The Prevention of Memory Loss and Progression to Alzheimer's Disease with B Vitamins, Antioxidants and Essential Fatty Acids: A Review of the Evidence

Patrick Holford, Bsc, DipION, FBANT, NTCRP[1]

[1] Food for the Brain Foundation, London, UK, email: patrick@foodforthebrain.org

Abstract *Memory loss and increased risk of Alzheimer's disease (AD) is strongly associated with low levels of B_{12} and folic acid, fish consumption and raised plasma homocysteine (Hcy). Placebo controlled trials have shown protection from memory loss and/or reduced brain shrinkage in older people with raised Hcy levels given high dose supplements of vitamin B_{12}, folic acid, B_6 or docosahexaenoic acid. In those with early stage AD there is some evidence of a reduction in cognitive decline in those given high dose B vitamins. There is inconclusive evidence regarding the combined supplementation of high dose vitamin C, together with vitamin E. The need for early screening for cognitive decline and raised Hcy is essential given the growing body of evidence that Hcy lowering nutrients arrest cognitive decline and accelerated brain shrinkage.*

Introduction

Alzheimer's disease (AD) is characterized by a progressive loss of cognitive functions including memory, language, judgment, praxis and orientation and is diagnosed on the basis of shrinking in the thickness of the medial temporal lobe, which is considered to be the primary pathology that generates the associated symptoms.[1] The detectable, preclinical phase of AD presents as mild cognitive impairment (MCI).[2,3]

Episodic memory impairment is the most common initial symptom of MCI.[4] Poor performance in verbal or visuospatial memory recall, processing speed, attention and executive function tasks requiring planning or judgement and semantic fluency are common predictors of Alzheimer's risk.[5-7] (These aspects of memory and cognitive function are included in Food for the Brain's Cognitive Function Test available free online at: www.cognitivefunctiontest.org).

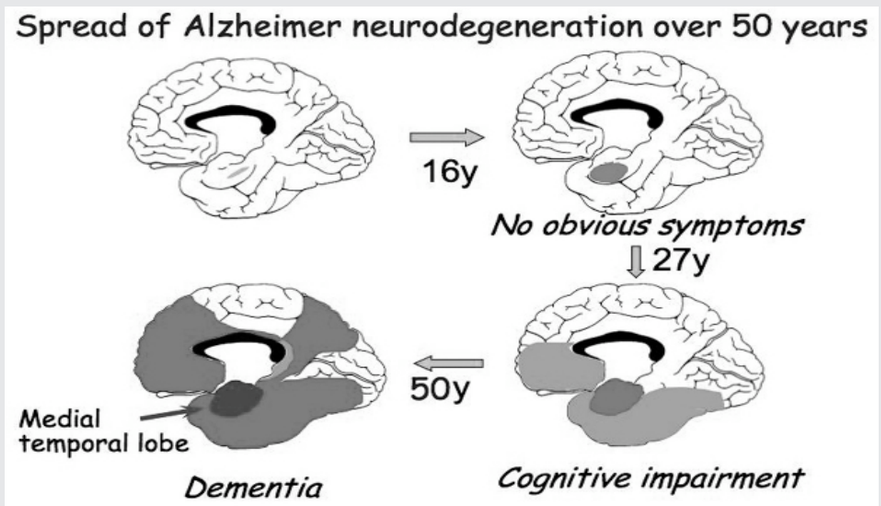
The process of memory decline and brain shrinkage associated with AD is thought to occur over a 30 to 40 year period, hence identifying the need for screening ideally from age 50 (see **Figure 1**, p.54).

High Homocysteine, and Low Folic Acid and Cobalamin Status as Markers

Both high plasma homocysteine (Hcy) levels and low folic and (cobalamin) B_{12} levels in blood correlate with increasing risk for AD according to a systematic review.[8] A review in 2008 concluded: "Seventy-seven cross-sectional studies on more than 34,000 subjects and 33 prospective studies on more than 12,000 subjects have shown associations between cognitive deficit or dementia and Hcy and/or B vitamins."[9] Hcy levels also predict and correlate with rate of cognitive decline,[10] as does B_{12} status.[11,12]

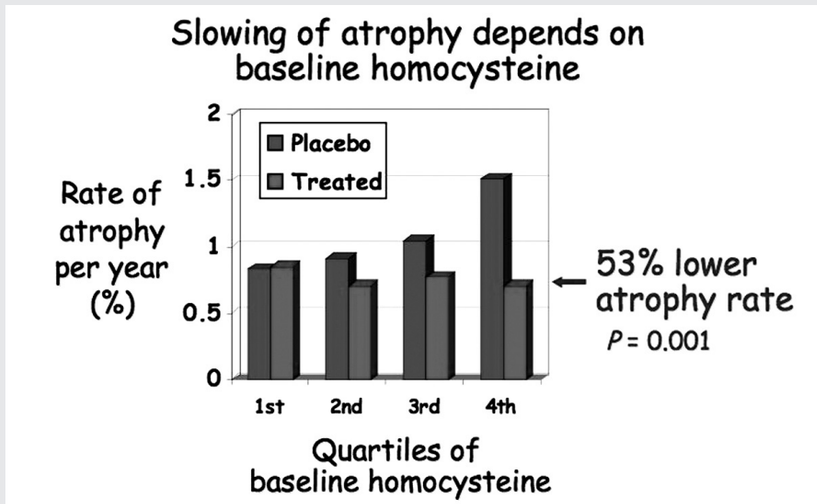
There is, therefore, ample evidence to propose that lowering Hcy by giving appropriate supplemental levels of Hcy lowering nutrients,

Figure 1. Spread of Alzheimer neurodegeneration over 50 years.



Used with permission of AD Smith[1]

Figure 2. Slowing of atrophy depends on baseline homocysteine



Used with permission of AD Smith[14]

including B_6, B_{12} and folic acid, would reduce risk. At what point in the process are cognitive decline reversible, and what dosage of nutrients confers maximum protection?

Clinical Trials of B Vitamins in Relation to Prevention of Memory Decline

Durga et al provided older adults (>50 years) without MCI, but with raised Hcy (>13 μmol/L), supplemental folic acid (0.8 mg/d) or placebo for three years.[13] The results demonstrated a highly significant improvement in memory, information processing speed and sensorimotor speed in the treatment group.

AD Smith et al. investigated the effects of giving B vitamins versus placebo in a randomized controlled trial to those with MCI, measuring brain shrinkage with an MRI scan, as well as cognitive function.[14] In this study a Hcy above 9.5 μmol/L correlated with accelerated brain shrinkage and cognitive decline. Those given folic acid (0.8 mg/d), vitamin B_{12} (0.5 mg/d) and B_6 (20 mg/d) had a significant reduction in the rate of brain shrinkage (p=0.001; **Figure 2**, p.55). Treated patients with baseline Hcy levels > 13 μmol/L had rates of atrophy that were 53% lower than other patients in the treatment group. Greater rates of atrophy were associated with lower final cognitive test scores.

De Jager evaluated changes in cognition in patients with MCI from the previous study, given B vitamins or placebo. These results, pending publication, indicate a greater decrease in cognitive function with higher baseline Hcy, with effectively no significant further decline in those taking the B vitamins. In patients with a baseline of Hcy above 11 μmol/L, the difference in cognitive decline between the placebo and supplemental group was significant.[15]

Aisen et al. gave Hcy-lowering B vitamins to those already diagnosed as suffering from mild to moderate AD.[16] Patients were not selected on the basis of Hcy values (mean Hcy was 9.1 μmol/L at baseline), and brain scans were not conducted. The patients received folic acid (5 mg/d), B_{12} (1 mg/d), and B_6 (25 mg/d over a period of 18 months). No overall difference occurred in rate of cognitive decline in those on the supplements versus placebo. However, when the patients were divided into those with high and low cognitive test scores at the start, those who had milder AD did significantly respond; those taking the B vitamins hardly got worse over 15 months, while those on the placebo showed a steady decline. Over the 18 months Hcy dropped from an average of 9.1 μmol/L to 6.8 μmol/L.

Kwok et al. studied 140 subjects with mild to moderate AD or vascular dementia given either methyl B_{12} (1 mg/day) and folic acid (5 mg/day) or placebo for 24 months.[17] They found a significantly smaller decline in the Mattis Dementia Rating Scale (construction domain) in the supplemented subjects with a baseline Hcy>13 μmol/L (p=0.003).

Ford et al. gave 299 older hypertensive men without cognitive impairment either B_{12} (0.4 mg), folic acid (2 mg), B_6 (25 mg) or placebo over two years.[18] No change was found in the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog). However this test is not sufficiently sensitive to changes outside of the scope of MCI and dementia. Also, homocysteine levels were not measured.

These studies suggest that Hcy-lowering B vitamins can, at least, arrest cognitive decline and possibly improve it in people over age 50, with or without cognitive decline, but with a raised Hcy level (>9.5 μmol/L), and may arrest or slow down cognitive decline in those with mild AD, but not in moderate to severe AD. However, it is conceivable that AD patients with raised Hcy may respond differently.

Further research is needed to determine if these improvements prevent the development of AD, and to determine what combination and intake of Hcy lowering nutrients have the most significant clinical effect. This is also the conclusion of a recent review.[19]

The effect of lowering Hcy could potentially have many positive effects on brain function. Hcy is itself a toxic amino acid capable of inducing neurotoxicity those NMDA receptor activation and oxidative stress through increasing NOS. It also damages blood vessels potentially impairing oxygen and nutrient flow to the brain, associated with vascular dementia. Raised Hcy also reflects faulty methylation. Methylation is required for the formation of neurotransmitters and phospholipids. Lowering Hcy is also associated with reducing oxidative stress.

The Role of N-Acetyl Cysteine, Glutathione, and MethylB_{12}

Methylation requires the synthesis of S-adenosyl methionine (SAM) from Hcy, a pathway that is B_{12} and folic acid dependent. SAM

synthesis is impaired by oxidative stress, while B_{12} is also vulnerable to oxidative deactivation. Oxidative stress increases the requirement for SAM but decreases its synthesis. In the liver, Hcy can also be metabolized via the transsulphuration pathway to synthesize the essential intracellular antioxidant, glutathione. Theoretically, by providing glutathione, or its precursor N-acetyl cysteine (NAC), together with methylB_{12}, SAM can be spared and Hcy lowered.

A small number of general practitioners have been implementing a B vitamin based Hcy management approach, including NAC and reported good outcomes. A series of case reports have been published.[20] Quoting the author: "Patients presenting with mild cognitive impairment frequently have raised blood Hcy levels; I routinely measure this in all such cases. There is now good evidence for lowering elevated levels with high dose B-vitamins. I also prescribe the antioxidant NAC to further lower Hcy. In my experience, I have found significant clinical improvement from this approach."

Hcy can also be processed in the liver by the betaine-homocysteine methyl transferase (BHMT) pathway, requiring trimethylglycine (TMG) and zinc. The addition of NAC, TMG and zinc to the usual combination of B_{12} (ideally as methyl B_{12}), folic acid and B_6 has yet to be tested in a clinical trial and may yield further reductions in Hcy with associated clinical improvements.

Vitamins C and E

A cross-sectional and prospective study of 4,740 Cache County Utah elderly residents found the combination of vitamin E and C to be associated with reduced AD prevalence of 78% and incidence of 63%. A trend toward lower AD risk was also evident in users of vitamin E together with multivitamins containing vitamin C, but there was no evidence of a protective effect with use of vitamin E or vitamin C supplements alone, with multivitamins alone, or with vitamin B-complex supplements. Lowest risk was reported in those supplementing at least 1,000 mg/day of vitamin C with at least 1,000 IU/day of vitamin E.[21] In a double-blind study, subjects with MCI were randomly assigned to receive 2,000 IU/day of vitamin E, 10 mg/day of donepezil, or placebo for three years. There were no significant differences in the rate of progression to AD between the vitamin E and placebo groups at any point.[22] These results suggest that there might be more therapeutic gains when treating patients that have yet to develop either MCI or AD. These results also suggest that both vitamins E and C are likely to be more beneficial than using vitamin E alone.

Fish Consumption and Omega-3 Essential Fatty Acid Supplementation

Eating fish once a week reduces risk of developing AD by 60%, according to a study by Morris et al.[23] They followed 815 people, aged 65 to 94 years, for 7 years and found that the dietary intake of fish was strongly linked to AD risk. They found that the strongest link was the amount of docosahexaenoic acid (DHA) in the diet; the higher the DHA intake the lower their risk of developing AD. The lowest amount of DHA per day that offered some protection was 100 mg. Eicosahexaenoic acid (EPA) intake did not reach significance; however, the highest intake of EPA consumed was 30 mg a day.

In a RCT, 900 mg of DHA was taken daily for 24 weeks with reported improvements in learning and memory function among those with age-related cognitive decline.[24] In a further trial by the same research group, 2,000 mg/day of algal DHA or placebo to 402 subjects with mild to moderate AD for 18 months resulted in no cognitive improvement.[25]

Clinical Recommendations

AD is an advanced disease process, requiring many years of progression before it is clinically diagnosed. Using nutritional supplements late in the disease process may yield limited benefits. However, the low cost and potential benefits of nutritional supplements make them attractive therapeutically. On the basis of the evidence, there is good logic to pursue specific clinical recommendations, especially among patients without any evidence of cognitive impairment. Patients 50 years or older should have their cognitive function tested. Hcy should also be tested in patients exhibiting signs of reduced cognitive function. Supplement Hcy-lowering nutrients daily if the Hcy result is above 9.5 µmol/L. These include:

- Folic acid: 400-800 mcg
- B_{12}: 500-1,000 mcg (preferably, methyl B_{12})
- B_6: 20-40 mg

There is good logic in using these additional daily nutrients:

- Zinc: 10-15 mg
- TMG: 1,000-2,000 mg
- NAC: 500-1,000 mg
- Omega-3 essential fatty acids (fish source): 500-1,000 mg DHA

While there might be some logic in supplementing with vitamin E (1,000 IU/day) and vitamin C (>1,000 mg/day) among elderly individuals without MCI or AD, further research is needed.

Contraindications

Folic acid supplementation, especially in those with low vitamin B_{12} status, may increase colorectal and other cancer risk in older people.[26] This issue remains unresolved since a recent large-scale study by the American Cancer Society involving almost 100,000 people reported a reduced, not increased risk of colorectal cancer with increasing folate intake.[27] Until more definitive conclusions can be made, daily doses exceeding 400 mcg should be used with caution, especially in countries that have implemented food fortification with folic acid. It is also unknown if this cautionary recommendation applies to those supplementing with a combination of HCy-lowering nutrients as a result of raised Hcy levels.

Dietary Guidelines

There is an increasing body of evidence linking metabolic syndrome, insulin resistance and diabetes with risk for dementia/AD. Following a low glycemic load diet, high in oily fish, nuts, seeds and beans, with plenty of antioxidant rich fruits and vegetables, is likely to be protective. Limit or avoid coffee, which is known to raise Hcy levels. Whether or not coffee intake increases or reduces risk for AD is currently inconclusive.

Competing Interests

The author receives royalties of nutritional supplement formulae in the UK and South Africa.

References

1. Smith AD: Imaging the progression of Alzheimer pathology through the brain. *Proc Natl Acad Sci USA*, 2002; 99: 4135-4137.
2. Morris JC: Mild cognitive impairment and preclinical Alzheimer's disease. *Geriatrics,* 2005; (Suppl): 9–14.
3. Winblad B, Palmer K, Kivipelto M, et al: Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med,* 2004; 256: 240–246.
4. Peterson RC: Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. *J Int Med,* 2004; 256: 183–194.
5. deJager CA, Hogervorst E, Combrinck M, et al: Sensitivity and specificity of neuropsychological tests for mild cognitive impairment, vascular cognitive impairment and Alzheimer's disease. *Psychol Med,* 2003; 33: 1039–1050.
6. Perry RJ, Hodges JR: Attention and executive deficits in Alzheimer's disease. A critical review. Brain, 1999; 122(Pt 3): 383–404.
7. Oulhaj A, Wilcock GA, Smith AD, et al: Predicting the time of conversion to MCI in the elderly. *Neurology*, 2009; 73: 1436–1442.
8. Van Dam F, Van Gool WA: Hyperhomocysteinemia and Alzheimer's disease: A systematic review. *Arch Gerontol Geriatr,* 2009; 48: 425-430.
9. Smith AD: The worldwide challenge of the dementias: a role for B vitamins and Hcy? *Food Nutr Bull,* 2008; 29(2 Suppl): S143–S172.
10. Oulhaj A, Refsum H, Beaumont H, et al: Hcy as a predictor of cognitive decline in Alzheimer's Disease. *Int J Geriatr Psychiat,* 2010; 25: 82-90.
11. Smith AD, Refsum H: Vitamin B-12 and cognition in the elderly. *Am J ClinNutr,* 2009: 89: 707S–711S.
12. Tangney CC, Tang Y, Evans DA, et al: Biochemical indicators of vitamin B_{12} and folate insufficiency and cognitive decline. *Neurology,* 2009; 72: 361-367.
13. Durga J, van Boxtel MP, Schouten EG, et al: The effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomized, double blind, controlled trial. *Lancet,* 2007; 369: 208-216.
14. Smith AD, Smith SM, de Jager CA, et al: Hcy-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. *PLoS One*, 2010; 5(9): e12244.
15. de Jager CA: Cognitive and clinical outcomes of Hcy-lowering B vitamin treatment in mild cognitive impairment: a randomized controlled trial. *Unpublished manuscript*. 2011.
16. Aisen PS, Schneider LS, Sano M, et al: High-dose B vitamin supplementation and cognitive decline in Alzheimer disease. *JAMA,* 2008; 300: 1774–1783.
17. Kwok TJ, Lee A, Lawb CB, et al: A randomized placebo controlled trial of Hcy lowering to reduce cognitive decline in older demented people. *Clin Nutr,* 2011 [Epub ahead of print].

18. Ford AH, Flicker L, Alfonso H, et al: Vitamins $B_{(12)}$, B(6), and folic acid for cognition in older men. *Neurology.* 2010 Oct 26; 75(17): 1540-1547.
19. Sachdev PS: Hcy and Alzheimer disease: an intervention study. Nature Rev *Neurology,* 2011; 7: 9-10.
20. McCaddon A: Homocysteine and cognitive impairment; a case series in a General Practice setting. *Nutr J,* 2006; 5: 6.
21. Zandi PP, Anthony JC, Khachaturian AS, et al: Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. *Arch Neurol,* 2004; 61: 82-98.
22. Petersen R, Thomas R, Grundman M, et al: Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med,* 2005; 352: 2379-2388.
23. Morris MC, Evans DA, Bienias JL, et al: Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Arch Neurol,* 2003; 60: 940-946.
24. Yurko-Mauro K, McCarthy D, Rom D, et al: Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. *Alzheimers Dement,* 2010; 6: 456-464.
25. Quinn JF, Raman R, Thomas RG, et al: Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. *JAMA,* 2010; 304: 1903-1911.
26. Smith AD, Young-In K, RefsumH: Is folic acid good for everyone? *Am J ClinNutr,* 2008; 87: 517–533; see also Ebbing M, Bonaa KH, Nygard O, et al: Cancer Incidence and Mortality after Treatment with Folic Acid and Vitamin B_{12}. *JAMA*, 2009; 302(19): 2119-2126
27. Stevens VL, McCullough ML, Sun J, et al: High levels of folate, from supplements and fortification, are not associated with increased risk of colorectal cancer. *Gastroenterology,* 2011 [in press].