Reviews

Plasma Homocysteine: A New Risk Factor for Alzheimer's Disease?

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Dementia is a common and devastating public health problem, affecting an estimated 5–10% of individuals over the age of 65 [1]. Two pathologically distinct subtypes of dementia – vascular dementia and Alzheimer's disease – constitute the majority of cases. Vascular dementia results from cerebrovascular disease causing brain ischemia, and was previously referred to as multi-infarct dementia. In contrast, Alzheimer's disease, with its characteristic amyloid plaques and neurofibrillary tangles, has often been considered to be independent of cerebrovascular involvement. However, vascular components of the pathophysiology of AD have been documented [2]. It was found that risk factors for stroke and vascular disease are associated with AD and cognitive decline [3]. Moreover, there is emerging recognition that AD is associated with atherosclerosis [4], cerebral microvascular abnormalities [5] and hypertension [6].

Research has shown that an elevated blood level of the sulphydryl amino acid homocysteine – termed hyperhomocysteinemia – is an independent risk factor for vascular disease [7]. Accordingly, the hypothesis that hyperhomocysteinemia may also play a role in the pathogenesis of AD has been proposed [8]

Homocysteine metabolism

Homocysteine is the demethylated metabolic product of methionine, an essential amino acid found in animal protein (meat, fish, eggs and milk) and to a lesser extent in vegetable proteins. In human plasma it is present in both reduced and oxidized forms [9]. Homocysteine is the reduced form and homocystine is the oxidized or disulfide form. Plasma also contains mixed disulfides sulphydryl homocysteine and free cysteine, and homocysteine and cysteine residues on protein (protein-bound homocysteine). "Total plasma homocysteine" refers to the sum of reduced and oxidized forms of homocysteine. The most abundant form is protein-bound homocysteine, which accounts for more than 70% of tHcy [Figure 1].

Homocysteine is metabolized by remethylation and trans-sulfuration pathways. In all body tissues, homocysteine undergoes a remethylation process catalyzed by methionine synthase. B12 acts as a co-factor for this enzyme, and N5-methyltetrahydrofolate, the product of 5,10-methlenetetrahydrofolate reductions by methylentetrahydrofolate reductase, serves as the methyl donor. Homocysteine can also be remethylated by betaine-homocysteine methyltransferase in the liver and the kidney [Figure 1]. In the trans-sulphuration pathway homocysteine is converted to cystathionine by cystathionine β-synthase and then to cysteine by γ-cystathionase with vitamin B6 (pyridoxine) acting as a co-factor for the two enzymes in this pathway. Cysteine, a precursor of glutathione, is also eventually metabolized to sulphate, which is excreted in the urine [Figure 1] [10].

Homocysteine metabolism is influenced by genetic background, dietary deficiencies, pernicious anemia, renal impairment, hypothyroidism, malignancies (acute lymphoblastic leukemia and carcinoma of the breast, ovary and pancreas), and severe psoriasis. Certain medications and toxins such as methotrexate, phenytoin, carbamazepine (folate antagonists), theophyline, azarabine, estrogen-containing oral contraceptive, and cigarette smoking (vitamin B6 antagonists) can influence homocysteine metabolism [11]. Premenopausal women have approximately 20% lower levels of plasma homocysteine than do men in the same age group [7].
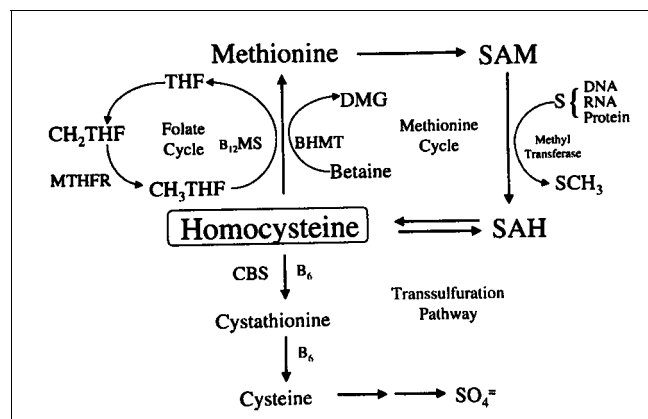
AD = Alzheimer's disease
tHcy = total plasma homocysteine

A positive relationship between an increase in tHcy and an increase in plasma cholesterol, smoking, lack of physical activity, and high blood pressure, was found by Nygard et al. [12]. Consumption of large amounts of caffeine [13] and alcohol can also increase tHcy levels. Chronic alcoholism increases tHcy through malnutrition and malabsorption [14]. Kidney metabolism, not urinary excretion, is the main clearance pathway for plasma homocysteine. Impairment of renal function indicated by an increase in serum creatinine can also raise tHcy levels [15]. Hypothyroidism can also cause an increase in total plasma homocysteine [16].

Homocysteine and cardiovascular disease

A possible association between high plasma homocysteine levels and cardiovascular disease has been recognized. In the last 10 years, more than 100 case-control and prospective cohort studies found a connection between high plasma tHcy levels and increased risk of coronary and vascular diseases [7]. The "normal" tHcy level, according to many investigations, is 5–15 mol/L [17]. However, there is a connection between the risk of coronary artery disease and tHcy, with the risk increasing when homocysteine levels are greater than 12 mol/L [18]. Chambers and colleagues [19], in a case-control study, examined male coronary artery disease patients and healthy male controls. Fasting plasma tHcy was higher in patients than in controls. The odds ratio of coronary artery disease for a 5 mol/L increase in fasting plasma tHcy was approximately 1.3 (95% confidence interval 1.1–1.6). The association between fasting plasma tHcy and coronary heart disease was independent of other well-known risk factors for coronary heart disease.

Elevated plasma tHcy can also contribute to the occurrence of stroke. In their hospital case-control study, Yoo et al. [20] compared 78 male patients who had suffered a non-fatal stroke to 140 male controls and found that the mean plasma tHcy levels were higher in the stroke patients. The use of magnetic resonance angiography in these patients revealed that elevated tHcy was a risk factor for stenosis of cerebral vessels. Kark and co-workers [21], in a prospective study among 1,788 Jewish middle-aged and elderly residents in Jerusalem, sought an association between non-fasting plasma tHcy levels and mortality. Their findings showed that even mild to moderate increases in non-fasting plasma tHcy served as a risk marker for cardiovascular and non-cardiovascular disease causes of death. In contrast, Folsom's group [22], in a prospective case-cohort design, found no association between tHcy levels and risk of coronary heart disease. Pollak et al. [23] did not find an association between the C677T mutation MTHFR gene and increased risk of AD or vascular dementia among Ashkenazi compared with non-Ashkenazi Jews, although the frequency of the mutation was significantly higher among the former.

Homocysteine, cognitive decline and Alzheimer's disease

Clinical data supporting the connection between tHcy and cognitive ability has been accumulating over the past decade. Bell and team

MTHFR = methylentetrahydrofolate reductase

[24] examined several elderly patients who were hospitalized for acute depression and found a statistically significant negative correlation between tHcy levels and cognitive ability. Riggs et al. [25], who examined 68 individuals aged 58 years and over, found a negative correlation between spatial copying skills and tHcy levels. McCaddon's group [26] studied 30 clinically diagnosed AD patients aged 65 years and older and found a statistically significant relationship between cognitive performance and tHcy levels. An important and recent study on the association between tHcy levels and AD was published in 1998 by Clarke et al. [27]. This was a case-control study comprising 164 clinically diagnosed Alzheimer's disease patients aged 55 years and older and 108 controls matched for age and gender. tHcy levels were significantly higher among 76 subjects who were diagnosed as having definite AD than in controls. A multiple regression analysis was carried out in order to find the odds ratio for high tHcy levels, low serum folate, and B12 as possible contributors to AD development. For tHcy an odds ratio of 4.5 (95% confidence interval 2.2–9.2) was found among subjects with AD pathologically proven by autopsy in the highest tertile of tHcy values (>14 µml/L) as compared to individuals in the lowest tertile (<11 µml/L). High odds ratio was also found for patients having folate and vitamin B12 in the low tertile (<17.1 nmol/L and <198 pmol/L, respectively) in comparison with subjects in the high tertile (>24.2 nmol/L and >280 pmol/L, respectively). These results suggest that people with high tHcy levels and lower folate and B12 may be at greater risk for AD. The results were not influenced by differences in smoking, apolipoprotein E genotype, or socio-economic status. One of the strengths of this study, compared to research done before, was that 76 of the 164 patients were diagnosed as having definite AD on the basis of postmortem examination, thus eliminating the argument that these relationships were due to clinical misdiagnosis of vascular dementia as AD. Because an association was found between tHcy levels and vascular disease, these results support the hypothesis that vascular disease might be a contributing factor in the process of developing AD [28].

Lehmann et al. [29] found a negative association between plasma tHcy levels and cognitive ability not only in patients with dementia but also among those with minor cognitive impairment. However, Kalmijn et al. in the prospective Rotterdam study [30] found no such association between cognitive decline and plasma tHcy levels.

Morrison and colleagues [31] demonstrated a reduced concentration of sadenosylmethionine and its demethylated product S-adenosylhomocysteine in cerebral cortex, hippocampus and putamen in postmortem brains of AD patients compared to matched controls. This suggests another possible mechanism of neuronal dysfunction in AD.

Homocysteine: a cause or a marker of AD?

It has been proposed that elevated plasma tHcy promotes atherogenesis and thrombogenesis. A possible mechanism for atherogenesis caused by homocysteine may be oxidative damage to the vessel wall, with migration and proliferation of vascular smooth muscle cells to the intima. Thrombogenesis may be a result of oxidative injury to the endothelium, followed by impairment in

coagulation pathways and changes in the vasomotor regulation of the endothelium [32]. These two possible mechanisms might interfere with blood supply to the brain and increase the susceptibility of neuronal death. Homocysteine may also cause direct neurotoxic effects by activating the N-methyl-D-aspartate receptor [33] or by conversion to homocysteic acid, leading to excitotoxic effects [34].

Blood levels of folate, vitamin B12 and vitamin B6 are inversely related to tHcy [35]. Even in a generally healthy population consuming a typical western diet, anyone with a nutritional deficiency that leads to low blood levels of folate, vitamin B12, or vitamin B6 is at increased risk for hyperhomocysteinemia [36]. It has been suggested that inadequate blood levels of one or more of these vitamin co-factors are responsible for approximately two-thirds of the cases of hyperhomocysteinemia [35]. According to these data, hyperhomocysteinemia might be a sensitive marker of B12 and folate deficiency, as was found by Nilsson et al. in a psychogeriatric population [37], while the low levels of these vitamins are related to AD or cognitive impairment [38]. Eastley et al. [39] showed that vitamin B12 treatment in patients with cognitive impairment and vitamin B12 deficiency can improve language and frontal lobe function. Lindeman and co-workers [40] demonstrated a significant inverse association between low serum folate levels among Hispanics and various measures of cognitive functions.

Conclusions

According to the recent data presented here, a debate still remains regarding the role of homocysteine in the development of cognitive decline and AD. Whether tHcy is the cause of these pathologic processes in AD or is a marker of vitamin deficiencies is yet to be determined.

In future studies, several factors that have great influence on homocysteine metabolism, and hence tHcy, should be investigated, such as micronutrient bioavailability. B12, B6, and folate are the main co-factors that drive homocysteine metabolism. They can be obtained through vitamin supplements or food products such as meat for B12, and orange juice for folate. AD patients in their premorbid state may not get enough of these vitamins in their diet, increasing the chance of developing AD in the future, compared to people with more balanced diets. Genetic defects, like in cystathionine β-synthase that might affect the metabolism of homocysteine warrant appropriate attention. Individuals with heterozygous genetic defects can have normal fasting homocysteine levels that may increase after eating food products containing high methionine, such as meat, fish, eggs and milk. By using the methionine-loading test and stressing the trans-sulphuration metabolism pathway, subjects with these genetic defects may be identified [36].

Another question that should be addressed is the benefit of consuming optimal levels of B12, B6 and folic acid on a daily basis, and lowering homocysteine levels. Lowering of tHcy may slow the progression of AD. We recommend that AD patients take B vitamin supplements in order to lower their tHcy.

The evidence presented here supports the concept that a relationship exists between plasma tHcy levels, vascular disease, and AD. It is time to conduct prospective studies to evaluate the relationship between AD and tHcy and test the hypothesis that by lowering tHcy the progression of AD can be slowed.

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