COMMENTARY

Homocysteine and stroke: another brick in the wall

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ABSTRACT

After a long debate, due to conflicting data from clinical studies, homocysteine is now largely accepted as a risk factor for cardiovascular diseases including stroke. To date, the role of elevated homocysteine levels in stroke recurrences has not been evaluated. In the present issue of Clinical Science, Zhang and co-workers prove that Chinese patients with high homocysteine levels have an increased risk of stroke recurrence and of all-cause mortality with respect to patients with lower levels. Remarkably, in their study, high homocysteine levels were associated with an increased risk of stroke recurrence for atherothrombotic stroke and intracerebral haemorrhage, but not lacunar stroke. The study by Zhang and co-workers provides important information for clinical practice and represents the basis for further investigations, as it raises questions referring to the puzzling relationship between homocysteine and cardiovascular disease. Moreover, the results support the hypothesis that, for undisclosed reasons, the relationship between homocysteine and cardiovascular disease may not be homogeneous for all the conditions encompassed in the category of cardiovascular disease, being peculiar for stroke patients. The finding of an association between high homocysteine levels and a risk of recurrent stroke or all-cause mortality in patients with intracerebral haemorrhage should be taken with caution until this same result is confirmed in other case series with different ethnicity.

Key words: atherothrombosis, homocysteine, intracerebral haemorrhage, methylenetetrahydrofolate reductase (MTHFR), mortality, stroke.

Abbreviations: CI, confidence interval; RR, relative risk.
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This result is in agreement with findings showing that, in patients with stroke, increasing plasma homocysteine levels were associated with ischaemic stroke caused by large-artery atherosclerosis and, to a much lesser extent, by small-artery disease, but not cardioembolic or other aetiological subtypes of ischaemic stroke [4]. Intriguingly, in the study by Zhang et al. [3], the MTHFR (methylene tetrahydrofolate reductase) variant C677T was not associated with a greater risk of stroke recurrence and all-cause mortality.

The study by Zhang et al. [3] gives important information for clinical practice and represents the basis for further investigations, as it raises questions referring to the puzzling relationship between homocysteine and cardiovascular disease. Several interventional prospective studies have demonstrated that administration of folic acid and vitamin B12 lower plasma homocysteine levels [5,6], but clinical trials failed to demonstrate any benefit from homocysteine-lowering therapy on secondary prevention of cardiovascular disease [7–11], making questionable any evidence in support of a possible reduction in cardiovascular risk through a decrease in homocysteine levels. Several interpretations were taken into account to explain the negative results of the trials, including (i) that mild hyperhomocysteinaemia may not represent a causative risk factor, (ii) that the statistical power of the trials was insufficient to exclude a small clinical benefit, (iii) that homocysteine-lowering therapy with combinations of B vitamins produces some adverse vascular effects that mask the benefit of lowered homocysteine levels, (iv) that the duration of the trials was too short, or (v) that mild hyperhomocysteinaemia is associated with an increased vascular risk not because it is directly involved in the pathogenesis of vascular disease, but because it is a marker of other harmful processes such as chronic kidney disease. Moreover, given our knowledge of the mechanisms of action of homocysteine, we cannot exclude that the effects of elevated homocysteine levels on the brain might be irreversible [12]. If this is the case, once the pathological changes have appeared the beneficial effects of vitamin supplementation would be limited. Consequently, trials to evaluate this possibility should examine the impact of B vitamin supplementation in the primary prevention of cardiovascular disease, especially giving treatment at an earlier point in the development of atherosclerosis, whereas the available trials evaluated the role of homocysteine in patients who already presented with cardiovascular disease. Moreover, results from the study by Zhang et al. [3] support the hypothesis that, for undisclosed reasons, the relationship between homocysteine and cardiovascular disease may not be homogeneous for all of the conditions encompassed in the category of cardiovascular disease, being peculiar for stroke patients. In fact, in the HOPE-2 (Heart Outcomes Prevention Evaluation-2) study, despite the finding that homocysteine-lowering B vitamin therapy was not better than placebo in terms of the primary composite outcome of cardiovascular death, myocardial infarction and stroke, the risk of stroke was reduced by 25% [10]. Similarly, a post-hoc analysis of results from the VISP (Vitamin Intervention for Stroke Prevention) trial, excluding patients likely to have vitamin B12 malabsorption, who were taking vitamin B12 supplements outside the study and patients with renal impairment, showed that high-dose vitamin therapy significantly reduced stroke, coronary events and death [13]. For the above-reported reasons, at present there are insufficient findings to reliably exclude a clinically important effect of B vitamins in preventing stroke, especially according to patient subgroups and stroke types. Studies evaluating the role of homocysteine-lowering treatment in primary and secondary stroke prevention focusing particularly on subtypes of ischaemic stroke are warranted.

Finally, a comment should be made to the reported association between high homocysteine levels and the risk of recurrent stroke or all-cause mortality in patients with intracerebral haemorrhage. This finding replicates what the authors have already reported in the same cohort of patients [14,15] and cannot be easily explained. We think that before going through mechanisms that might explain the reported association, the same findings should be confirmed in other case series with different ethnicity in order to reveal whether race is the main determinant of such an association.

REFERENCES


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