

Homocysteine is a risk factor for cerebral small vessel disease, acting via endothelial dysfunction

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Introduction

Lacunar infarction accounts for about 25% of ischaemic strokes. Infarcts can be isolated or accompanied by more diffuse changes known as leukoaraiosis. Both lacunar infarction and leukoaraiosis are thought to be caused by cerebral small vessel disease (SVD). The proposed mechanism is via endothelial dysfunction. This can be detected *in vivo* by elevated levels of the soluble plasma markers intercellular adhesion molecule 1 (ICAM1) and thrombomodulin (TM).

Homocysteine is known to be toxic to the endothelium and it thought to affect endothelial function. The most frequent genetic defect associated with hyperhomocysteinaemia involves the enzyme methylene tetrahydrofolate reductase (MTHFR). The polymorphism C677T is associated with highest homocysteine levels.

Issue addressed in paper

This paper investigated whether a) elevated homocysteine levels and b) the MTHFR polymorphism C677T are risk factors for SVD as a whole and whether they have differential effects in the two SVD subtypes. It was also determined whether the effects of elevated homocysteine were mediated via endothelial dysfunction.

Summary of Findings

Serum homocysteine and ICAM1 and TM levels were analysed and MTHFR genotyping performed in 172 SVD patients and 172 controls. The main findings were as follows:

- Mean homocysteine levels were higher in SVD patients than in controls (14.55 μ mol/l compared to 12.01 μ mol/l).
- Homocysteine levels also correlated with the extent of disease (grade of both large focal lesions and leukoaraiosis).
- Homocysteine was a more significant risk factor with ischaemic leukoaraiosis compared to isolated lacunar infarction.
- Homocysteine levels were associated with the markers of endothelial dysfunction ICAM1 and TM.
- **Inclusion of these markers as covariates reduced the association with homocysteine but improved the overall logistic regression model for prediction of SVD.**
- These findings are consistent with the hypothesis that endothelial dysfunction is an important mechanism through which homocysteine mediates its effects in SVD.
- The MTHFR C677T polymorphism was only overrepresented in patients with ischaemic leukoaraiosis and was only found to be a risk factor in this group.

Conclusions

Current treatment of patients with SVD is limited. Homocysteine levels may be modified using folate and vitamin B12. This treatment may be particularly effective in patients with SVD because:

1. Homocysteine levels in SVD correlate with low vitamin B12 and folate levels.
2. It has been found that in individuals with the MTHFR C677T genotype (overrepresented in SVD) folate status is particularly influential of homocysteine levels.
3. Lowering homocysteine with folic acid has been shown to have beneficial effects on endothelial dysfunction.

Therefore vitamin supplementation may offer therapeutic benefit in different stroke subtypes and be especially beneficial to patients with ischaemic leukoaraiosis.