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Left Atrial Thrombus Despite Anticoagulation: The Importance Of Homocysteine

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Abstract

Patients in atrial fibrillation may have left atrial thrombi or strokes despite adequate anticoagulation. It is important to consider elevated plasma total homocysteine (tHcy) as a treatable clotting factor that may explain such cases. Metabolic B12 deficiency is common even in patients with a "normal" serum B12. Measurement of holotranscobalamin, methylmalonic acid or, in folate-replete patients, tHcy are necessary to diagnose metabolic B12 deficiency when the serum B12 is below 400 pmol/L. Elevated tHcy quadruples the risk of stroke in atrial fibrillation, and is far more common than the usual clotting factors for which testing is commonly performed: among patients attending a secondary stroke prevention clinic, tHcy > 14 µmol/L is present in 20% at age 40, and in 40% at age 80. B vitamin therapy does reduce the risk of stroke; key issues are renal impairment and adequacy of vitamin B12. This intervention should be considered routinely in patients with AF.

Introduction

The recent case report by Florea et al.[1] answers a question that has arisen from time to time in my secondary stroke prevention clinic, when a patient in atrial fibrillation (AF) who appears to be adequately anticoagulated has a recurrent stroke. It becomes necessary to reconsider the cause of stroke, because we tend to assume that anticoagulation is effective in preventing stroke in AF.

I have thought in the past that most of these cases were due to an unrecognized period of low INR, during which a thrombus formed, with insufficient time for the thrombus to dissolve when the INR rose again to the therapeutic range. However, I have also seen this problem in patients anticoagulated with the new oral anticoagulants (dabigatran, rivaroxaban, apixaban).

An issue that should be considered in such cases is whether the patient may have a high plasma level of total homocysteine (tHcy), which increases the formation of red thrombus in the setting of deep vein thrombosis, retinal vein thrombosis, cerebral vein thrombosis, and quadruples the risk of stroke in atrial fibrillation.[2,3]

In the era of folic acid fortification, the main nutritional cause of elevated tHcy is metabolic B12 deficiency. This condition is much more common than most physicians suppose, because it is usual to consider that a serum B12 in the "normal" range excludes B12 deficiency. However, measuring total serum B12 is not adequate to occlude B12 deficiency, because only small and variable fraction of serum B12 is active (around 6-20%). Measurement of holotranscobalamin is more accurate for diagnosis of B12 deficiency,[4,5] but this test is often not available. The specific diagnosis of metabolic B12 deficiency is made by measuring methylmalonic acid (MMA), but in folate-replete patients the tHcy can substitute for MMA. The serum B12 below which both MMA[6] and tHcy[7] begin to rise is 400 pmol/L, well within the usual "normal" range of serum B12 (~ 160-600 pmol/L).

Among my vascular patients, metabolic B12 deficiency is present in 12% below age 50, 13% of those age 50-70, and 30% age >718. Among patients attending my vascular prevention clinics, the prevalence of tHcy > 14 rises from 20% at age 40 to 40% by age 809 (at which age AF is far more common). (Figure 1.) This means that elevated tHcy is far more common than the clotting factors for which testing is commonly carried out (protein C, protein S, Factor V Leiden etc. This is probably why in the subgroup analysis of the Vitamin Intervention in Stroke Prevention (VISP) trial10 from which participants who received B12 injections were excluded (along with patients in renal failure), high-dose vitamins significantly reduced stroke, death and myocardial infarction. B vitamins also reduced the risk of stroke in the HOPE-2 trial11 (the only one to use an adequate dose of B12 for elderly patients), and in the SufolOM3 trial12.

It is now clear that vitamin therapy to reduce tHcy does reduce the risk of stroke.[13-15] key reasons for the widespread belief that they did not are related to vitamin B12 dose and renal failure. Those issues have recently been reviewed.[13,14] B vitamin therapy should not be called

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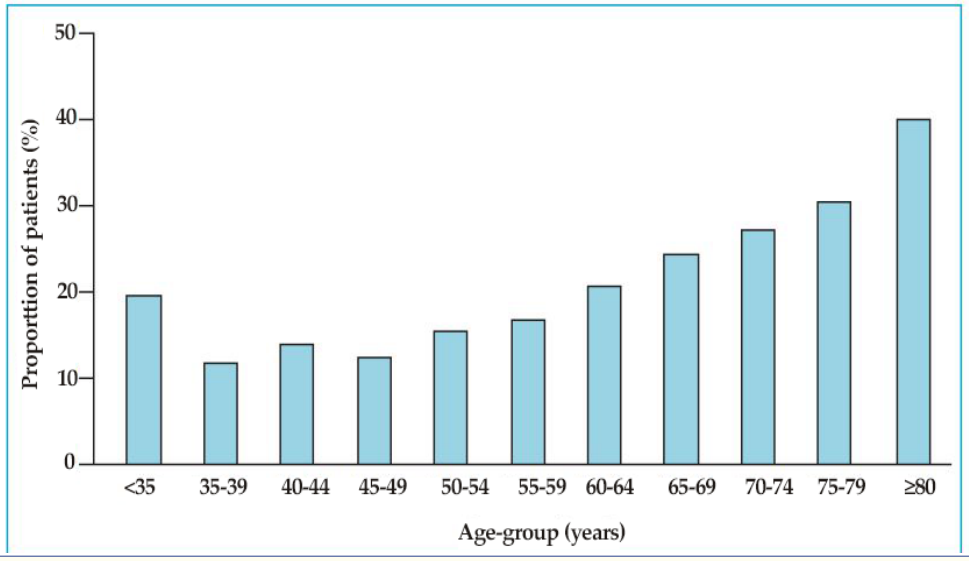

Figure 1: **Age distribution of increased plasma total homocysteine (≥14 µmol/L) among patients referred to vascular prevention clinics (Permission requested from Elsevier to reproduce this figure from 9)**

"folate therapy", and B vitamins that include cyanocobalamin are harmful in patients with renal failure (GFR<50). We should be using methylcobalamin instead of cyanocobalamin, and in patients with atrial fibrillation this intervention should be a routine consideration.

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