CAN SUPPLEMENTATION WITH FOLIC ACID AND VITAMINS PREVENT STROKE AND DEMENTIA? VITAMIN B12 MAY BE THE KEY

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Metabolic deficiency of vitamin B12 is much commoner than most physicians suppose, because laboratory reports giving the "normal" range commonly provide a range that includes many patients with metabolic B12 deficiency (eg 160-600 pmol/L). Absorption of vitamin B12 is very complex: it requires a salivary factor (haptocorrin), gastric acid, intrinsic factor, pancreatic third factor, an intact ileal mucosa, and transport proteins including transcobalamin I and II. Thus there are many ways for B12 absorption to become defective. Above age 65, 20% of the population have metabolic B12 deficiency(1), which can be defined by a serum B12<258 pmol/L and an elevated level of methylmalonic acid (or in folate-replete subjects, a total homocysteine level >14 µmol/L)(2). In our patients with vascular disease, metabolic B12 deficiency was present in 11% of patients age <50, 12% of those age 50-71, and 30% of those age >71(3).

With folate supplementation of the grain supply, only 1.7% of the population are deficient in folate(4), and In folate-replete subjects, the key factor determining plasma tHcy is B12(3). Since folate fortification of the grain supply in North America, we showed that serum B12 is directly related with plasma total homocysteine, and patients with lower B12 levels have significantly more carotid plaque than those with higher levels of serum B12(3). Although folate supplementation has not been shown to reduce the risk of myocardial infarction, a meta-analysis showed a significant reduction of stroke(5).

In elderly patients with serum B12 in the lowest quartile, 1000 mcg per day of oral B12 is needed to achieve adequate absorption (2). The only clinical trial to use that dose of B12, the HOPE study, showed a 23% reduction of stroke with vitamin therapy (p<0.03). When patients who received B12 injections and those with renal failure were excluded from the VISP population, high-dose vitamin therapy reduced stroke, death and coronary events by 34% (p=0.02)(6).
The HOPE-2 trial, which was the only trial to use as high a dose of B12 as 1mg/day, showed a significant 23% reduction of stroke (p=0.03)(7). Reasons why stroke might be reduced when myocardial infarctions were not were reviewed recently(8). Whereas virtually all myocardial infarctions are due to plaque rupture with in situ thrombosis of a coronary artery, only a small fraction of stroke (perhaps 5%) is due to carotid occlusion. Except for lacunar infarctions (which are mostly attributable to hypertensive small vessel disease or diabetes), most strokes are embolic: either atheroembolic events from proximal disease in the extracranial arteries, or embolic from the heart. Elevated total homocysteine (and B12 deficiency) increases thrombosis in deep veins(9;10), cortical veins(11), retinal veins and cerebral venous sinuses(12); it increases the risk of stroke in atrial fibrillation more than 4-fold (13).
Vitamin therapy for lowering of homocysteine should no longer be called "folate therapy". With the high prevalence of undiagnosed B12 deficiency in the elderly, and with the disappearance of folate depletion with folate supplementation, the key factor in prevention of stroke and dementia associated with elevation of total homocysteine is vitamin B12.

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