News and Views on Folate and Elderly Persons

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Elderly persons are especially exposed to folate deficiency, where normal/subnormal folate levels do not exclude tissue deficiency. Accompanying diseases, medication, and lifestyle factors may contribute to cause deficiency. Symptoms of deficiency can be hematological, neurological, or neuropsychiatric, but it is likely that there are also cardiovascular manifestations as well as associations with malignancies. The physician should make an individualized investigation to establish the probable cause. Among the available determinants of the folate/cobalamin state, plasma homocysteine (Hcy) is a swift and sensitive marker and has the strongest connection to cognitive function. The association is generally stronger between Hcy levels and symptoms than between vitamin-related levels and symptoms. The duration as well as the severity of symptoms are of importance in terms of the improvement of neurological and neuropsychiatric symptoms when substitution is performed. The issue of general folate fortification of flour is complex, and there are as many pros and cons as there are countries in which it is considered to be launched. It is important to bear in mind that in our modern society, deficiency of folate/cobalamin—overt or latent—mainly is a problem of the elderly and a challenge to the doctor.

FOLATES are water-soluble vitamins in the vitamin B group and are found in food in fruit, fresh vegetables, and corn products (1). Insufficient food intake of folate is a common cause of low folate levels (2). Elderly people are shown to have increased risk of low folates, but there are no exact figures on the prevalence or incidence of folate deficiency (3,4). An important fact is that most folate and vitamin B12 (cobalamin) deficiencies detected in elderly people may be subclinical (5). Even age-related disturbances in transport and metabolism may cause folate as well as vitamin B12 deficiency (6,7). The metabolism of the B vitamins folate and cobalamin is intimately associated. This is reflected in the fact that a lack of 1 of the 2 vitamins may cause megaloblastic anemia and a series of neurological and mental symptoms, which cannot be distinguished. A cobalamin deficiency may cause a “folate trap” with normal or increased serum folate levels but functional folate deficiency, which is thought to cause some of the biochemical and clinical symptoms occurring in folate/cobalamin deficiency (8,9) (Table 1).

Elderly people often lack the classical megalocytic anemia. The initial symptoms are more often neuropsychiatric, where a lack can be the cause, but more frequently may deteriorate organic and nonorganic neuropsychiatric diseases (10). Cognitive decline and dementia have been associated with lack of folate (11,12). A recent Swedish longitudinal study on 370 nondemented persons aged 75+ years showed that low levels of folate (<10 nmol/l) and/or cobalamin (<150 pmol/l) doubled the risk of developing Alzheimer’s dementia during the 3-year follow-up (13). It is supposed that a deficient folate status may play an independent key role in the onset and progression of cognitive impairment (14). When trying to treat a deficiency, suspected by clinical symptoms or laboratory signs, you supplement with the lacking substance(s). However, most supplementation studies of the elderly in this field are done with cobalamin in cognitively impaired persons. Some patients benefit from folate/cobalamin supplementation with improved cognitive function and better test results in different memory scales (15). Some authors have found an association between the duration and seriousness of dementia and treatment response (16). Moreover, results indicate that delirium as well as disorientation are common manifestations of cobalamin deficiency, which in turn may worsen a state of dementia (17).

FOLATE/COBALAMIN AND HOMOCYSTEINE

Most studies on psychogeriatric patients with a lack of folate/cobalamin have measured the blood concentration of the vitamins. These are not considered to correctly reflect the availability in the tissues (18). There are many reasons for this, which are outlined in Table 2.

Plasma homocysteine (Hcy) has got an increased interest as it reflects the intracellular interaction of the folate/cobalamin metabolism of the “methylation cycle” and is considered to mirror the functional relations close to the cells (19). Hcy is considered to be the most sensitive and the swiftest of the markers of folate/cobalamin deficiency (18,20). It is formed in a transmethylation process by which S-adenosylmethionine (SAM) is converted to S-adenosylhomocysteine, which in turn is converted to Hcy (Figure 1). However, low serum folate values are more indicative of deficiency in elderly persons than in younger persons, and high serum folate values most likely rule out a deficiency (4). It has been calculated that 75% of high levels of Hcy are attributable to vitamin deficiency (21). The elimination of Hcy is affected by the renal function and, subsequently, renal insufficiency may cause Hcy elevation (22).

Folates are important substrates in monocarbon transfer reactions and serve as a source of 1-carbon units in different
oxidative states. Folate acts as a donator of a methyl group when Hcy is remethylated to methionine (23). Several studies have shown that Hcy inversely correlates with cobalamin and folate (24,25). Homocysteine is also affected when the transporting mechanisms of vitamins into the cell are disturbed and when enzymes are defective. The association is generally stronger between Hcy levels and symptoms than between vitamin-related levels and symptoms (26). Whether an increased Hcy is a marker of vitamin-related processes only or a part of the pathogenesis is not fully understood. However, there are several ongoing prospective Hcy-lowering trials, which we hope will clarify causality or effect association (27). A common (5–15%) cause of increased Hcy is a genetic polymorphism of an enzyme (MTHFR = methyltetrahydrofolatereductase) in the folate/cobalamin metabolism (28). It is foremost expressed at a limited access of folate (29). There are also a number of other causes of elevated Hcy levels (6,30) (Table 3).

**DEFICIENCY SYMPTOMS**

**Neuropsychiatric Symptoms**

Low folate/cobalamin levels have been linked to delirium, confusion, psychosis, depression, and dementia (Alzheimer-related dementia as well as the vascular type) (31,32). A recently performed Swedish study on nondemented persons aged 75+ years found impaired cognitive performance correlating to low folate levels (33). Another controlled study on psychogeriatric patients showed that Hcy was best associated with cognition and behavior among the variables folate, cobalamin, Hcy, and methylmalonic acid (MMA)—another vitamin marker (34). Hcy as well as folate correlated positively with the severity of dementia, Katz ADL-scale, and symptomatology. No correlation was found between cobalamin and MMA. However, it is unclear whether vitamin deficiency contributes to psychogeriatric symptoms or rather results from them (35). Several studies have reported elevated Hcy in psychogeriatric patients and an inverse correlation with cognition (18,36–39), where 1 study reported 39% dementia association (40). There is also a correlation with Alzheimer’s disease independent of renal function and hypertension (41,42) as well as of nutrition (43,44). Folate/cobalamin levels were also significantly lower in the demented. In 1 of the studies, patients with the highest Hcy levels showed a more rapid disease progression during the 3-year follow-up period (37). Recent study results from 1092 healthy persons in the Framingham study showed a relative risk of 1.8 of developing Alzheimer’s disease per Hcy increase of 1 SD at baseline and 1.6 per Hcy increase of 1 SD 8 years after baseline (45). However, a recent follow-up study indicates that elevated Hcy levels are not the primary cause of Alzheimer’s disease, but rather it is more likely that it is the result and might be a reflection of concomitant vascular disease in those patients (46). Cross-sectional studies consistently indicate that elevated Hcy levels increase the risk of cognitive im-

![Figure 1. The methylation cycle and the interaction between folate, cobalamin, and homocysteine.](https://academic.oup.com/biomedgerontology/article-abstract/58/4/M354/605025)
The symptomatology is similar to that of the more because of the close interaction between the two B vitamins and folic acid (1 mg), B12 (400 μg), and pyridoxine (10 mg) daily (59). Following percutaneous coronary intervention in patients, the same vitamin dosage intervention for 6 months showed a significant decrease in the incidence of major adverse events defined as death, myocardial infarction, and need for repeat revascularization, compared with controls (60).

Cardiovascular Symptoms

Several studies have reported covariation of low folate/cobalamin levels and cardiovascular diseases (50,51). However, recently performed studies have focused on Hcy levels and the Hcy–folate–cobalamin triad, possibly constituting a determinant of atherogenesis and cardiovascular disease (52). Correlations have been found for stroke (53), in which case the association has been reported to be strong and graded (54), coronary heart disease (55), cardiovascular mortality (56), and carotid stenosis (57). There is also a reported lower risk of cardiovascular disease in those who eat folate-rich foods (58). However, it still remains unclear whether Hcy elevation is caused by the clinical manifestation or is a pathogenic factor and whether supplementation may improve, stop, or postpone development of symptoms. There is, however, a recent study reporting decreased levels or is a pathogenic factor and whether supplementation may improve, stop, or postpone development of symptoms.

Neurological Symptoms

Polyneuropathy may occur in the case of folate deficiency because of the close interaction between the two B vitamins and folate (59). The symptomatology is similar to that of the more often-described cobalamin deficiency. Patients with this deficiency exhibit a number of neurological symptoms, such as impaired sense of vibration, paresthesia, impaired skin sensation, gait anomalies, and dizziness (62).

Malignancies

It has been suggested that in the case of carcinogenesis, an impaired methylation of DNA and polyamines is involved (63,64). Folates act as a major methyl donor in many biological processes. Folate deficiency may lead to hampered cell proliferation as a result of disturbed DNA and RNA synthesis and deteriorated repairing capacity (65) and diminished suppression of excessive cell proliferation (66). There are also a number of studies that report a positive correlation between low folate levels and different forms of cancer (67) as well as data indicating that maintaining adequate folate levels may be important in lowering the risk of colorectal cancer (68). Increased risk of cervical cancer (69), colorectal cancer (70,71), and breast cancer (72,73) have been found in patients with low folate levels. Additionally, long-term use of multivitamins containing folic acid confers a substantial reduction of colorectal cancer risk (74). A gene–nutrition interaction involving the MTHFR polymorphism is reported to be of importance (75). However, the associations are complex, with many different factors involved, and are not fully understood (76). Although folate depletion may predispose an individual to the initiation of a neoplastic process, folate supplementation, on the other hand, might potentiate the progression of an already established neoplastic clone (77). Additionally, findings are not always consistent (71), bringing a cautionary note to the debate on folate fortification. Moreover, hyperhomocysteinemia has been observed in cancer patients, even though they were not treated with anti/folate drug, thereby suggesting that Hcy may be an accurate tumor marker for monitoring patients during cancer treatment (78).

CAUSES

Folate deficiency may occur for many reasons (79) (Table 4). In the absorption process, dietary folates require liberating enzymes in the intestinal mucosa and transporting proteins in blood and over cell membranes. The absorption is optimized within a certain pH-interval, and achlorhydria, which is common in the elderly, can decrease the absorption considerably (80). The nutritional intake decreases with increasing age, and a 30% decrease is reported in 80-year-old patients (2). Connective tissue and small bowel diseases may cause folate deficiency (81,82). Protracted warming
and heating may reduce the dietary folate content (83). Alcoholism is associated with reduced folate levels, likely as a result of impaired nutrition, decreased absorption, and disturbed metabolism in alcoholic individuals (84). Certain medications, such as trimethoprim, salazopyrine, and the folate antagonist methotrexate, interact with folate (85). Some antiepileptic drugs reduce the folate levels, and low levels have been found to covariate with depressive symptoms in patients (86,87). Folate/cobalamin are of importance for the metabolism of dopamine and levo-dopa in Parkinsonism, and elevated Hcy levels are reported in those patients (88,89). The origins of folate deficiency also include enzymatic failure in the folate pathway (28).

INVESTIGATION

The investigation should be conducted in order to obtain valuable and broad information on the patient’s dietary intake, medication, lifestyle, and metabolic balance. Blood samples of folate, cobalamin, and Hcy are mandatory and should be complemented with hemoglobin, sedimentation rate, creatinine, iron, glucose, and thyroid function. Sometimes, and particularly when there is a suspicion of malabsorption, pepsinogen, gastrine, and gliadine antibodies should be analyzed. Gastroscopy may sometimes be necessary to examine an atrophic gastritis or gluten-induced enteropathy (90). However, it is important to balance the spectrum of options against the limits of resources. It is a pragmatic view to first exclude nutritional factors and effect on the kidney and focus the investigation toward atrophic gastritis or celiac disease, which are thought to be the most common causes of vitamin deficiency in otherwise healthy persons.

A single reduced/normal folate with an accompanying increased Hcy level can only be correctly estimated in the light of the somatic status, anamnesis, and laboratory parameters of the patient.

Hcy is a broad determinant of malnutrition and malabsorption, with bearing on the uptake of folate, cobalamin, and vitamin B6. Conversely, a normal Hcy probably implies no chronic malnutrition or malabsorption, which could impair the uptake of folate or cobalamin. It was recently reported that 25% of patients aged 70+ years had elevated Hcy levels (91). Despite the fact that most patients had normal serum levels of folate as well as cobalamin, a combined folate/cobalamin treatment normalized Hcy levels.

The virtues of Hcy as a broad and swift marker of deficiency were clear to leading biochemists in Scandinavia by 1994 (92). However, the implications were not generally accepted by Swedish GPs and geriatricians in the period extending from 1996 to 1998 (93–95). Based on the consensus conference in Gothenburg, Sweden, in November 2000, Hcy is now generally accepted by Swedish physicians as the first screening test for folate/cobalamin deficiency (96).

Deficiencies of folate and cobalamin are mainly a problem of the elderly population in general and of the elderly population with neuropsychiatric symptoms specifically (97). Therefore, controlling folate/cobalamin and Hcy levels should be considered in elderly patients with cognitive impairment and atherosclerotic cardiovascular manifestations.

TREATMENT

Practical Treatment

When there is a clinical correlate with neurological, neuropsychiatric, or hematological manifestations combined with elevated Hcy levels and/or low folate/cobalamin levels, there are many treatment traditions. Not only do they vary between clinics but also within clinics, depending on the reference values of the laboratory, tradition, the doctor’s experiences, the patient’s situation and wishes. Noticeable is that the reference values of the laboratory are appointed according to healthy younger persons, whose possible state of deficiency is not known. It is also important to remember that the reference values of the laboratory are not “decision limits” for treatment or no treatment but rather are cut-off limits that define the statistical “normality” in a “healthy” reference population. However, mainly it is advisable to “treat and test” with folate/cobalamin, especially when accompanying symptoms of deficiency are present. Regardless of cause, the Hcy levels can always be lowered and even normalized with supplementation of folate and cobalamin and in certain cases with additional vitamin B6. On the other hand, it has not yet been proved that such a lowering improves clinical variables like prognosis or quality of life.

Folate/cobalamin deficiency and increased Hcy level with neurological and neuropsychiatric symptoms respond differently to supplementation. Most patients with neurological dysfunction and folate/cobalamin deficiency may have a complete or partial improvement of their symptoms after treatment. However, the remaining posttreatment symptoms are often related to the pretreatment severity and duration of the dysfunction (16). At remission, treatment of neuropsychiatric symptoms with sufficient doses must be assured. Such treatment is considered to be “no risk,” as therapeutic doses of both folate and cobalamin are nontoxic doses. Remission doses of folate are often high: initial oral daily doses of up to 20 mg, followed by maintenance doses of 1–5 mg (98). However, no guidelines have been agreed upon with regard to the appropriate dose, formulation, or duration of therapy for neuropsychiatric or cardiovascular disorders. In contrast to the response of hematological disorders, mental disorders respond more slowly and more incompletely, probably because of the rapid turnover of blood cells compared to the slow or nonexistent turnover of nervous system cells. Folate is actively transported into the nervous system through the blood–brain barrier, thereby limiting the entry of high doses (99).

When it comes to folate supplementation, on the other hand, some of the new insights into folate and nutrition are of significance from a public health perspective (100). Folate intake recommendations (i.e., RDI [recommended daily intake]) vary under different conditions. To maintain normal Hcy levels, 350 μg is required, and almost twice as much is required for those with elevated Hcy (101). Accordingly, the daily folate supplement should be at least 0.5 mg/day (102). This raises the question of whether the RDI provides a margin of safety to allow for individual variability, increased requirements, and decreased intake, particularly in vulnerable groups. It is imperative that recommendations provide a safety margin for these variabilities.
Current Cornerstone Treatment Studies

A study on 151 ischemic heart patients with different doses of folate supplementation found 0.8 mg/day to be an optimal dose of Hcy lowering, whereas folate levels rose linearly with 5.5 nmol per 0.1 mg folate (103). Willems and colleagues reported improved coronary endothelial function after 6 months of treatment with folic acid (5 mg) and cobalamin (400 μg) on patients with coronary artery disease and elevated Hcy levels (104). In an Hcy-lowering dose titration study with folate on women at the upper end of the normal range for Hcy, dosing was sufficient with as few as 100 μg regular intake of folate (105). A Swedish study on elderly persons with folate/cobalamin levels within reference values reported a decrease in the initially increased Hcy levels in all persons after 3 months of cobalamin treatment (106). However, a supplementation of folate was needed in 20% of the cases. This emphasizes the close interaction between folate/cobalamin, and it also illustrates the notion that persons with folate/cobalamin levels within the reference range may need a folate supplementation to lower Hcy levels.

A recent U.S. study of dietary folate and Hcy in persons aged 65+ years showed an inverse relation, which was limited to persons who did not have vitamin supplementation (107). However, in persons who did receive supplementation with folate/cobalamin, the Hcy level was 1.5 μmol/l lower, independent of dietary folate.

Another study has reported that folate-fortified food (400 μg/d), with or without pharmacological supplementation, significantly decreases the Hcy levels of the elderly (108). Likewise, a diet rich in vegetables and citrus fruits has been reported to increase folate and decrease Hcy, respectively (109). Additionally, pharmacological multivitamin supplementation decreases the Hcy level and increases the folate levels in the elderly who already partake of folate-fortified food (110). It has been estimated that the serum folate level increases with 0.94 ng/ml for each 0.1 mg of folate supplementation, and there is also a 50% reduction of neural tube defect with a doubling of the serum folate level (111).

The U.S. experience of physiological amounts of folate-fortified grain products (140 μg/100 g) have reduced the prevalence of low-folate status (<3.0 Ng/ml) by more than 90% and the prevalence of mildly elevated Hcy levels (>13.0 mmol/l) by 50% in middle-aged and elderly persons (112). It is unlikely that there will be a large increase in the proportion of older persons who are likely to consume more than the upper safety level of intake with folate fortification (113). It is also theoretically calculated that such a fortification may be cost effective and could have a major epidemiological benefit for primary and secondary prevention of coronary heart disease (CHD) if trials confirm that Hcy lowering decreases CHD event rates (114). However, a recent study reported that such a fortification will only achieve a small proportion of the achievable Hcy reduction (107).

The effects of increased folate intake on reducing the risk for neural tube defects or possibly vascular disease need to be balanced against concerns about the risk of masking anemia of vitamin B12 deficiency (115), an increased risk of twin births (116), an increased risk of a genetic selection of a folate-related enzyme mutation implying increased demands of folate (117), a general lack of data about safety of continuous high intakes, and the possible risk of promoting seizures in epileptic patients (118,119).

Given that causes have been diagnosed and adequately treated, folate appears to be the most powerful Hcy lowering agent. Rydlewicz and colleagues reported in a dose finding study that a daily intake of 926 μg of folic acid would be required to ensure that 95% of the elderly population would lower Hcy levels to the extent that there would be no cardiovascular risk from folate deficiency (120). This is unlikely to be achieved by diet alone. However, combination treatment with folate and cobalamin is often warranted. A controlled study with oral versus parenteral cobalamin substitution on persons with low serum cobalamin, normal blood folate, and increased Hcy was recently performed (121). Persons were randomized to either 2 mg/day oral or 9 doses of 1-mg intramuscular cobalamin during 4 months. The Hcy levels were normalized in all but 15% of the patients. These were found to have a combined folate–cobalamin deficiency, as the serum cobalamin was normalized but not the Hcy. The initial normal blood folate was probably attributable to the “folate trap,” and the functional deficiency was unmasked by the isolated cobalamin treatment (8). The Hcy was not normalized until a 4-week complementary supplementation with folate was added. Patients affected with neuropsychiatric symptoms were also equally improved. These findings show the close metabolic and clinical interaction between folate and cobalamin, and these findings add a contribution to the debate on the adequacy of oral versus parenteral cobalamin treatment, one that is in line with other recent studies (122–124) as well as with studies conducted in the 1960s (125).

Recently it was found that a combination of 2 months of oral cobalamin (1 mg/day) and folate (5 mg/day) improved the clinical state of mildly/moderately demented patients with elevated Hcy levels (126). Severely demented patients and patients with normal Hcy levels did not improve clinically, which indicates that Hcy today can be an interesting determinant to identify treatable dementias.

In summary, it is important to bear in mind that in our modern society, deficiency of folate/cobalamin—overt or latent—is mainly a problem of the elderly and a challenge to the doctor.

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