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Thoughts on B-vitamins and dementia

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Abstract

The B-vitamins, including vitamins B12, B6, B1, B2, niacin (B3) and folate (B9), have been implicated as protective risk factors against cognitive decline and Alzheimer's disease. This commentary reviews the evidence to support protective relations of these vitamins, including consideration of known vitamin deficiency syndromes, theories of underlying biologic mechanisms, and the epidemiologic evidence. We also comment on the potential benefits and harms of vitamin supplementation as well as make recommendations for the direction of future studies.

Keywords

Alzheimer disease; B-vitamins; dementia; folate

1. Introduction

The B-vitamins, particularly folate, vitamin B12, and vitamin B6, are widely believed to be protective against Alzheimer's disease and age-related cognitive decline. The last several years have seen a number of new drug formulations that include the B-vitamins, along with increased prescribing of these products to lower homocysteine levels and to preserve brain function. But how strong is the evidence or the biologic bases to support this belief? Here we re-examine the biologic mechanisms thought to underlie the relations, and evaluate the available scientific evidence. We argue that none of the B-vitamins has a strong basis of association with Alzheimer's disease, and at this point in the research, only deficiency in vitamin B12 can be linked credibly to mental decline in the US population. In our view, the evidence for or against possible relations with the B-vitamins is inconclusive, and we identify a number of issues that need to be addressed by future studies.

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1.1. B-Vitamin deficiency syndromes and dementia

The class of B-vitamins includes thiamine (B1), riboflavin (B2), niacin (B3), pyridoxine (B6), folate (B9), and cobalamin (B12). Of all the B-vitamins, vitamin B12, niacin, and thiamine have the most clearly established relations with deterioration in mental state. For example, vitamin B12 deficiency has a well-recognized neurologic syndrome that is characterized by cognitive and psychiatric disturbances, as well as by subacute combined degeneration of the spinal cord, and peripheral neuropathy [1,2] Exclusion of vitamin B12 deficiency as an explanation of dementia is a standard procedure in the diagnosis of Alzheimer's disease. In addition, high-dose vitamin B12 therapy can resolve symptoms of the neurologic syndrome, including cognitive disturbances [3,4]. There is a strong clinical understanding that vitamin B12 deficiency syndrome is irreversible if left untreated. Vitamin B12 deficiency is common with older age, occurring in more than 20% of persons 65 years and older [5] as the result of increased prevalence of gastritis and other digestive conditions that interfere with absorption [6].

Two rare neurologic syndromes are caused by niacin and thiamine deficiencies. Niacin deficiency is a known cause of pellagra, a disease characterized by symptoms of dementia, diarrhea, and dermatitis that can be resolved through niacin supplementation [7–9] Disease effects on the central nervous system begin with neurasthenia followed by symptoms of psychosis, including disorientation, memory loss, and confusion. Pellagra is endemic to populations that consume maize or sorghum as the primary food, but can occur as the result of alcoholism and gastrointestinal disease.

Wernicke-Korsakoff syndrome is caused by thiamine (vitamin B1) deficiency [10] The Wernicke phase of the syndrome involves damage to the central and peripheral nervous systems, causing problems with vision and muscle coordination [10] The primary features of the Korsakoff phase are loss of memory, confabulation, and hallucinations. This rare syndrome is most commonly the result of chronic alcoholism [11] Even if there is adequate nutritional intake, chronic alcoholism affects thiamine metabolism.

There is no neurologic syndrome associated with folate deficiency, the primary feature of which is macrocytic anemia, although some clinical studies report effects on cognition and mood, particularly depression [12].

1.2. The homocysteine theory

Current interest in vitamin B12 and folate as risk factors for dementia is based on their relations as co-factors in the metabolism of homocysteine. Homocysteine has been related to the risk of developing Alzheimer's disease in some [13,14] but not all studies [15], and remains a topic of interest. The mechanism for association is not known, although homocysteine and folate deficiency have been shown to be neurotoxic in mouse models of Alzheimer's disease [16–18].

If, indeed, elevated homocysteine is a cause of neurodegenerative decline, it is important to note that it is *deficiencies* in these nutrients that cause homocysteine elevations. On the basis of this proposed mechanism, increased levels of folate among persons who are not deficient would have no effect on the risk of Alzheimer's disease risk or of cognitive decline. Furthermore, in the US and other countries where low folate status is rare due to folic acid fortification, widespread or indiscriminant supplementation with folic acid would not be warranted for the purpose of lowering homocysteine. Whether vitamin supplementation would be beneficial in countries that do not fortify food with folic acid is another question. Vitamin deficiency is not the only factor that can elevate homocysteine. Other potential causes include, but are not limited to, renal disorders [19] genetic defects [20] lifestyle

behaviors (e.g. alcohol consumption, smoking, obesity) [21] and neurodegenerative disease processes [22,23].

2. Other potential biologic mechanisms of folate

Data are limited on potential mechanisms of folate effects on dementia other than homocysteine concentration. One possibility is that folate deficiency may decrease acetylcholine, a neurotransmitter that is reduced in Alzheimer's disease. Folic acid is involved in the metabolic pathway for acetycholine synthesis. At least one animal model, however, did not find evidence of dietary folate effects on acetylcholine metabolism [24]. Another possibility is that folate deficiency increases oxidative stress, but again, data on the antioxidant effects of folate are limited [25].

2.1. Evaluating the epidemiologic evidence

Even while there is a general impression of strong epidemiologic evidence to support associations between the B-vitamins (particularly folate) and cognitive decline, in actuality, the evidence is weak. The impression may be driven by the numerous cross-sectional and case-control studies that relate dietary or biochemical levels of the B-vitamins to cognition or disease status. A primary limitation of these types of studies is that one cannot determine whether the observed association is a cause or effect of the disease. For example, both serum and dietary intake levels of folate have been reported to decline with prolonged institutionalization [21], and duration of dementia [26]. In addition, studies that use a one-time cognitive assessment cannot separate attained or lifetime cognitive ability from cognitive decline due to age or disease. Confounding bias is highly likely in these types of studies because cognitive ability is related to many factors, including education, socio-economic status, and healthy lifestyle behaviors. Depression may be another source of confounding in these studies, as it is a common condition in persons with dementia [27], and has been associated with folate deficiency [28].

Prospective cohort studies that assess vitamin exposure in a group initially unaffected by disease and follow the group over time to determine incident disease provide the correct temporal relation for a cause-effect interpretation of observed associations. Five prospective studies examined levels of the B-vitamins in relation to incident Alzheimer's disease [13,14,29–31]. Of three studies that used serum measures [13,14, 31] one found significantly greater risk of developing Alzheimer's disease among the persons who had subnormal levels of either vitamin B12 (<150 pmol/L) or folate (<10 nmol/L) [31] and another with low serum folate levels (≤11.8 nmol/L) [14]. In an investigation of Framingham participants [13] there was no association with serum measures of these vitamins, although homocysteine concentration was positively associated with higher risk of incident Alzheimer's disease. Two studies examined dietary intake of folate with incident Alzheimer's disease, and again, the results were inconsistent. In the Baltimore Longitudinal Aging Study, low folate intake was associated with increased risk of developing Alzheimer's disease over 9 years of follow-up [30]. In the CHAP study, there was no association of vitamin supplement and/or food intake of folate, vitamin B12, or vitamin B6 to 4-year risk of Alzheimer's disease [29]. However, the CHAP study did find greater AD risk and faster rate of cognitive decline among persons whose consumption of niacin was low [32].

Longitudinal studies of cognitive decline are useful for understanding risk factor associations with incident Alzheimer's disease, the central characteristic of which is gradual decline. Among the seven studies [22,23,33–37] with this type of design, only two studies [35,36] found protective associations with folate, and one (the CHAP study) [34] even found a deleterious effect, with faster decline among persons who had high supplement or food intakes >400 mcg/d. The CHAP study also found a statistical interaction between total

vitamin B12 intake (food plus supplements) and older age, such that the rate of cognitive decline over 6 years was slower the higher the vitamin B12 intake and the older the age of the participant [34].

In summary, the existing epidemiologic evidence for protective associations of the B-vitamins is limited and inconsistent. The few studies showing protective associations cannot be readily distinguished from the negative studies. That is, the inconsistencies do not appear to be explained by features of study design, such as length of follow-up, or type of exposure (e.g. serum, plasma, dietary intake). A major limitation of the vast majority of these studies is the absence of statistical control for dietary risk factors of dementia. Confounding bias is particularly likely for folate as it is associated with many other dietary factors that have been implicated as risk factors for Alzheimer's disease and cognitive decline, including antioxidant nutrients [38, 39] niacin [32] and dietary fats [40–42] A limitation of many of the studies of cognitive decline is the use of single cognitive tests, or only two points of cognitive assessment. The most valid assessments employ a composite score of multiple tests (to reduce error of the individual tests) and a methodological design that incorporates multiple periods (3 or more) of cognitive assessment. This type of longitudinal design allows for the differentiation of change due to a disease process from spurious changes due to measurement error and bias [43,44] The three studies that employed this type of design found no protective association of folate with cognitive decline [23,33,34] even though folate was associated with higher cognitive scores at the baseline.

2.2. What's the harm with B-vitamin supplementation?

Vitamin B12 supplementation appears to be safe. However, this may not be the case for folic acid. There is at least one epidemiologic study [34] and a number of clinical case reports [45–47] that suggest possible adverse effects. In fact, there is a tolerable upper limit established for folate based on the concerns of the noted clinical sequela [48]. It is unclear whether folic acid supplementation may mask vitamin B12 deficiency or may exacerbate the neurodegenerative decline associated with the syndrome. Because there is little scientific study on this issue, it is probably safest to avoid folic acid supplementation unless there is evidence of clear folate deficiency and continual monitoring for vitamin B12 deficiency. Serum or plasma levels of vitamin B12 or homocysteine are not adequate tests for detecting vitamin B12 deficiency. A more specific test for vitamin B12 deficiency is another one of its metabolites, methylmalonic acid, but even this test is less than desirable as a diagnostic tool [5,49,50].

2.3. Directions for future studies

The most important issue for future studies is whether B-vitamin supplementation is of benefit or harm for the prevention of neurodegenerative diseases. Clinical trials can address the issue in persons without vitamin deficiency, but cannot address the issue for a large segment of the older population who are vitamin B12 deficient, as it would be unethical not to treat known deficiency. In the absence of a suitable animal model, we must rely on epidemiologic studies. These studies should be of prospective (for Alzheimer's disease) or of longitudinal (for cognitive decline) design. The longitudinal studies of cognitive decline should include multiple cognitive tests measured at multiple time points, and use analytic methods such as mixed models to measure cognitive decline. Very importantly, these studies should adjust for the important dietary and non-dietary confounders, and use multiple diagnostic methods to diagnose vitamin B12 deficiency. These types of studies require large samples to obtain informative results. Finally, these studies need to be conducted in diverse, population-based samples that include the oldest old, as the medically underserved and older segments of the population are the most likely to have unrecognized or untreated vitamin B12 deficiency.

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