Review Article

Vitamin B12 and folate depletion in cognition: A review

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In cross-sectional studies, low levels of folate and B12 have been shown to be associated with cognitive decline and dementia Evidence for the putative role of folate, vitamin B12 in neurocognitive and other neurological functions comes from reported cases of severe vitamin deficiencies, particularly pernicious anemia, and homozygous defects in genes that encode for enzymes of one-carbon metabolism. The neurological alterations seen in these cases allow for a biological role of vitamins in neurophysiology. Results are quite controversial and there is an open debate in literature, considering that the potential and differential role of folate and B12 vitamin in memory acquisition and cognitive development is not completely understood or accepted. What is not clear is the fact that vitamin B12 and folate deficiency deteriorate a pre-existing not overt pathological situation or can be dangerous even in normal subjects. Even more intriguing is the interaction between B12 and folate, and their role in developing hyperhomocysteinemia. The approach to the rehabilitation of the deficiency with adequate vitamin supplementation is very confusing. Some authors suggest it, even in chronic situations, others deny any possible role.

Starting from these quite confusing perspectives, the aim of this review is to report and categorize the data obtained from the literature. Despite the plausible biochemical mechanism, further studies, based on clinical, neuropsychological, laboratory and (lastly) pathological features will be necessary to better understand this fascinating biochemical riddle.

Key Words: Folate, B12 , serum, cognition, nutrition, diet, dementia, neurodegeneration

Introduction

Apart from the natural aging, there are many conditions that lead to cognitive impairment; so far, there are some laboratory tests which are recommended by the National Institutes of Health Consensus Conference on Differential Diagnosis of Dementing Diseases, and these include vitamin B12 and folate levels.[1,2,3,4,5,6,7]

Folate and vitamin B12 are required both in the methylation of homcysteine to methionine and in the synthesis of S-adenosylmethionine. The latter is involved in numerous methylation reactions involving proteins, phospholipids, DNA, and neurotransmitter metabolism. Both folate and vitamin B12 deficiency may cause similar neurological depression, dementia, and a demyelinating myelopathy. A current theory proposes that a defect in methylation processes is central to the biochemical basis of the neuropsychiatric manifestations of these vitamin deficiencies. Folate deficiency may specifically affect central monoamine metabolism and aggravate depressive disorders. In addition, the neurotoxic effects of homocysteine may also play a role in the neurological and psychiatric disturbances that are associated with folate and vitamin B12 deficiency.

In spite of the theoretical importance of the determination of folate and vitamin B12 blood levels, there is a general confusion on their possible role in neuropsychiatric alterations.

Plenty of questions have been debated in last few years:

1. the role of folate, vitamin B12, and homocysteine in neurological practice.
2. the intrinsic relationship between folate and vitamin B12.
3. vitamin B12 alone is a sufficient, causative factor for the onset of neuropsychiatric symptoms.
4. the independent role of folate.
5. the isolated role of homocysteine.

Our group reviewed the literature and summarized the evidence relating to the above mentioned questions. Relevant articles were identified from a search of the Cochrane Dementia and Cognitive Improvement Group's Specialized Register using the terms: folic acid, folate, vitamin B9, leucov-

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orin, methyltetrahydrofolate, vitamin B12, cobalamin and cyanocobalamin. Relevant articles were identified by searching MEDLINE, EMBASE, Biosis. Key search terms were folate, vitamin B12, defect, homocysteine, degeneration, dementia, age, food supplementation. The following areas were evaluated: degenerative dementia, reversible dementia, food supplementation and dietary intake, malabsorption, treatment, consequence of treatment, consequence of no treatment. All English-, Italian-, French-, German- and Spanish-language articles published on the topic from 1940 to August 2003 were reviewed. Excluded were non-systematic reviews or single case reports. A very large amount of studies have been found, many more than the ones we cite; some of them will be summarized in tables; we include in the text for discussion only the most rigorously done studies.

The role of folate, vitamin B12, and homocysteine: what is known

The central nervous system requires a constant supply of glucose, and adequate brain function and maintenance depend on almost all the essential nutrients. For those B vitamins that participate in one-carbon metabolism (i.e. folate, vitamin B12, and vitamin B6) deficiency of or congenital defects in the enzymes involved in these pathways is associated with severe impairment of brain function. Although severe vitamin deficiencies and congenital defects are rare, milder subclinical vitamin deficiencies are not uncommon in the elderly.[8,9,10,11]

Folate and vitamin B12 are both required in the methylation process.

The evidence has come from a number of experimental studies (Figure 1).

Methylation processes are central to the biochemical basis of the neuropsychiatry of folate and B12 deficiencies. The *de novo* synthesis of methionine requires vitamin B12, which is involved directly in the transfer of the methyl group to homocysteine. In turn, methionine is required in the synthesis of S-adenosylmethionine (SAM) the sole donor in numerous methylation reactions involving proteins, phospholipids and biogenic amines. Upon transfer of its methyl group, SAM is converted to S-adenosylhomocysteine (SAH), rapidly and subsequently hydrolyzed to homocysteine and adenosine.[12,13] This hydrolysis is a reversible reaction that favors SAH synthesis. If homocysteine is allowed to accumulate, it will be rapidly metabolized to SAH, which is a strong inhibitor of all methylation reaction, competing with SAM for the active site on the methyltransferase enzyme protein.[14,15,16,17] The biochemical basis of the interrelationship between folate and cobalamin is the maintenance of two functions, nucleic acid synthesis and the methylation reactions. The latter is particularly important in the brain and relies especially on maintaining the concentration of S-adenosylmethionine which in turn, maintains the methylation reactions whose inhibition is considered to cause cobalamin deficiency-associated neuropathy.

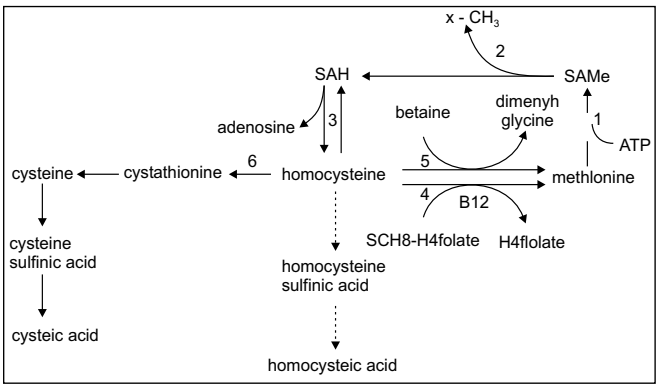

Figure 1: Metabolic relationship between folate, vitamin B12, homocysteine. 1. methionine adenosyltransferase; 2. x-methyltransferase; 3. S-adenosylhomocysteine hydrolase; 4. methionine synthetase; 5. betaine-homocysteine methyltransferase; 6. cystathionine-beta synthetase

In case of folate or vitamin B12 deficiency, the methionine synthetase reaction is severely impaired. In particular, vitamin B12 is the necessary coenzyme, adequate for the correct functioning of the methyl donation from 5 methyltethrahydrofolate in tetrhahydrofolate, necessary for methionine synthetase. Folate is a cofactor in one-carbon metabolism, during which it promotes the remethylation of homocysteine— a cytotoxic sulfur-containing amino acid that can induce DNA strand breakage, oxidative stress and apoptosis.[18,19,20,21] Theoretically, in the key point of methylation previously underlined, it might be hypothesized that folic acid "obliges" the entire vitamin B12 to subserve as coenzyme, and therefore enforces the otherwise limited damage caused by the vitamin B12 defect, per se.

Homocysteine and Methylmalonic Acid

In humans, only two enzymatic reactions are known to be dependent on vitamin B12. In the first reaction, methylmalonic acid is converted to succynyl-CoA using vitamin B12 as a cofactor. Vitamin B12 deficiency can lead to increased levels of serum methylmalonic acid. In the second reaction, homcysteine is converted to methionine by using vitamin B12 and folic acid as a cofactors. In this reaction, a deficiency of vitamin B12 or folic acid may lead to increased homocysteine levels.

Normally, methylmalonic acid and its precursor (propionic acid) are found in very small amounts in body fluids because methylmalonyl CoA is converted to succinyl CoA, which is further metabolized to produce energy or is involved in the synthesis of porphyrins. When methylmalonyl CoA builds up to an abnormal level, it will be converted to methylmalonic acid.[22,23]

It has been hypothesized that a pathway of oxidation of homocysteine to homocysteic acid is the potential explanation of the dangerous effect of homocysteine (Figure 2). In fact, homocysteic acid is a mixed excitatory agonist preferentially at N-Methyl- D-Aspartate (NMDA) receptors.[24] These

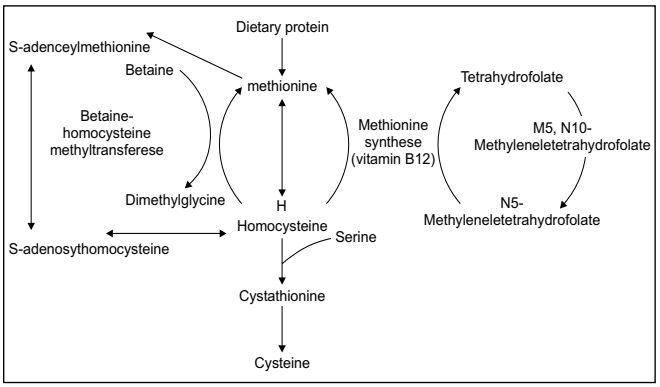

Figure 2: Three different pathways for homcystein metabolism in the human body

receptors are well known in memory long-term potentiation system: hyper or abnormal activation of NMDA receptors results in a rise of intracellular calcium, consequent release of cellular proteases and eventual cell death.[25]

Elevated levels of homocysteine in the blood predispose to arteriosclerosis and stroke.[25] Indeed it has been recently estimated that as many as 47% of patients with arterial occlusions manifest modest elevations in plasma homocysteine.[26] Included among the many causes are genetic alterations in enzymes such as cystathionine beta-synthase, a defect found in 1-2% of the general population, and deficiencies in vitamins B6, B12, and folate whose intake is suboptimal in perhaps 40% of the population.[26] The strength of the association between homocysteine and cerebrovascular disease appears to be greater than that between homocysteine and coronary heart disease or peripheral vascular disease. During stroke or head trauma, disruption of the blood-brain barrier results in exposure of the brain to near plasma levels of amino acids, including homocysteine and glycine.

Diagnosis of vitamin B12 deficiency

The diagnosis of vitamin B12 deficiency has traditionally been based on low serum vitamin B12 levels, usually less than 200 pg per mL (150 pmol per L), along with clinical evidence of disease. However, studies indicate that older patients tend to present with neuropsychiatric symptoms in the absence of hematologic findings.[27,28] Furthermore, measurements of metabolites such as methylmalonic acid and homocysteine have been shown to be more sensitive in the diagnosis of vitamin B12 deficiency than the measurement of serum B12 levels alone.[29,30,31] In a large study[32] of 406 patients with known vitamin B12 deficiency, 98.4% had elevated serum methylmalonic acid levels, as only one patient out of 406 had normal levels of both metabolites, resulting in a sensitivity of 98% when methylmalonic acid and homocysteine levels are used for diagnosis. Twenty-eight per cent of the patients in this study[32] had normal hematocrit levels, and 17% had normal mean corpuscular volumes. This finding suggests that methylmalonic acid and homocysteine levels can be early markers for tissue vitamin B12 deficiency, even before hematologic manifestations occur. If increased homocysteine or methylmalonic acid levels and a normalization of these metabolites in response to replacement therapy are used as diagnostic criteria for vitamin B12 deficiency, approximately 50% of these patients have serum vitamin B12 levels above 200 pg per mL.[29] This observation suggests that use of a low serum vitamin B12 level as the sole means of diagnosis may miss up to one half of patients with actual vitamin B12 deficiency. Vitamin B12 or folic acid deficiency can cause the homcysteine level to rise, so folic acid levels also should be checked in patients with isolated hyperhomocysteinemia. In addition, folic acid deficiency can cause falsely low serum of vitamin B12 levels.[29] Looking at the reactions that use vitamin B12, an elevated methylmalonic acid level is clearly more specific for vitamin B12 deficiency than an elevated homocysteine level. Also, methylmalonic acid levels can be elevated in patients with renal disease: thus, elevated levels must be interpreted with caution.

Is vitamin B12 alone a sufficient, causative factor for the onset of neuropsychiatric symptoms?

Data obtained from the literature state that vitamin B12 is somehow bound to cognition and to the implementation of active strategies to coordinate and do well in active problem solving.[32]

Larner et al[33,34] reported an overview of literature, and it emerges that the effective number of vitamin B12 defect-dementia is extremely small.[3,4,5,19,20] Though, elderly individuals with cobalamin deficiency may present with neuropsychiatric or metabolic deficiencies, without frank macrocytic anemia.[35] Psychiatric symptoms attributable to vitamin B12 deficiency have been described for decades.[35] These symptoms seem to fall into several clinically separate categories: slow cerebration, confusion, memory changes, delirium with or without hallucinations and or delusions, depression, acute psychotic states, and more rarely, reversible manic and schizophreniform states.[36]

A higher prevalence of lower serum vitamin B12 levels have been found in subjects with AD,[37] other dementias[38] and in people with different cognitive impairments,[31,39] as compared with controls. In contrast, other cross-sectional studies [40,41] have failed to find this association (more data are reported in Table 1).[42,43,44,45,46,47,48] The most recent study[49] on the topic examined the relationship between vitamin B12 serum levels and cognitive and neuropsychiatric symptoms in dementia; in AD, the prevalence of low vitamin B12 serum levels is consistent with that found in community-dwelling elderly persons in general but is associated with greater overall cognitive impairment.

Furthermore, some intervention studies have shown the effectiveness of vitamin B12 supplementation in improving cognition in demented or cognitively impaired subjects. Chronic

Table 1: A synopsis of different studies on B12 defect and cognitive impairment

Authors	Subjects	Low B12	Age	Comments
Goodwin et al, 1983	260 healthynon institutionalized Compared top *10%* with bottom 5% and 10%	Blood concentration	>60 age	Also found sman positive correlations forriboflavin and vitamin C with verbal memory. No protein, correlations were found *for* thiamine, and pyridoxine
Karnaze and Carmel, 1987	Priamry degenerative dementia (A)patients (n=17) and secondary dementia (B) patients (n=11)	B greater than A (p<0.001)	Mean(A)=70.5 yMean (B)=70.9y	No disease was responsible for the low B12 status
Lindenbaum et al, 1988	40 neuropsyciatric patients with coalamin deficiency but no anemia or macrocytosis		>17 y	MMA concentrations were 3 SDs above normal in 36 of 37 patients before treatments but fell in all but 2 after treatment with cobalamin
Nijst et al. 1990	293 neurologic patients	Serum concentrations for AD (p<0.001)	>11y	Vitamin B12 in CSF was lower in DAT patients (p<0.05) and in MS patients (p<0.05) than in control groups
Kristensen et al. 1993	AD patients (n=26) (A) patients with other dementia (n=24) (B) patients with mental disorders (n=25) (C) Control subjects (n=20) (D)	A <0.05	Mean A=73.2 Mean B=68.9 Mean C=77.9 Mean D=73.4	Higher MMA concentrations in AD patients than in any other group; positive correlation between red blood cells, folate and B12 concentrations (p<0.001)
Crystal et al, 1994	410 volunteers	NS	>75	No conclusions can be drawn owing to lack of significant results and limited number of observations
La Rue et al, 1997	Elderly community residents (n=137)	Plasma p<0.10 Dietary intake: p<0.10	>66	Positive correlations of abstraction performance with thiamine, riboflavin, niacin; visuospatial performance with ascorbate; dietary protein with memory and serum albumin or transferrin with memory, visuospatial performance, or abstraction
Joosten et al, 1997	AD patients (n=52; A) hospitalized control subjects (n=50; B) healthy elderly (n=49; C)	P<0.05 for AD p<0.01 for confirmed AD subgroup	>55	MMA for A compared with B, p<0.01

dementia responds poorly but should nevertheless be treated if there is a metabolic deficiency (as indicated by elevated homocysteine and/or methylmalonic acid levels).[35] These data have been confirmed by other studies.[50,51,52,53] However, a treatment effect was demonstrated among the patients presenting with cognitive impairment, improving when compared to matched patients on the verbal fluency test. On the contrary, other works have failed to confirm the optimistic results [54,55] even testing executive functions.

Our conclusion could be that vitamin B12 treatment may improve frontal lobe and language function in patients with cognitive impairment, but rarely reverses dementia.

The clinical independent role of folate

One of the most recent reviews on folic acid[56] clearly states its importance in neuropsychiatric disorders.[56,29] Dietary folate is required for the normal development of the nervous system, playing important roles in regulating neurogenesis and programmed cell death.[57] Recent epidemiological and experimental studies have linked folate deficiency and resultant increased homocysteine levels with several neurodegenerative conditions, including stroke, AD, and Parkinson's disease.[57,58] Folate deficiency sensitizes mice to dopaminergic neurodegeneration and motor dysfunction caused by neurotoxin MPTP.[58] Additional experiments indicate that this effect of folate deficiency may be mediated by homocysteine. These findings suggest that folate deficiency and hyperhomocysteinemia might be risk factors for Parkinson's disease.[58]

Depression is more common in patients with folate deficiency, and subacute combined degeneration with peripheral neuropathy is more frequent in those with vitamin B12 deficiency.[59] Bottiglieri et al[59] have suggested that nearly one-third of their severely depressed inpatients have folate deficiency, as indicated by a red cell folate concentration below 150 ug/l.[59]

Experience from the early part of the 20th century suggests that of the one-third of patients with anemia who have no psychiatric disorder, most would go on to develop such complications if left untreated[60,61] (more data have been reported in Table 2).[62,63,64,65,66,67,68,69,70]

To examine the effects of folic acid supplementation, with or without vitamin B12, on elderly healthy and demented people, in preventing cognitive impairment or retarding its progress, a review has been made.[71] All double-blind placebo-controlled randomized trials, in which supplements of folic acid with or without vitamin B12 were compared with placebo for elderly healthy people or people with any type of dementia or cognitive impairment were reviewed. Analysis of

Table 2: A synopsis of works on low folate deficits and cognitive defect

Study	Methods	Participants	Interventions	Outcome
Brocker et al. (1986)	Surveys of folate levels. Open clinical study, non controlled	1000 Geriatric inpatients of whom 75% were found with folate deficiency.50 Patients with heterogeneous diagnoses and with folate deficits were randomly assigned to a treatment study	50 mg of folic acid (im.) for 21 days	3 Patients with dementia had a complete recovery.
Rapin et al. (1988)	Open clinical study	Aged patients with memory disorders without overt signs of dementia and with low levels of folate in their blood	50 mg/week of folic acid	Patients showed significant improvements in visuomotor performance and visuospatial memory, associative memory, and activities of daily living after 4 months
Regland et al. (1988)	Comparative analysis of vitamin B12 levels in different clinical groups of aged vascular patients status	35 AD patients, 56 SDAT patients, 54 dementia patients, 10 confusional patients	None	Low B12 was found to be associated with low serum folate level in SDAT patients and this level was lower than in other patients of the same age group
Spindler and Renvall (1989)	Analytic review of the biochemical and physiological literature. Survey of nutritional and biochemical parameters related to scores of cognitive functioning	Aged subjects participating in community-sponsored programs for alimentary education	None	Cognitive deterioration was found correlated with low levels of folate/cobalamine. Appropriate studies are necessary to verify the role of vitamin supplementation in ameliorating cognitive deficits of demented patients
Bell et al. (l990a)	Survey of B12 and folate levelin psychogeriatric patients	102 Patients	None	Concomitant lower levels of BI2 and folate were associated with poorer cognitive status
Bell et al. (l990b)	Comparative survey of folate level in different clinical groups of aged patients	Psychotic depressed patients, nonpsychotic depressed patients, bypolar depressed patients, dementia patients	None	No relationship was found between folate serum in level (normal in all patients) and cognitive deficits
Levitt and Karlinsky (1992)	Survey of cognitively impaired patients assessing B12 and folate deficiency in relation to cognitive functioning as assessed by MMSE	97 Consecutive patients; 40 with AD, 31 with other dementias, 26 with mild cognitive impairment	None	Only patients with AD evidenced a significant correlation between BI2 low levels and MMSE scores indicating cognitive impairment. Folate levels were found related to cognitive functioning
Regland and Gottfries (1992)	Review of literature on psychobiology of folate in dementia	None	None	Folate and cobalamin are considered essential nutrients with the function of coenzymes in the metabolic pathways necessary for the synthesis of DNA and S- adenosyImethionine (SAM). DNA synthesis and integrity of neurons are maintained by these compounds which have been characteristically found reduced in AD patients
Bottiglieri and Hyland (1994)	Review	None	None	Folate is essential in the metabolism of S -adenosyhnethionine, an important factor in methylation of cellular components

the included trials found no benefit from folic acid with or without vitamin B12 in comparison with placebo on any measures of cognition or mood for healthy or cognitively impaired or demented people. Folic acid plus vitamin B12 was effective in reducing serum homocysteine concentrations. Folic acid was well tolerated and no adverse effects were reported. The available studies are limited in size and scope but provide no evidence that folic acid, with or without vitamin B12, has a beneficial effect on cognitive function or mood of health or cognitively impaired older people.[71] Folate deficiency has been described in epileptic patients: treatment of folate deficient epileptic patients with folic acid daily for one to three years resulted in improved drive, initiative, alertness, concentration, mood, and sociability in most.[72,73] The highest incidence of folate deficiency as measured by serum and red cell folate concentrations is in elderly populations. A close association with dementia and the apparent depression, apathy, withdrawal, and lack of motivation has been noted.[74] One reason for a

high incidence of folate deficiency in elderly people is that folate concentrations in serum and cerebrospinal fluid fall and plasma homocysteine rises with age, perhaps contributing to the ageing process.[75,76] Considering that recent epidemiological studies[77,78,79,80,81] have shown an association between low serum folate levels and risk of vascular disease, including stroke and various types of vascular cognitive impairment, some authors[76] examined data from the Canadian Study of Health and Ageing. After adjusting for covariates, the risk estimate for an adverse cerebrovascular event associated with the lowest folate quartile compared with the highest quartile was OR 2.42 (95%CI; 1.04-5.61). Results from stratified analyses also showed that relatively low serum folate was associated with a significantly higher risk of an adverse cerebrovascular event among female (OR 4.02, 95%CI; 1.37-11.81) subjects. There is a concern that low folate status may represent a proxy for low socio-economic status or some related status. In general medical patients admitted acutely to hospital, 71% of those with severe folate deficiency had organic brain syndrome, compared with 31% of a control group.[82,83,84] In a prospective community-based study of 370 healthy elderly Swedish subjects, folate or B12 deficiency doubled the risk of subsequently developing AD.[85] In a survey of nutritional status and cognitive functioning in 260 healthy elderly subjects aged 60 to 94 years in the community, there was a significant relation between impaired abstract thinking ability and memory and lower folate levels intake.[86] Recently, the much larger and longer Framingham community-based study confirmed that a raised plasma homocysteine (bound to low folate level) concentration doubled the risk of developing Alzheimer's and non-Alzheimer's dementia.[87] On the basis of neuroimaging, another work concluded that chronic folate deficiency could induce cerebral atrophy.[88] In a relatively small sample,[89] serum folate had a strong negative association with the severity of atrophy of the *neocortex*. In the Kingsholmen ageing and dementia project in Stockholm, impaired episodic memory was related to low serum concentrations of folate.[90] In other case-control studies in patients with Alzheimer's disease, cognitive decline was significantly associated with raised plasma homocysteine and lowered serum folate (and vitamin B12) concentration.[91,92] In open studies[83,93] reviewing experiences with folic acid, authors emphasized the effects of the vitamin on mood and cognitive function. An ad-hoc double blind, controlled versus placebo pilot study to evaluate the efficacy of folic acid in aged patients with abnormal cognitive decline and low serum folate[94] demonstrated a significant improvement in both memory and attention efficiency in patients treated, when compared with a placebo group. Above all, the intensity of memory improvement positively correlated with the initial severity of folate deficiency. Our conclusions can be that correlational studies show an association between low folate and psychiatric disorders, even if this association does not mean causality. Only prospective studies can show causality. Correlational studies show an association between low folate and psychiatric disorder, but the available prospective studies are limited in size and scope, and provide no evidence that folic acid, with or without vitamin B12, has a beneficial effect on cognitive function or mood of healthy or cognitively impaired older people.

Homocysteine: what is its clinical relevance?

Plasma homocysteine and serum methylmalonic acid reflect the functional status of cobalamin and folate in the tissues.[95] Hyperhomocysteinemia is an important risk factor for a vascular disease, including stroke, independent of long-recognized factors such as hyperlipidemia, hypertension, etc.[96] In addition to its association with cerebrovascular disease, homocysteine may play a role in neurodegenerative disorders, even if only as a marker of functional vitamin B12 deficiency.[96] A recent study[97] showed that B vitamins and homocysteine have been associated with cognitive variation in old age, accounting for 7-8% of the variance in cognitive performance.

Serum total homocysteine levels were significantly higher and serum folate and vitamin B12 levels were lower in patients with dementia of AD type and with histological confirmed AD than in controls.[91] After 3 years of follow-up, there was significantly greater radiological evidence of disease progression assessed by medial temporal lobe thickness, among those with total homocysteine levels in the middle and upper tertile. Those in the lower tertile showed less cortical atrophy.[91] The stability of total homocysteine levels over time and the lack of relationship with the duration of symptoms argue against these findings being a consequence of disease and warrant further studies to assess the clinical relevance of these associations for AD.[91]

Homocysteine has a direct consequence for neurotoxic effects on hippocampal and cortical neurons.[98,99,100] Two putative effects of homocysteine support a casual association between higher plasma homocysteine levels and brain atrophy, due to a direct damage to the arteries and due to its neurotoxic effect.[99,100]

In a recent study,[101] significantly elevated homocysteine levels were found in patients with AD as well as in patients with vascular dementia, probably indicating similar pathophysiological pathways. On the contrary, some other authors[102] affirmed that there is some evidence from recent observational studies that hyperhomocysteinemia is a risk factor for cognitive dysfunction, including AD and vascular dementia.

Our conclusion seems to be that there are only few intervention studies, and the results are disappointing for such a frequent disease. Prospective double-blind and placebo-controlled intervention studies are not available. If homocysteine-lowering therapy has to be in the running for the prevention and treatment of dementia, we must be able to diagnose the disease at a preclinical stage 5 to 20 years before the disease

becomes clinically overt for AD).

Vitamin B12 And Folate: A Clinical Relationship

Potential benefits[103,104] of food folic acid fortification for an elderly population might be relevant, but there is the risk of precipitating clinical manifestations related to vitamin B12. Cyanocobalamin deficiencies should be excluded before folate supplementation is commenced; if in doubt, it may be safer to supplement folate and vitamin B12 together.[104,105] These ideas have been rejected by the study conducted by Dickinson et al.[105]

Actually, however, general guidelines recommend that only specific and separate dosage of folate and B12 should be done and, whenever possible, a correct implementation of the depletion status should be effected, in order to avoid, if not sure, almost possible cognitive impairment.[106]

Many different studies have tried to describe a possible consequence of the combined defect of vitamin B12 and folate. Riggs et al[107] investigated the relations between plasma concentrations of folate, vitamin B12, vitamin B6, and homocysteine and scores on a battery of cognitive tests in 70 men, aged 54-81, participating in the Normative Aging Study. Lower folate and vitamin B12 concentrations were associated with poorer spatial copying skills. In addition, plasma homocysteine concentration, which is inversely correlated with plasma folate and vitamin B12 concentrations, was a stronger positive predictor of spatial copying performance than either folate or vitamin B12 concentrations.[108] Among markers of cobalamin/folate status, plasma homocysteine shows the best association with neuropsychiatric dysfunction.[109]

A recent work[110] examined the relationship between low levels of serum vitamin B12 and folic acid and cognitive functioning in very old age. In general, the effects of folic acid exceeded those of B12.

Quite different results emerged from Fioravanti et al.[94] There were no clear signs of slowing the progression of dementia, when treating patients with subnormal serum levels, with supplements of vitamin B12. Neither vitamin B12 nor folic acid supplementation[111] affected recognition or primary memory in very old age, even though the subjects with low folic acid levels showed impairment in both word recall and object recall. Very recently, a longitudinal, multi-center study including a baseline study, a follow-up study, and a finale study[111] has been conducted, to describe 5-year changes of mental health in SENECA participants and to examine whether mental health is associated with the status of vitamin B12 and folate in those born between 1913 and 1918. SENECA is a longitudinal study. The population consisted of 1091 men and 1109 women aged between 70-75 years from Europe. This study includes data on diet, lifestyle, and health. The study population followed for 10 years, and measurements were performed in 1988/89 (baseline), 1993, and 1999.[112] Among the subjects that participated in the finale study,[111] no significant correlations have been observed between mental health and vitamin B12/folate status.

Another study[113] showed that patients with mild-moderate dementia and elevated plasma homocysteine levels improved clinically with increased test scores after vitamin B12 substitution, while severely demented patients and patients with normal plasma homocysteine levels did not improve clinically. Based on research demonstrating associations between folate, B12 and B6 vitamins and cognition and mood, another work[114] investigated the effects of short-term supplementation of folate, vitamin B12 and B6 in healthy young, and middle-aged and older women. Supplementation had a significant positive effect on some measures of memory performance only, and no effect on mood.[114]

Conclusions

What clearly emerges from the literature is the general conviction that vitamin B12 and folate, directly, through the maintenance of two functions, nucleic acid synthesis and the methylation reactions, or indirectly, due to their deficiency which causes SAM-mediated methylation reactions' inhibition by its product SAH, and through the related toxic effects of homcysteine which causes direct damage to the vascular endothelium and inhibition of N-methyl-D-Aspartate receptors, can cause neuropsychiatric disturbances. Evidence of the importance of folate, vitamin B12 in neurocognitive and other neurological functions derives from reported cases of severe vitamin deficiencies, particularly pernicious anemia, and homozygous defects in genes that encode for enzymes of one-carbon metabolism. The neurological alterations seen in these cases allow for a biological role of vitamins in neurophysiology.

What is not clear is the fact that vitamin B12 and folate deficiency deteriorate a pre-existing, not overt pathological situation or can be dangerous even in normal subjects. Moreover, though in recent years new methodologies for the detection of both folate and vitamin B12 deficiencies became available (homocysteine and methylmalonic acid), a correct diagnosis of B12 or folate deficiency is actually a challenge. It is difficult to compare many studies as the diagnosis of B12 deficiency is made by different methods.

The approach to the rehabilitation of the deficiency with adequate vitamin supplementation is very confusing. Some authors suggest it, even in chronic situations, others deny any possible role. Moreover, all forms of vitamin B12 currently available as pharmaceutical preparations require conversion to glutathionylcobalamin, which requires glutathione for its synthesis. Therefore, it might not be utilized by neurons under conditions of oxidative stress because of a scarcity of gluthatione.

Despite the plausible biochemical mechanism, further studies, based on clinical, neuropsychological, laboratory and

(lastly) pathological features will be necessary to better understand this fascinating biochemical riddle.

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