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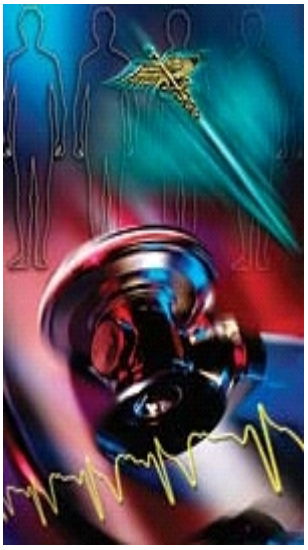
REPORT

Elevated Homocysteine Raises Risk of Stroke, Dementia

Protecting Your Brain and Heart Through Folic Acid and B Vitamin Supplementation

By Carmia Borek, Ph. D.



The most common form of senility is Alzheimer's disease, which accounts for more than 70% of all dementia cases. People with cardiovascular risk factors and a history of strokes have an increased risk of both vascular (arteriosclerotic) dementia and Alzheimer's disease.

Elevated plasma homocysteine (hyperhomocysteinemia) is now recognized as a strong, independent risk factor for stroke and dementia.

Hyperhomocysteinemia is caused by deficiencies in vitamins B6, B12 and folic acid.[1] The adverse vascular and neurotoxic effects of homocysteine are associated with excess free radical generation (oxidative stress).[2]

Elevated plasma homocysteine, however, is a reversible risk factor. Consumption of foods containing B vitamins and supplementation with folic acid and vitamins B6 and B12 are the primary preventive and therapeutic treatments. The intake of antioxidants through diet and supplements protects against oxidant stress and helps maintain the normal function of the vascular system and brain.[1,3]

Elevated Homocysteine—Potentially Lethal

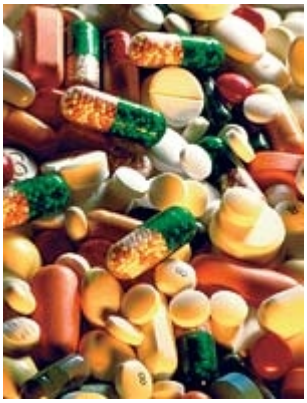
Homocysteine is a toxic, sulfur-containing amino acid formed from the amino acid methionine. Under normal metabolic conditions, homocysteine is removed from the circulatory system by recycling back to methionine, in a chemical reaction (re-methylation) that requires folate and vitamin B12. Another means of homocysteine disposal is its conversion (transsulforation) to the amino acid cysteine, in a reaction that requires vitamin B6.

In hyperhomocysteinemia, homocysteine levels can range from 14 micromoles/liter all the way up to 100 micromoles/liter in severe cases.[1] Genetic factors such as mutations in genes that regulate folate and vitamin B6 metabolism, as well as severe renal disease, increase homocysteine levels.

Elevated homocysteine damages endothelial cells that line blood vessels and induces thrombosis that can lead to heart attacks and stroke. Homocysteine produces breaks in DNA and induces apoptosis (a programmed cell suicide) that is a major cause of neuronal death in dementia.[4]

An increase in homocysteine affects multiple organs during aging. Humans with inherited defects in enzymes involved in homocysteine detoxification show features of accelerated aging and a marked propensity for age-related diseases.

Homocysteine, B Vitamins Closely Linked



Recent studies in the UK and Norway of people 65 years and older and of young people ages 4 to 18 found that plasma homocysteine levels increase progressively with age and are directly related to plasma levels of folate and vitamins B12 and B6. The lower the B vitamin levels, the higher was the homocysteine concentrations.[5]

Along the same lines, a high intake of vitamins B6 and B12 along with folic acid substantially lowers homocysteine, as reported recently by Dr. den Heijer at the XIX Congress of the International Society on Thrombosis and Haemostasis, held in July 2003 in the UK. In a randomized study, 353 patients received high daily doses of folic acid (5 mg), vitamin B6 (50 mg), and vitamin B12 (0.4 mcg), while 353 patients received a placebo. Three months later, the vitamin-supplemented group had a 30-40% decrease in homocysteine levels, compared to patients on placebo. The results emphasize the importance of B vitamin supplementation to offset age-related declines in vitamin levels and counteract age-related increases in homocysteine.

High Homocysteine Implicated in Dementia

The association between high levels of homocysteine and dementia—including Alzheimer's disease—has been observed in epidemiological studies and confirmed in case-control studies in which patients with vascular dementia and Alzheimer's disease had higher levels of homocysteine than did healthy people.[6]

A direct link between increases in plasma homocysteine and loss of cognition was shown by Seshardi et al at the Boston University School of Medicine and reported in the *New England Journal of Medicine* (Feb. 14, 2002). The study, part of the ongoing Framingham Heart Study, provides compelling evidence that in adults with intact cognition, an elevation in plasma homocysteine over time is associated with an increased incidence of dementia, including Alzheimer's disease. The results also underscore the importance of B vitamin supplementation for preventing homocysteine-associated dementia.[1]

The study enrolled 1,092 elderly subjects without dementia (667 women and 425 men), with a mean age of 76 years. Over a median follow-up period of eight years, dementia (including vascular dementia and other types of non-Alzheimer's dementia) developed in 111 subjects (10.2%; 74 women and 37 men), and 83 of these subjects (62 women and 21 men) were diagnosed with Alzheimer's disease. Hyperhomocysteinemia (plasma homocysteine higher than the baseline of 14 micromoles per liter) doubled the risk of dementia or Alzheimer's disease in the subjects with the highest levels of homocysteine. An estimated 16% of the observed incidences of Alzheimer's disease were attributable to hyperhomocysteinemia.

Increases in homocysteine levels occurred well before the onset of clinical signs of dementia, and there was a strong association between homocysteine levels and risk; that is, an increment increase of 5 micromoles per liter of homocysteine raised the risk of Alzheimer's disease by 40%.

The study's authors also found that the homocysteine-related doubling of risk of dementia was of the same magnitude as the increased risk of death from cardiovascular disease and stroke (a twofold increase) seen in earlier studies.

The study concluded that "An increased plasma homocysteine level is a strong, independent risk factor for the development of dementia and Alzheimer's disease" and that "vitamin therapy with folic acid, alone or in combination with vitamins B6 and B12 and dietary supplementation with enriched-grain products and breakfast cereal containing folate can reduce plasma homocysteine levels."[1]

A recent study in Australia examined the brains of 36 healthy seniors and found that those with high homocysteine levels were twice as likely to show a loss of brain cells compared to those with normal homocysteine levels.[7]

Another study, from Queens University in Belfast, Northern Ireland, published in Stroke in October 2002, found that moderately high levels of homocysteine were associated with significant increases in the risk of Alzheimer's disease, vascular dementia, and stroke, compared with people with lower levels of homocysteine. Increases in homocysteine were not related to any genetic defect that affects folate metabolism and raises homocysteine. The study concluded that since B vitamins and folate-fortified foods can reduce homocysteine levels, B-vitamin supplementation may be appropriate for most adults, and that the study results warrant a placebo-controlled study of folate and vitamins B6 and B12 in people who are at risk for stroke and dementia.[8] An accompanying editorial advised that because people differ in their dietary habits, supplementation with 2000-5000 mcg of folic acid daily and a similarly safe dose of vitamin B12 may be appropriate.

How Hyperhomocysteinemia Leads to Dementia

Numerous studies offer clues as to the various ways in which high levels of homocysteine induce the vascular and neuronal damage implicated in the development of dementia.

Vascular effects. The Nun study of aging and Alzheimer's disease dementia found a worsening of dementia when areas of dead tissue (infarcts) were present in the brain, indicating that homocysteine contributes to dementia by inducing vascular changes that result in insufficient blood flow to the brain and cell death.[9]

DNA damage and cell death. Other events contribute to neuronal cell death by homocysteine. Experiments in cell cultures show that homocysteine can directly kill neurons of the hippocampus, the area of the brain associated with memory. Cell death was induced by oxidative stress, DNA damage, and apoptosis.[10] Such events occurring in vivo would result in a deficit in cholinergic neurons and faulty transmission of signals in the brain that characterize dementia.

Folate deficiency and loss of DNA repair. Homocysteine's damaging effects on DNA are worsened

by folate deficiency. Studies show that a lack of folate prevents the repair of DNA in hippocampus neurons following exposure to homocysteine, resulting in the accumulation of DNA damage and cell death. Investigators from the Laboratory of Neuroscience at the National Institute on Aging in Baltimore, MD, found that a lack of folic acid rendered hippocampus neurons vulnerable to death by amyloid beta peptide, a free radical producing toxic molecule found in the brains of Alzheimer's disease patients. Thus, folate deficiency increases the toxicity of amyloid beta peptide, and when occurring in vivo, could lead to accelerated neuronal cell death and dementia.[11] This was seen in experimental mice that were genetically modified to have high levels of amyloid beta peptide and kept on a folic acid-deficient diet. The mice showed increased DNA damage and neurodegeneration in the hippocampus, further demonstrating that folic acid deficiency sensitizes cells to oxidative damage induced by amyloid beta peptide.[11]

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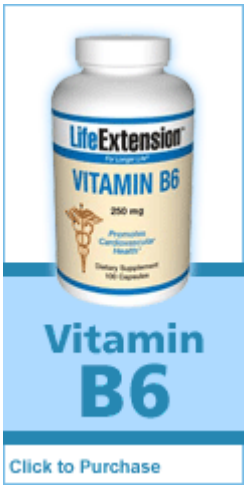
Physical changes in the brain. Elevated homocysteine in Alz-heimer's disease is associated with atrophy of the temporal medial lobe of the brain, the site of the hippocampus. Other studies show a relation between increased plasma homocysteine and a significant decrease in the width of the cerebral cortex and the width and volume of the hippocampus.[4]



Folate, B Vitamins Key to Prevention

A basic regimen of folate and B- vitamin supplementation has been shown effective in preventing hyperhomocysteinemia.

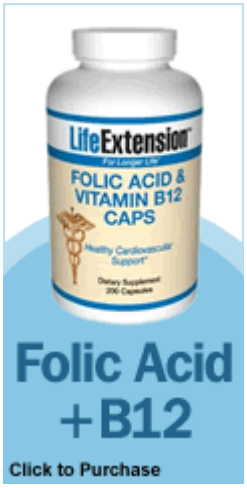
Folate and folic acid. Folate is found in foods such as green leafy vegetables, legumes, citrus fruits, grain, berries, and liver; folic acid is the form in which folate appears in supplements and fortified foods. Dietary folate from a mixed diet, however, has a 50% lower bioavailability than synthetic folic acid.[12]

Vitamin B6. Requirements for vitamin B6 rise with increased intake of protein. The richest dietary sources of vitamin B6 include chicken, fish, liver, and eggs; other sources are soybean, oats, whole wheat products, peanuts, and walnuts. Dairy products and red meat are relatively poor sources of vitamin B6.[12]

Vitamin B12. Vitamin B12 or cobalamin, a cofactor with folate in the recycling of homocysteine to methionine, is essential in many aspects of human metabolism. Bacteria, fungi, and algae synthesize vitamin B12 but yeasts, higher plant forms, and animals cannot. Animal products are the source of vitamin B12 in the human diet.[12]

The therapeutic effects of folic acid and B-vitamin supplementation were reported in a recent Austrian study, in which 9 of 31 patients with dementia and hyperhomocysteinemia were treated with 50 mg of vitamin B1, 50 mg of vitamin B6, 5000 mcg of folic acid, and 5 mcg of vitamin B12. After four weeks of treatment, serum homocysteine concentrations returned to normal in all nine patients, dropping from 17.3 to 10.7 micromoles/liter.[13]

Vegetarians, especially vegans, are at a high risk for vitamin B12 deficiency, which can lead to anemia, elevated homocysteine levels, and irreversible neurological damage. A one-year study of healthy vegetarians found that while all subjects exhibited low levels of vitamin B12, these levels were inversely related to the amount of animal (e.g., dairy) products they consumed. While vegans had the lowest vitamin B12 levels and the highest concentrations of plasma homocysteine, those who took vitamin supplements had plasma vitamin B12 concentrations similar to those of non-vegetarians. The study also found that vitamin B12 levels declined and homocysteine levels increased with advancing age.[14]



Antioxidants Counter Risk of Dementia

Oxidative stress and neuronal apoptosis are pathological features in dementia; the presence of amyloid beta peptide, a feature of Alzheimer's dementia, increases neurotoxicity. Antioxidants thus have an important role in blocking these oxidative reactions and preventing apoptotic death of neurons. In a recent study, Alzheimer's disease patients taking vitamin E showed a slowing down of cognitive decline[15]; in experimental studies, a wide variety of antioxidants, including phytochemicals, have shown the ability to prevent oxidative damage.[16]

Vitamins E and C. Combined treatment with antioxidants has been found to be effective in improving memory in animal studies and in reducing the risk of Alzheimer's disease dementia. In a study from Brazil, investigators tested homocysteine's effects in inducing memory impairment in rats and antioxidants' ability to prevent the deleterious homocysteine effects. Rats pretreated for a week with vitamins C and E were injected with homocysteine before and after being trained to master a task. Memory was severely impaired in the homocysteine-treated group while "treatment with vitamins E and C prevented amnesia."[17]

A study of 633 persons aged 65 years and older, with a follow-up period of 4.3 years, found that none of the participants taking vitamin C and E supplements had Alzheimer's disease at the end of the follow-up period, compared with the predicted incidence of 3.9 observed in non-users of supplements.[18]

Antioxidant levels decrease with age and are low in people with cognitive impairment.

In a study from the University of Perugia in Italy, investigators measured antioxidant levels in the plasma and cells of 25 elderly patients with mild cognitive impairment, 63 patients with Alzheimer's disease, and 53 controls. The antioxidants measured were uric acid; vitamins A, E, and C; and carotenoids, including lutein, zeaxanthin, beta-cryptoxanthin, lycopene, and alpha and beta carotene. Also measured were the activities of plasma and red blood cell superoxide dismutase (SOD) and plasma glutathione peroxidase. The findings showed that patients with cognitive impairment and Alzheimer's disease had low antioxidant levels, compared to control subjects. The study's authors suggested that as mild cognitive impairment represents an early stage in Alzheimer's disease and oxidative damage is an early pathological event in dementia, "an increased intake of antioxidants in patients with mild cognitive impairment "[19]

Phytochemicals Also Offer Protection

Ginkgo biloba, curcumin, and aged garlic extract are phytochemicals that have been shown to reduce oxidative damage, thus counteracting vascular damage and neurodegeneration.

Ginkgo. Ginkgo biloba supplementation has been shown to improve cognition in people with certain forms of dementia.[20] Studies now suggest that some of its protective effects in vascular dementia may be due to reducing oxidative stress and preventing platelet aggregation that give rise to blood clots.

Curcumin. Present in curry, curcumin is a potent antioxidant with anti-inflammatory effects. Studies on an Alzheimer's disease mouse model show that dietary curcumin reduced oxidative damage and decreased amyloid beta peptides in the brain by 43-50%. In studies on the PC12 neuron cell model, curcumin was more effective than alpha tocopherol in preventing amyloid beta peptide toxicity.[21]

Aged garlic extract. Garlic contains a wide range of active constituents, which are enhanced by a special process that yields aged garlic extract (Kyolic™).[22] Aged garlic extract protects the vascular system by inhibiting platelet aggregation, reducing inflammation, and preventing coronary plaque in humans; aged garlic extract also has neuroprotective effects, reducing homocysteine levels[23], preventing amyloid beta peptide toxicity in PC12 neurons,[24] and apoptotic death, and improving memory in senility-prone mice.[25]

In a four-week study at Penn State University, researchers fed rats a folate-deficient diet and Kyolic aged garlic extract, and compared their homocysteine levels to those in rats fed a folate-fortified diet and aged garlic extract. Aged garlic extract reduced plasma homocysteine by 30% in folate-deficient animals, but not at all in animals with adequate folate. The results suggest that aged garlic extract may serve as a surrogate for folate treatment in hyperhomocysteinemia.[25]

Summary: Lowering Homocysteine Lowers Dementia Risk

Elevated plasma homocysteine (hyperhomocysteinemia) is a major risk factor for dementia, including Alzheimer's disease. Hyperhomo-cysteinemia commonly results from a deficiency in folate and vitamins B6 and B12, and supplementation with these nutrients is the mainstay preventive and therapeutic treatment for hyperhomocysteinemia. Vegetarians, especially vegans, often have low levels of vitamin B12 and elevated homocysteine, but supplementation with vitamin B12 can return their plasma concentrations to levels of nonvegetarians.

Antioxidant levels decline as a result of normal aging and dementia. Increasing your intake of vitamins C and E—along with phytochemicals such as aged garlic extract, ginkgo biloba, and curcumin that have been shown in experiments to prevent oxidant damage and brain cell death by apoptosis—also may help stave off dementia.

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