Nutrition and the brain – Review article

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Association of vitamin B_{12}, folate, homocysteine and cognition in the elderly

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Abstract

Normal and subnormal serum levels of vitamin B_{12} and/or folate do not exclude functional deficiency, and elderly people are specifically exposed to deficiency owing to impaired nutrition, malabsorption, accompanying diseases and current medication. Several studies report that low levels of vitamin B_{12} are more common in people with Alzheimer's disease (AD) than in non-demented people. Low levels of folate are also correlated with other types of dementia. Current studies suggest that low levels of vitamin B_{12} as well as folate may be part of the aetiology in AD. A functional deficiency of vitamin B_{12}/folate may be present despite serum levels within reference limits. The amino acid homocysteine (Hcy) is a sensitive but non-specific marker of deficiency of vitamin B_{12} and folate and appears to have the strongest association with cognitive function. The association between Hcy levels and cognitive function is also stronger than that of the levels of vitamin B_{12}/folate. The clinical manifestations of vitamin B_{12}/folate deficiency are non-specific, but when they are connected with laboratory findings adequate investigation should be performed. A generous attitude to treatment with vitamin B_{12}/folate is advocated, combined with a compulsory evaluation of treatment effect. Clinical regress of neuropsychiatric symptoms by cobalamin and folate therapy is dependent on the duration and severity of symptoms, but on a group level, not necessarily in individual patients.

Keywords: *cognition*; *folate*; *homocysteine*; *vitamin B_{12}*

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Background

Vitamin B_{12} is a water-soluble, heat-sensitive vitamin of the B-vitamin group. Only microorganisms are able to synthesize vitamin B_{12}. It is almost only provided through food of animal origin, the largest amounts being found in liver and kidney and considerable amounts in meat, dairy products and eggs (1). Vitamin B_{12} often occurs protein bound as methylcobalamin, hydroxycobalamin and deoxyadenosycobalamin in nutrients (2). A complex with intrinsic factor from the stomach mediates the absorption of the B_{12} complex in the distal part of ileum through endocytosis (3). Diseases and dysfunction of the stomach, pancreas and intestines may affect the physiology of absorption and thereby also the serum and tissue levels of vitamin B_{12}. It is only B_{12} bound to transcobalamin II, holotranscobalamin, which is absorbed through the cells, while 70% is bound to haptocorrines circulating for a long time in the blood (4). Since the 1950s, however, the focus of vitamin B_{12} deficiency has moved from classical haematology (pernicious anaemia), through the neurological speciality (neuropathy, myelopathy) to the geriatric speciality, with neuropsychiatric manifestations such as depression, mild cognitive impairment and dementia (5).

Humans have a daily vitamin B_{12} requirement of about 3 μg, but also have enormous reserves covering 5–10 years' needs. However, vitamin B_{12} deficiency is common in the older population and a recent study reported a 13% prevalence of B_{12} deficiency (6). The prevalence was 8% in those 46% taking B_{12} supplementation compared with 17% in those having no supplementation.

Folate or folic acid is a joint name for folate and a number of folate derivatives, which are also heat sensitive and water soluble, closely linked to B_{12} in its metabolism (7). They are found in certain vegetables. The daily folate requirement is 400 μg and the reserves cover 3–4 months. The symptoms

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of deficiency are similar to those of vitamin B_{12}. Furthermore, folate treatment of B_{12} deficiency may correct the haematological changes, but the neurological and neuropsychiatric changes will continue to progress. Conversely, B_{12} treatment of folate deficiency may also mitigate the haematological symptomatology.

There are several causes of inadequate serum levels of vitamin B_{12} and folate:

- The binding proteins of the vitamins may be falsely high or low.
- The distribution to the cell may be disturbed.
- Enzymatic defects may demand higher vitamin levels.
- Serum levels do not mirror tissue levels.

Serum levels of vitamin B_{12} and folate within reference limits do not exclude tissue deficiency. Serum levels may be considered as specific, however non-sensitive (Table 1).

Surrogate markers of deficiency are currently used as an alternative and complement to serum levels of vitamin B_{12} and folate. Methylmalonic acid (MMA) (8) and homocysteine (Hcy) represent two of these markers, of which Hcy has a vast body of documentation (9–11). They are intimately involved in joint metabolism with vitamin B_{12} and folate. Hcy has recently been recommended before MMA in an academic thesis (8). There is an inverse relationship between Hcy elevation and vitamin B_{12} as well as folate deficiency. Hcy is an amino acid that does not occur in nature, but is only synthesized in close relation to metabolism of the amino acid methionine (11) (Fig. 1).

Causes of vitamin B_{12} and folate deficiency

Hcy is a sensitive but non-specific marker of vitamin B_{12} and folate deficiency. However, there are several other causes of Hcy elevation (12, 13) (Fig. 2)

Table 1. Reference limits of vitamin B_{12}, folate and homocysteine

Serum B_{12}	170–600 pmol l^{-1}	
Serum folate	< 5 nmol l^{-1}	
Erythrocyte folate	250–750 nmol l^{-1}	
Plasma homocysteine	15–30 mmol l^{-1}	Moderately elevated
	30–100 mmol l^{-1}	Intermediately elevated
	> 100 mmol l^{-1}	Severely elevated

Is there an association between cognition, homocysteine, vitamin B_{12} and folate?

There are several associations between deficiency of either one or both vitamins B_{12}/folate and/or elevated Hcy and morbidity (14). Correlations between neurological, cardiovascular and certain cancer diseases are reported, as well as birth defects, abortions, cognitive impairment and dementia (15). Age-related cognitive variations may range between benign mild cognitive impairment (MCI) and progressive dementia (16). There are many studies confirming an association between vitamin B_{12}/folate deficiency and/or elevated Hcy levels and cognitive impairment (17). The results are mostly reported from cross-sectional, cohort and case-control studies. Therefore, causal and time factors are uncertain, and the context of Hcy as a risk factor is inappropriate. The context of risk marker would be more appropriate. The context of risk factor should only be used when there is an association between one independent variable and an effect variable, where the effect variable is conversely affected when the independent variable changes.

Other associations

Selhub et al. reported an association between elevated Hcy levels and the degree of extracranial carotid stenosis in elderly patients (18). A Swiss group also performed an intervention with an oral combination of the B-vitamins B_{12} (400 μg), folate (1 mg) and B_6 (10 mg) on patients undergoing percutaneous coronary angioplastic surgery (19). These patients showed a lower degree of restenosis than control patients when treated for 6 months.

Low folate levels have long been known to be associated with neural tube defects in newborn babies (20, 21). Hence, many countries, including the USA, launched folate fortification (140 mg 100 g^{-1}) of flour in 1998 (22). Increased folate levels are then naturally observed, but also a decrease in Hcy and, importantly, a decrease in neural tube defects (21, 22). However, fortification is not completely harmless as other fortification studies have reported an increase in twin births with accompanying complications, selection of people with a genetic folate-dependent enzyme (C677T type), which tends to increase in the population, causing an increased need for folate (5, 15, 23), lower threshold values for epilepsy in epilepsy-prone patients, and an unmasking effect of a latent vitamin B_{12} deficiency with

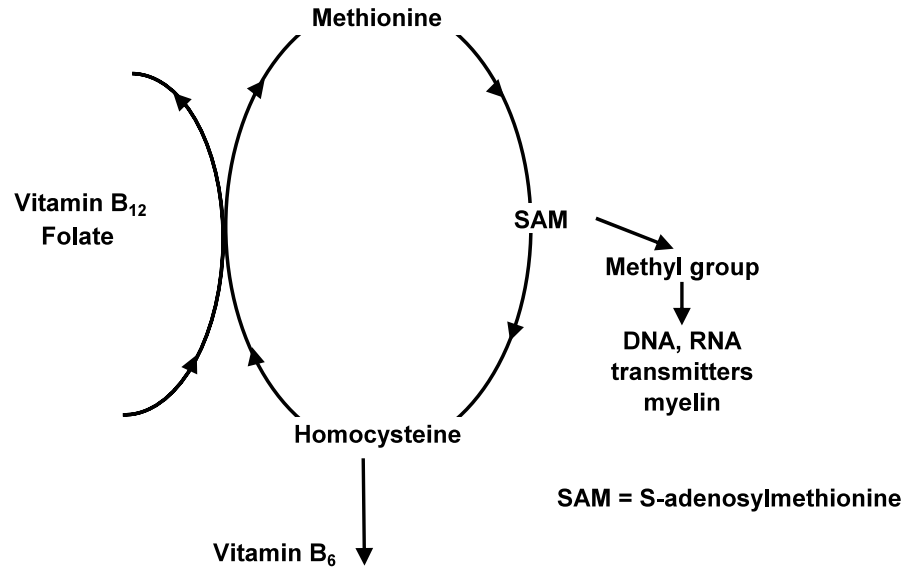

Fig. 1. Interaction between vitamin B_{12}, folate and homocysteine.

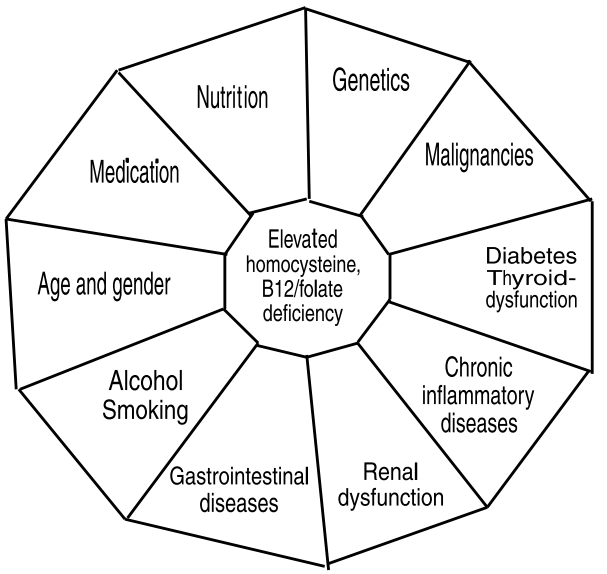

Fig. 2. Factors affecting vitamin B_{12}, folate and homocysteine.

development or progression of neurological or neuropsychiatric symptoms despite normal blood findings (24). Epidemiological studies have also shown that folate modulates the risk of developing cancer in certain tissues, especially colorectal tissues (25). Folate deficiency seems to speed up carcinogenesis, while folate supplementation above basal needs has a protective effect.

Pathogenesis

Several factors may contribute to the development of cognitive impairment and dementia, e.g. infection, thyroid dysfunction, electrolyte disturbances, nutritional factors and toxins (26). A lack of the two intimately linked B-vitamins B_{12} and folate with an accompanying Hcy elevation are important nutritional factors. Age-related changes in absorption, metabolism and physiological systems may result in elderly people having insufficient amounts of B_{12} and folate, causing elevated Hcy levels, contributing to the development of neuropsychiatric symptomatology in different ways (27, 28). McCaddon reported that a majority of AD patients is sensitive to decreased transcobalamin saturation with increasing age, or there may be a dysfunction of transcobalamin or the tissue receptor megaline (29). Transcobalamin is the transporting and active mediator of cobalamin.

The vitamins are necessary for the synthesis of *S*-adenosyl-methionine (SAM), which is the most important methyl-group donor of the brain (30). It is needed for the synthesis of DNA, RNA, myelin and transmitter substances. Thus, vitamin B_{12}/folate deficiency decreases the access of SAM, thereby changing cellular methylation reactions and normal brain function. Supplementation with SAM is reported to improve cognitive functions (31).

Hcy affects the brain by:

- leading to ischaemia owing to vascular effects
- activating *N*-methyl-d-aspartate receptors
- sensitizing neurons to excitotoxins
- causing DNA damage
- activating the cell cycle
- decreasing the release of nitric oxide.

Cross-sectional studies

Since the first research groups (32) reported an association between vitamin B_{12} deficiency and neuropsychiatric symptoms and the use of markers for tissue deficiency of B_{12} and folate, there has emerged a great body of cross-sectional studies confirming this association (33–40). Elevated Hcy levels are found in AD (41) independent of renal function (42). There were no signs of malnutrition as contributing cause, as a nutritional marker with a retinol-binding protein was at the same levels as in cognitively intact control patients. There were no correlations between retinol-binding protein, the B-vitamin state and the duration of dementia. This could have been suspected if malnutrition developed in parallel with the progression of disease. Moreover, there were no correlations between the duration of dementia and Hcy levels, which argues against Hcy levels being a consequence of dementia progression. It is more probable that metabolic changes develop as a result of changed absorption, transport or biochemical processes. The metabolic effects of a slightly reduced vitamin state are thereby greater than the actual nutritional effects. Recently, a correlation of many medical and psychological variables with Hcy levels was reported above a cut-off limit of 15 μmol l^{-1} (39). There were also correlations with vision, impaired memory and walking performance. The majority (73%) of these elderly people (aged ≥ 80 years) needed vitamin supplementation.

A recent study found that 45% of AD patients and 62% of patients with vascular dementia also had Hcy levels >15 μmol l^{-1} (33). Swedish 80-year-old people with Hcy levels >15 μmol l^{-1} were reported to have significantly impaired memory, more depression and greater concentration difficulties than those with lower levels (34). The OPTIMA project in Oxford reported a significant correlation between Hcy levels and the degree of cognitive function in 156 healthy people living at home (40). A Swedish study of 336 patients in an outpatient memory clinic found elevated Hcy levels in 39% of mildly cognitively impaired patients and that Hcy in general correlated negatively with memory performance (43). Hcy levels are also reported to correlate significantly and progressively with the severity of dementia in the same type of patient (44). From the folate-fortified USA it was recently reported that 23% of elderly people in the study population were cobalamin deficient, associated with impaired cognition and elevated Hcy levels (45).

Longitudinal studies

Prospective studies have also found an association between vitamin B_{12}/folate deficiency and dementia. In a 5 year follow-up of 369 healthy people (aged ≥ 65 years), impaired cognitive function was observed to be 2.5 times more common in those having initial serum folate levels within the lowest quartile compared with those within the highest (46). Wang et al. in the Swedish Kungsholmsproject reported that of 370 cognitively intact people (aged ≥ 70 years) those with initial low B_{12}/folate levels were at greater risk of developing AD (36). Those with folate levels <10 mmol l^{-1} or B_{12} levels <150 pmol l^{-1} had twice the risk of developing AD 3 years later. Impaired cognition is also associated with elevated Hcy levels in healthy elderly people (38). These associations were not altered when adjusting for renal function, smoking and blood pressure. Patients developing AD were found to have elevated Hcy levels many years before the onset of disease.

A British research group observed that the Hcy levels of healthy elderly people were an independent risk determinant in performing cognitive tests 5 years later (47). Seshadri et al. observed 1100 cognitively intact people (mean age 75 years) for 8 years, and found twice the risk of developing AD in those with Hcy levels >14 mmol l^{-1} compared with those with levels <14 mmol l^{-1}. The relative risk of developing AD was 1.6 for every increase of 1 SD from study start (48). A research group from Rotterdam also reported a correlation of elevated Hcy levels in 1000 non-demented elderly people with the development of impaired cognitive function, mostly expressed in psychomotor speed. This association was independent of magnetic resonance imaging findings of the brain (49). A cohort study in 1999 from Scotland on 347 persons (born 1932 and 1947) reported that levels of B_{12} and folate were positively correlated and Hcy was negatively correlated with cognition in the elderly cohort (50).

Treatment studies

Despite vitamin B_{12} and folate levels being low and the functional deficiency marker Hcy being elevated, the clinical experience from remission treatment with B_{12} and/or folate is seldom completely successful. The cell damage has probably been so

pronounced that it has become irreversible. However, the selection of patients, diagnoses, follow-up and the dosage of vitamins may vary, thereby confounding the results. Some studies have reported improvement of cognition with vitamin B_{12} and folate (51, 52). The best effects have been achieved in patients with short duration of disease and mild to moderate cognitive impairment. A Swedish study on patients with mild to moderate cognitive impairment and Hcy levels >20 mmol l^{-1} found an improvement in 14 out of 17 patients with a daily treatment combination of 1 mg vitamin B_{12} and 5 mg folate for 2 months (53). The same research group also found an improvement by intramuscular injections of vitamin B_{12} in mild to moderately cognitively impaired patients with low B_{12} levels, but there was no effect in severe cases (54). Kuzminsky et al. showed that oral and parenteral treatment with vitamin B_{12} was equivalent regarding clinical and laboratory effects in B_{12}-deficient patients (55). However, in five of 30 (16%) patients there was also a concomitant folate deficiency being unmasked through treatment. Complementing folate supplementation normalized all vitamin markers.

There is a lack of results from larger population studies, although many are ongoing (56). Until the results of these are reported, the responsible doctor must try to treat according to current knowledge, personal experience and the patients' medical situation. Treatment with vitamin B_{12} and/or folate has the advantage of being simple, safe and cheap, with few adverse effects. Thus, a generous attitude towards treatment could be advocated as the effects for the individual patient cannot be predicted from the results of even the most well-designed and performed randomized, controlled studies.

Investigation

It is especially important in elderly people to determine whether there is a B_{12}/folate deficiency, as these people often have multiple diseases and diffuse symptoms. Vitamin B_{12}/folate deficiency has many manifestations and may act as an imitator of other diseases. It is not possible to investigate all people showing some kind of symptom. Despite the high prevalence of B_{12} deficiency and the potential for developing severe symptoms, no studies have reported benefits of a general screening of the population (57).

The investigation should provide an answer to the questions: Who has symptoms associated with deficiency? Who is at risk of developing deficiency? Who should be treated? and What is the purpose?

The investigating doctor should analyse vitamin B_{12}, folate and Hcy, and complement with haemoglobin, SR, creatinine, iron, glucose and thyroid profile. Sometimes, and above all when there is a suspicion of malabsorption, pepsinogen, gastrin and gliadin antibodies are recommended. Gastroscopy can be used to rule out an atrophic gastritis or coeliac disease (58). In elderly people with elevated Hcy levels it is a good starting point to exclude nutritional factors and renal dysfunction and focus the investigation on atrophic gastritis, which tends to be the most common cause of deficiency in otherwise healthy people. The older person is at risk of functional B_{12}/folate deficiency, and a recent study suggested a correlation between low income and education and the vitamin B_{12} deficiency marker MMA (59). Cognitive impairment or cardiovascular manifestations in elderly people may be typical cases for checking Hcy levels.

Treatment

There are many treatment guidelines and they vary not only between departments but also within departments depending on tradition, experience, the patient's situation and desire, and the reference limits of the laboratory. These are, however, no limits of action for the initiation of treatment. Hcy levels can always be lowered with B_{12} and folate, although it has not been clearly shown that such treatment is clinically beneficial (17, 41, 56). Daily supplementation with 0.5–5 mg folate reduces Hcy levels by 25%, and 0.5 mg vitamin B_{12} by another 7%, while 16.5 mg vitamin B_6 has no additional effect at Hcy levels 12 mmol l^{-1} (60). However, the reduction in Hcy is greater at higher Hcy levels than at lower ones. Oral vitamin B_{12} treatment (2–37.5 mg d^{-1}) is associated with higher B_{12} levels and lower Hcy and MMA levels, which can be sufficient to prevent deficiency in many elderly people (61). A "cardiovascular lifestyle" should be appropriate to reduce Hcy, with an increased intake of fruit and vegetables, low coffee consumption, regular exercise and cessation of smoking (62).

Remission treatment requires initial high doses of folate of about 5–10 mg daily followed by supplementation doses of 1–5 mg daily. Corresponding doses of oral cobalamin can be 4 mg daily for 1

month followed by 1 mg daily, or 1 mg subcutaneously or intramuscularly every day or every other day five times, followed by 1 mg per month (63). Such a regimen is a practical compromise between current recommendations and batches provided at the pharmacy. However, the dose intervals of parenteral supplementation treatment are highly individual and the goal is to keep the patient mitigated or free of symptoms and compliant to medication.

Follow-up and therapy control are important as the response to treatment can be of diagnostic value but may take a long time, perhaps months or years. In addition to an evaluation of the clinical picture, it is better to measure the metabolites Hcy or MMA rather than the vitamin B_{12}/folate serum level (64). These markers react within a couple of days, but it is more practical to check them after several months of medication.

The responsible doctor should prescribe a profiled treatment and follow-up in co-operation with the patient. Thus, it is also reasonable to recommend and supply the patient with other vitamins and minerals to secure an optimal treatment effect.

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