of these papers confirmed the data from a recent meta-analysis showing that among people homozygotic for the MTHFR T allele, the risk of stroke increased near the predicted differences in homocysteine concentrations conferred by this variant.⁴ This finding is very important both for young patients with stroke, where the pathogenesis often remains undetermined, and for patients with CAD, where the pathogenesis is not wholly understood. An interaction between endothelial damage due to hyperH(e) and acute weakness of the arterial wall (ie, vascular stress in minor trauma) has been proposed.⁵ It is not known why hyperH(e) and the MTHFR T allele mutation might lead to CADs, which are known to be unique vascular events in young patients who do not have ulterior signs of atherosclerosis. Two possibilities are that (1) CAD follow-ups tend to be too short and (2) risk factors in young patients with CAD are generally better controlled so as to prevent recurrences. The correlation between multiple dissection and the MTHFR 677 TT mutation claimed by Kloss *et al* seems to be an important step

towards explaining the pathogenesis of CAD.

Pezzini *et al*² provide evidence of, in addition to the phenotype and genotype interaction, a differential effect of hyperH(e) influenced especially by smoking and hypertension. Therefore, there is a synergy between hyperH(e) and conventional risk factors. Vitamin supplementation for patients with stroke would be a cost-effective treatment in patients with hyperH(e). However, for the last word on vitamin supplementation for patients with stroke, results from the Vitamins to Prevent Stroke trial should be awaited.

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