The role of homocysteine in dementia

It has been estimated that more than one million people in Europe alone succumb to dementia each year [1] and this figure is set to rise as the proportion of elderly in the population increases. It is estimated that almost 50% of people over the age of 85 currently suffer from dementia [2]. UN world population projections estimate that there will be close to 370 million individuals over the age of 80 by the year 2050, and a considerable proportion of these will be affected. The prospect is frightening. Every strategy to identify modifiable risk factors and prevent dementia should be considered.

Dementia is a complex disorder; genetic, environmental and/or lifestyle factors may be involved in the onset and progression of disease. This article discusses the evidence to suggest that elevated levels of homocysteine in the body may be a significant risk factor. Importantly, homocysteine levels are measurable and generally modifiable. It may be possible, therefore, to slow or prevent the onset or progression of dementia by controlling homocysteine levels. Immunoassays have made it possible to monitor homocysteine levels and determine who is at risk.

What is homocysteine?

Homocysteine is a sulphur-containing amino acid formed during the metabolism of methionine, an essential amino acid provided in food. Methionine metabolism takes place in the methylation cycle, an important metabolic pathway that generates S-adenosylmethionine (SAM), a methyl group donor that regulates protein, lipid, biogene amine, and DNA methylation, as well as many other methylation reactions.

Three important enzymes are directly involved in homocysteine metabolism and are, therefore, involved in regulating homocysteine levels in the body: methionine synthase (MS), betaine homocysteine methyltransferase (BHMT), and cystathionine β-synthase (CBS). These enzymes cannot function alone, however, and require vitamins B6 and B12, which are cofactors to their reactions. The MS-mediated reaction, in addition, requires folate as a substrate [Figure 2].

Homocysteine and dementia

The first evidence that elevated homocysteine levels might be involved in mental disorder was recorded in 1962, when homocysteine was identified in the urine of a group of mentally retarded children [3]. Later, genetic defects were discovered, which affect enzymes involved in homocysteine metabolism. Common manifestations of these defects include homocystinuria and vascular pathology, as well as mental disturbances.

In 1990, Regland and co-workers reported elevated homocysteine levels in the plasma of patients with cognitive impairment [4]. A large number of reports have since followed, in which elevated homocysteine levels have been found in cognitively impaired patients or patients with dementia [5].

Studies have also shown; an association between the degree of cognitive impairment and homocysteine levels; that an elevated homocysteine level is a risk factor for later development of dementia; and that there is an inverse association between cerebral tissue volume and homocysteine levels in patients with dementia.

How does homocysteine cause dementia?

Many possible mechanisms have been proposed to explain how homocysteine levels could affect brain function. These include both indirect and direct pathways. Elevated homocysteine can cause direct injury to small cerebral arteries and arterioles. Evidence suggests that it can damage endothelial cells, increase platelet activity, has pro-coagulant effects, increases collagen synthesis, and enhances proliferation of smooth muscle cells by several different biochemical mechanisms. These changes result in vascular damage, where elevated homocysteine can cause indirect damage to the brain by compromising oxygen supply; stroke is the most obvious example.

Studies of interactions between homocysteine and nitric oxide (NO) strongly support the idea that elevated homocysteine results in oxidative stress. This can cause both vascular and neurological damage, and seems to play a major role in aging and neurodegenerative disorders such as Alzheimer’s disease [6]. Adaptive changes by different antioxidant systems support this theory, as does evidence that the use of antioxidants can counter vascular damage, even though homocysteine levels are not lowered.

Another possible mechanism is that homocysteine may be neurotoxic by interacting with receptors for the neurotransmitter glutamate, the most important excitatory transmitter in the brain. In addition, disturbed homocysteine metabolism may indicate altered turnover of another folate dependent cofactor in neurotransmitter metabolism, tetrahydrobiopterin, which may compromise nerve function. Furthermore, elevated homocysteine can impact on SAM, the only
Why do homocysteine levels increase?
A large number of single nucleotide polymorphisms affecting enzymes implicated in homocysteine turnover have recently been identified. A common polymorphism of MTHFR, the C677T polymorphism, is present in its homozygous form in about 10% of most western populations. This polymorphism is associated with decreased enzyme activity and homocysteine levels approximately 25% above the norm [7]. In a recent study, an increased frequency of the homozygous genotype was found to be more common in patients with dementia (25.2% versus 12% in controls) [8]. In a Swedish study of Alzheimer’s patients, 17% were homozygous for the polymorphism. This polymorphism is also associated with an increased risk of ischaemic stroke. Folate supplementation efficiently reduced homocysteine levels in these subjects [9].

Many other factors influence homocysteine levels, but as described earlier, folate, vitamin B$_{12}$ and vitamin B$_{6}$ are important in homocysteine turnover. A deficiency in these compounds, or variations in their distribution, may disturb this metabolism, which results in an accumulation of homocysteine. Numerous studies have reported low serum and/or cerebral spinal fluid (CSF) levels of vitamin B$_{12}$ and folate in dementia patients. Two recent studies have also shown that low folate and/or vitamin B$_{12}$ status is a risk factor for the development of dementia [10, 11].

Besides vitamin deficiencies and genetic defects, lifestyle, age-related physiological changes, disease and drugs can directly, or indirectly, disturb homocysteine metabolism. Levodopa (L-dopa), for example, which is thought to contribute to dementia in Parkinson’s disease, substantially increases the requirement for SAM and increases homocysteine levels.

Some of these factors are non-modifiable, such as increasing age, kidney disease, certain drugs, diseases and genetic traits. Modifiable causes include B vitamin deficiency (from poor diet, smoking, excessive coffee consumption), low physical activity, and excessive alcohol intake.

Assessing risk
The apparent link between high levels of homocysteine and dementia, and the link between vitamin status and homocysteine turnover, raises the question: can either of these be used to measure the risk of developing the disease?

The relationship between vitamin status and risk of cognitive impairment in the elderly is complex. Many studies have found that elderly and cognitively impaired patients can have high homocysteine levels in spite of normal blood concentrations of folate and vitamin B$_{12}$. This is proposed, at least partly, to be a consequence of enzymatic defects. Enzyme activity may also decline with age. In addition, it is proposed that the C677T polymorphism has a stronger impact in elderly persons with a poor vitamin status, and some individuals may have higher vitamin requirements than ‘normal’ because of enzyme polymorphisms.

Several studies have demonstrated low CSF levels of both vitamin B$_{12}$ and folate in dementia patients, although serum levels were normal. This suggests that vitamin levels, and consequently the distribution of homocysteine levels, may be altered in the elderly. This was also indicated by the findings of significantly increased homocysteine levels in both demented and non-demented hospitalised elderly subjects compared with healthy elderly subjects living at home, although neither serum folate nor B$_{12}$ levels differed between the groups. The explanation might involve the formation of inactive vitamin analogues, which may not be detectable by current analytical methods; three studies have reported a lower ratio of active B$_{12}$ / analogues in demented patients. Disturbed transport of the vitamin may be another explanation.

Holo-transcobalamin (holoTC), the biologically active form of vitamin B$_{12}$, is a new marker for vitamin B$_{12}$ deficiency which seems to be a more reliable marker of vitamin B$_{12}$ status. Much lower holoTC levels have been found in elderly dementia patients than in healthy younger controls, although total serum B$_{12}$ levels were the same. Furthermore, a highly significant correlation between homocysteine level and holoTC is found in dementia patients, whereas there is no correlation with total serum B$_{12}$ levels.

Homocysteine mirrors the functional status of vitamins and the interactions between vitamins and genetic factors. It is, therefore, a sensitive marker of the whole methylation and folate metabolism process.

Treating dementia with vitamins
Once elevated homocysteine levels have been established, is it then possible to correct homocysteine levels with vitamin intake to restore normal cognitive function? Early cognitive decline associated with elevated homocysteine levels may regress, but treatment of dementia patients with vitamins is seldom successful. Considering the findings of vascular damage and loss of neurons in these patients, this is hardly unexpected. Studies have shown, however, that atherosclerotic plaque development may be reduced after vitamin treatment.

Vitamins may have value as a preventive measure, or as a treatment, very early in the disease development process. The value of this strategy is being assessed in large, ongoing clinical studies, such as the Alzheimer’s disease cooperative study. This will hopefully indicate to what extent preventive homocysteine-lowering therapy may prevent or postpone the onset of dementia.

Even if homocysteine-lowering treatment is successful in just 10% of cases, several hundred thousands of people per year would be spared from dementia worldwide [12]. In addition to the personal suffering involved, care of dementia is already estimated to cost more than the care of cancer and vascular patients combined [13], which is another strong argument for monitoring homocysteine levels and taking preventative measures where appropriate.

References
Figure 3. Determinants of homocysteine (courtesy of J. Schneede).

(Further references to studies mentioned in this article can be can be obtained from the author, or in the book: Homocysteine, Related Vitamins and Neuropsychiatric Disorders by Christina Bolander-Gouaille and Teodoro Bottiglieri. Springer Verlag 2003. ISBN:2-287-04393-4. The book provides over 1000 references).

The author
Christina Bolander-Gouaille, BSc
gouaille@telia.com