

Homocysteine and Cognitive Impairment



I have had a research interest in B vitamins and Alzheimer's Disease since 1990. During that year, as a GP Trainee, I met a fifty-three-year-old patient with memory problems and a strong family history of dementia. The family were later found to be one of the first kindreds with a mutation in the amyloid precursor gene¹. I was particularly intrigued by the finding of very low vitamin B₁₂ levels in my patient and his family², and set about researching the vitamin's relationship to dementia.

One consequence of vitamin B₁₂ deficiency is a raised blood level of homocysteine³. This non-essential amino acid is derived from dietary protein. Its conversion to useful metabolites (S-adenosylmethionine and the antioxidant glutathione) requires methyl-folate and vitamins B₁₂ and B₆ as cofactors. Blood levels of homocysteine therefore rise with deficiency of these important vitamins. Prompted by my finding of low B₁₂ levels in the family with early onset dementia, I decided to look for evidence of deficiency in patients with late onset dementia. In 1998, together with colleagues working at my local hospital, I discovered elevated homocysteine levels in patients with clinically diagnosed Alzheimer's disease (AD)⁴.

We later showed that homocysteine is an independent predictor of cognitive decline in healthy elderly individuals over a five-year period⁵. Others have since confirmed this observation⁶. For example, a high homocysteine in midlife is an independent risk factor for the development of late-life AD in women up to thirty-five years later⁷. Patients with vascular dementia and mild cognitive impairment (MCI) frequently also have 'hyperhomocysteinemia', and it is now a well-recognised risk factor for cognitive decline and incident dementia^{4,8,6}.

Although cognitive disorders have been the focus of such research in recent decades there are also reports of hyperhomocysteinemia

in other chronic neurodegenerative disorders such as Multiple Sclerosis and Parkinson's Disease⁹. This has led to speculation as to whether hyperhomocysteinemia is an independent causal risk factor for AD or a secondary epiphenomenon related to neurodegeneration itself¹⁰. For example, one suggestion is that it likely reflects B vitamin depletion due to neuro-inflammatory oxidative stress¹¹. In any event, hyperhomocysteinemia appears to be an important component of the dementia process and is related to neurotransmitter deficits, tau hyperphosphorylation and amyloid deposition^{12,13}.

Homocysteine can be lowered by B vitamin supplementation. Case-studies in cognitively impaired hyperhomocysteinaemic patients in my own general practice population showed improved cognition following B vitamin and antioxidant supplementation¹⁴. Clinical evidence has been equivocal for cognitively intact individuals and negative for patients with established AD^{15,16,17}. However, a Cochrane review summarised intervention studies by suggesting that long-term supplementation of folic acid, with or without vitamin B₁₂, might benefit healthy older people with high homocysteine levels¹⁸.

VITACOG is a recently completed randomised placebo-controlled two-year trial of high-dose B vitamin supplementation in elderly individuals (>70 years) with MCI¹⁹. Treatment comprised 0.8mg folic acid, 0.5mg vitamin B₁₂ and 20mg of vitamin B₆. The primary outcome was brain atrophy rate measured by serial volumetric MRI scans, but the trial also evaluated clinical and cognitive function.

Complete scans were available for 83 placebo and 85 treated subjects. In these subjects, homocysteine levels fell by 22.5% in treated subjects but increased by 7.7% in the placebo group. Consistent with earlier reports, higher homocysteine levels were associated with an increased rate of brain atrophy. Atrophy was significantly slowed by 30% in treated individuals

with a baseline homocysteine level >9.5 $\mu\text{mol/L}$. Those with the highest baseline level (>13 $\mu\text{mol/L}$) had a rate of atrophy 53% lower than the placebo group.

In the larger cohort of subjects completing the cognitive component of the trial (113 received placebo and 110 B vitamins) there was a significant benefit of B vitamins amongst those with homocysteine > 11 $\mu\text{mol/L}$ in scores of global cognition, episodic memory and semantic memory²⁰. There was also an improvement in clinical rating scales (the Informant Questionnaire on Cognitive Decline in the Elderly and the Clinical Dementia Rating) in the B vitamin group, but only in subjects with a homocysteine >13 $\mu\text{mol/L}$. Remarkably, treatment more than doubled the number of subjects with a Clinical Dementia Rating of zero (equating to no dementia) compared with no effect in the placebo group.

In summary, the VITACOG trial shows that the combination of oral **high-dose** B₁₂, folic acid and B₆ significantly slows brain atrophy and cognitive decline in patients with MCI and raised homocysteine. Importantly, these two effects are highly dependent on baseline levels of homocysteine, perhaps partly explaining discrepant results in earlier trials^{15,16}.

Although very welcome news, there were several practical implications and difficulties in the light of these results. Physicians and public alike are generally unaware of the association of elevated homocysteine and the risk of developing dementia, and even less aware of the latest evidence showing beneficial effects of homocysteine reduction. Currently homocysteine assays are neither routinely nor widely available, although they can be a useful screening test for B₁₂ and folate deficiency²¹. Testing for high homocysteine in elderly subjects with early MCI may also have a place in determining the appropriate treatment of such patients.

The VITACOG trial suggests that patients with MCI and elevated Hcy will undoubtedly benefit from a combination of oral folic acid (0.8mg),

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vitamin B₁₂ (0.5 mg) and vitamin B₆ (20 mg). However, no such single high-dose licensed prescription formulation exists, at least in the United Kingdom. Treatment therefore requires a multiple-item prescription with its ensuing cost to the patient and the associated issue of poor compliance.

In the light of the very positive results seen in the VITACOG trial I therefore set about full-scale development of such a combination product. My own practice with patients presenting with MCI is to measure their homocysteine level and, if >10 µmol/L, I had seen successful results from treating them with 0.8mg of folic acid, 20mg vitamin B₆ and 1mg of oral vitamin B₁₂ daily; the latter was not available on NHS prescription but available over the counter at many health stores. I had also found considerable additional cognitive benefit from including the antioxidant N-acetylcysteine (600mg) together with B vitamins¹⁴. This addresses oxidative stress, further lowers homocysteine by increasing its urinary excretion, and can benefit cognitive scores in patients with established AD²².

I therefore formulated Betrinac® based on these components. The vitamins used in Betrinac® are within the allowable dose range for EU food supplements, hence it is available as an "over-the-counter" rather than prescription product. It is of course not yet confirmed whether such intervention on a larger scale will ultimately reduce the incidence and burden of dementia. However, a recent estimate is that homocysteine lowering has the potential to lead to a 20% reduction in risk of dementia, the financial and social implications of which are of course considerable²³.

Another issue is how frequently should patients with MCI have homocysteine levels tested? Current guidelines suggest an assessment of B vitamin status every 3–5 years because dietary or drug changes may lead to deficiency, the symptoms of which may be mistakenly attributed to insidious dementia and hence go undetected²¹.

Importantly, VITACOG now sets the stage for larger and longer trials to study the effects of B vitamins on conversion rates from MCI to dementia. The results also offer a

glimmer of hope in treating a condition that has otherwise become associated with a degree of therapeutic nihilism. Physicians can now also avoid the twin trap of overtreatment by clearly defining those individuals who are most likely to benefit.

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Andrew McCaddon MD

is a Principal GP in Wrexham and an Honorary Senior Research Fellow in the

School of Medicine, Cardiff University. His research interest in B vitamin deficiency and Alzheimer's disease led to the formulation of Betrinac® – a high-dose B vitamin and antioxidant supplement.

Email: mccaddon@sky.com



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Email: mccaddon@sky.com