Lead Article

Advances in clinical determinants and neurological manifestations of B vitamin deficiency in adults

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B vitamin deficiency is a leading cause of neurological impairment and disability throughout the world. Multiple B vitamin deficiencies often coexist, and thus an understanding of the complex relationships between the different biochemical pathways regulated in the brain by these vitamins may facilitate prompter diagnosis and improved treatment. Particular populations at risk for multiple B vitamin deficiencies include the elderly, people with alcoholism, patients with heart failure, patients with recent obesity surgery, and vegetarians/vegans. Recently, new clinical settings that predispose individuals to B vitamin deficiency have been highlighted. Moreover, other data indicate a possible pathogenetic role of subclinical chronic B vitamin deficiency in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. In light of these findings, this review examines the clinical manifestations of B vitamin deficiency and the effect of B vitamin deficiency on the adult nervous system. The interrelationships of multiple B vitamin deficiencies are emphasized, along with the clinical phenotypes related to B vitamin deficiencies. Recent advances in the clinical determinants and diagnostic clues of B vitamin deficiency, as well as the suggested therapies for B vitamin disorders, are described.

INTRODUCTION

B vitamin deficiency is a frequent cause of neurological impairment and disability throughout the world.[1–3] Major neurological disorders associated with deficiency of one or more B vitamins simultaneously are often only a subset of multiple organ complications. They encompass a broad spectrum of pathological states, show extreme phenotypic variation, and have a roughly age-related distribution (Table 1).[4–18]

In developed countries, special populations at risk are the elderly, the poor, the homeless, chronic misusers of alcohol, vegetarians/vegans, patients with multiple gastrointestinal, cardiac, and neuropsychiatric disturbances, patients with gastrointestinal surgery, individuals on dietary commercial formulae, and patients receiving inadequate parenteral nutrition.[2,3] Recently, some cases of B vitamin dependency and/or deficiency, mainly in infants and children, have been found to be definitively associated with genetic disorders of B vitamin metabolism, resulting in severe neurological manifestations (Table 1).[4–18]

The family of B vitamins includes thiamine (vitamin B_1), riboflavin (vitamin B_2), niacin (vitamin B_3), pantothenic acid (vitamin B_5), pyridoxine (vitamin B_6), biotin (vitamin B_7), folate (vitamin B_9), and cobalamin (vitamin B_{12}).[14] These are structurally dissimilar organic compounds that share the common features of being essential for normal cellular functions, growth, and development in all tissues.[14] The majority of these water-soluble vitamins, in their biologically active forms, work synergistically as essential coenzymes in

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Table 1 **Age-related distribution of nervous system disorders related to B vitamin deficiency**

Age	Deficiency disorders	Vitamins	References
Embryogenesis	Neural tube defects	B_1, B_9, B_{12}	Safi et al. (2012),[4] Wallingford et al. (2013)[5]
Childhood	Seizures and epilepsy	B_1, B_3, B_6, B_7, B_9, B_{12}	Baumgartner (2013),[6] Micó et al. (2012),[7] Rahman et al. (2013)[8]
	Encephalopathy (acute or chronic)	B_1, B_3, B_6, B_7, B_9, B_{12}	Baumgartner (2013),[6] Clayton (2006),[9] Oldham & Ivkovic (2012)[10]
	Mental retardation	B_1, B_3, B_5, B_6, B_7, B_9, B_{12}	Baumgartner (2013),[6] Kumar (2014)[11]
	Polyneuropathy	B_1, B_2, B_6, B_9, B_{12}	Baumgartner (2013),[6] Chawla & Kvarnberg (2014),[12] Kumar (2007)[13]
	Optic neuropathy	B_1, B_2, B_7, B_9, B_{12}	Micó et al. (2012),[7] Kumar (2014)[11]
	Deafness	B_1, B_2, B_7	Sechi & Serra (2007),[2] Micó et al. (2012)[7]
	Language impairment	B_1, B_9, B_{12}	Kumar (2010),[3] Baumgartner (2013)[6]
	Childhood-onset motor neuron diseases	B_2	Said (2011)[14]
	Pantothenate-related neurodegeneration	B_5	Leoni et al. (2012)[15]
Adult	Encephalopathy (acute or chronic)	B_1, B_3, B_9, B_{12}	Baumgartner (2013),[6] Kumar (2014)[11]
	Polyneuropathy	B_1, B_6, B_9, B_{12}	Baumgartner (2013),[6] Spinazzi et al. (2010),[16] Kumar (2007)[13]
	Autonomic dysfunction	B_1, B_6, B_9, B_{12}	Baumgartner (2013),[6] Kumar (2007)[13]
	Myelopathy	B_9, B_{12}	Baumgartner (2013),[6] Kumar (2014)[11]
	Optic neuropathy	B_1, B_{12}	Spinazzi et al. (2010),[16] Kumar (2014)[11]
	Behavior disorders	B_1, B_3, B_9, B_{12}	Sechi & Serra (2007),[2] Baumgartner (2013),[6] Kumar (2014)[11]
	Mood disorders	B_3, B_9, B_{12}	Baumgartner (2013),[6] Kumar (2014)[11]
Late life	Encephalopathy (acute or chronic)	B_1, B_3, B_9, B_{12}	Baumgartner (2013),[6] Kumar (2014)[11]
	Polyneuropathy	B_1, B_6, B_9, B_{12}	Baumgartner (2013),[6] Spinazzi et al. (2010),[16] Kumar (2007)[13]
	Autonomic dysfunction	B_1, B_6, B_9, B_{12}	Baumgartner (2013),[6] Kumar (2007)[13]
	Myelopathy	B_9, B_{12}	Baumgartner (2013),[6] Kumar (2014)[11]
	Optic neuropathy	B_1, B_{12}	Spinazzi et al. (2010),[16] Kumar (2014)[11]
	Behavior disorders	B_1, B_3, B_9, B_{12}	Baumgartner (2013),[6] Kumar (2014)[11]
	Mood disorders	B_3, B_9, B_{12}	Baumgartner (2013),[6] Kumar (2014)[11]
	Neurodegeneration/cognitive decline (?)	B_1, B_6, B_9, B_{12}	Lu'o'ng & Nguvên (2012),[17] Douaud et al. (2013)[18]

several biochemical pathways in the brain, mainly in the production of cellular energy, and are essential to the development, myelination, and proper functioning of the central and peripheral nervous system.[3,19] None of these vitamins, except niacin, can be synthesized by the human body, and thus they need to be consumed in food as part of the diet on a regular basis.[19] Niacin, when deficient in the diet in humans, can be synthesized from the essential amino acid tryptophan.[19]

In individuals at risk for B vitamin deficiencies, an unbalanced supply of a single B vitamin may simply shift the rate-limiting step in cells to another pathway of the energy cascade and mask a deficiency in other B vitamins (e.g., the masking of vitamin B_{12} deficiency by folic acid).[1,19,20] Consequently, the persistent energy failure in cells can result in further neurological deterioration with subsequently (or concomitantly) poor clinical outcomes.[1,20]

In light of these findings, a review of both the clinical manifestations of B vitamin deficiency and the impact of B vitamin deficiency on the adult nervous system is warranted. This review will emphasize the interrelationships of multiple B vitamin deficiencies and will examine the clinical phenotypes related to B vitamin deficiencies. Recent findings about the clinical determinants of B vitamin deficiency, along with diagnostic clues and suggested therapies of B vitamin disorders, will be described.

EPIDEMIOLOGY OF B VITAMIN DEFICIENCY

A plethora of conflicting published information exists regarding the prevalence of B vitamin deficiencies in populations at risk. Among the B vitamin deficiencies researched, the deficiency of vitamins B_1, B_2, B_6, B_{12}, and folate has been particularly studied, whereas that of other B vitamins, such as vitamins B_5 and B_7, remains largely unstudied. Importantly, most of the studies focus either on dietary data or on tissue levels of B vitamins, with evidence of deficiency or normality based only on biochemical data. Moreover, there are no guidelines for monitoring the status of many B vitamins, and thus it is difficult to know the true prevalence of B vitamin deficiencies. Four kinds of populations at risk have been particularly investigated: the elderly, patients with heart failure, postoperative bariatric surgery patients, and vegetarians/vegans (Table 2).[20–36]

Table 2 **Prevalence of B vitamin deficiency in special populations at risk**

Population	Prevalence (%) of deficiency								References
	B_1	B_2	B_3	B_5	B_6	B_7	B_9	B_{12}	
Elderly	22.9	11.7	–	–	1–75	–	30	20–25	Kjeldby et al. (2013),[21] Hoorn et al. (1975),[22] Chen et al. (2005),[23] Gonzalez-Gross et al. (2007),[24] Selhub et al. (1993)[25]
Heart failure	13–93	27	–	–	38	–	CD	ND	Soukoulis et al (2009),[20] Keith et al. (2009),[26] Makarewilz-Wujec et al. (2011),[27] Zafarullah et al. (2008)[28]
Vegetarians/vegans	ND	30	–	–	ND	–	ND	11–90	Pawlak et al. (2013),[29] Majchrzak et al. (2006)[30]
Obesity surgery	1.0	13.6	–	–	17.6	–	9–38	26–70	Becker et al. (2012),[31] Vargas-Ruiz et al. (2008),[32] Levinson et al. (2013),[33] Shankar et al. (2010),[34] Rudnicki (2010),[35] Clements et al. (2006)[36]

Abbreviations: CD, conflicting data; ND, no deficiency; –, not studied.

In particular, the most commonly observed deficiencies of B vitamins in the elderly are those of B_1, B_2, B_6, B_{12}, and folate,[21–25] those of B_1, B_2, and B_6 in patients with heart failure,[20,26–28] and those of B_2 and B_{12} in vegetarians/vegans.[29,30] The prevalence of B vitamin deficiencies after bariatric surgery varies according to the particular type of bariatric surgery procedure.[31] In patients with Roux-en-Y gastric bypass, which is the most commonly performed bariatric surgery procedure, deficiencies of vitamins B_1, B_2, B_6, B_{12}, and folate have been reported,[32–36] at prevalence rates that may vary greatly depending on the time elapsed after the procedure and the compliance of the patient with multivitamin supplement therapy.[34,37,38] Notably, neurological complications of bariatric surgery that can involve both the central and peripheral nervous system are due mainly to B vitamin deficiency and have an estimated global incidence of up to 16% annually.[39]

PATHOPHYSIOLOGY OF B VITAMIN DEFICIENCY

B vitamin deficiency may lead to central and/or peripheral nervous system lesions, frequently restricted to peculiar, vulnerable cerebral regions (e.g., the mammillary bodies and medial thalami in thiamine deficiency) or a cell type (e.g., the Schwann cells in pyridoxine deficiency),[2,40] that develop relative to the length of time necessary to deplete the body's stores of the specific vitamin.[2,3] In particular, tissue storage is very limited for vitamins B_1, B_2, B_3, B_5, B_6, and B_7 (i.e., depletion of the body's stores may occur after 1–4 weeks of deficiency), intermediate for folate (depletion may occur after weeks or few months of deficiency), and sufficient for vitamin B_{12} (depletion may occur after months to years of deficiency).[2,3]

The biologically active forms of the B vitamins play an active role in several vital metabolic processes as well as in the glial and neuronal cells in the nervous system. Interestingly, some B vitamins, such as cobalamin, are involved in only two known metabolic reactions in humans,[41] while others, as thiamine, niacin, and pyridoxine, may act as cofactors for over 100 enzyme-catalyzed reactions in the body.[2,9]

The main physiological processes regulated by B vitamins include the metabolism of carbohydrates for energy production (vitamins B_1, B_2, B_3, B_6, and B_7), the metabolism of amino acids and the synthesis of proteins (vitamins B_1, B_3, B_5, B_6, B_7, and folate), the synthesis of neurotransmitters (vitamins B_1, B_3, B_5, and B_6), the metabolism of fatty acids and lipids and the synthesis of cholesterol and steroids (vitamins B_1, B_2, B_3, B_5), and the synthesis of methionine, *S*-adenosyl methionine, and nucleotide bases for DNA and RNA production (vitamin B_{12} and folate) (Table 3).[1,2,9,10,42–45]

Moreover, B vitamins play several different physiological roles in the body. For example, vitamins B_1, B_3, and B_6 directly interact with specific cellular receptors.[2,43,46] Vitamin B_1 plays a role in ion channel function and nerve conduction.[2] Regulation of the immune system is dependent upon the actions of vitamins B_3, B_6, and B_7.[6,9,46] Vitamins B_1, B_2, and B_6 all have definitive roles as antioxidants.[42,43] Vitamins B_1 and B_6 may have a chaperone role during folding of nascent proteins.[9,47]

INTERACTION BETWEEN B VITAMINS

In patients with multiple B vitamin deficiencies, therapeutic failure of a treatment may result from inadequate doses of the administered vitamin or from failure to identify a concomitant deficiency in other B vitamins. Frequently, B vitamins work synergistically in biochemical processes, thus an understanding of the role and function of individual B vitamins at different metabolic stages may help guide which nutrients should be provided in combination.

Table 3 **Main biochemical processes regulated by B vitamins**

Vitamin	Active forms	Biochemical processes	References
Vitamin B_1 (thiamine)	Thiamine pyrophosphate Thiamine triphosphate	Metabolism of carbohydrates, some amino acids, lipids Production of glutamate, GABA Action on some ion channels Antioxidant	Sechi & Serra (2007),[2] Yu & Welge-Lussen (2013)[42]
Vitamin B_2 (riboflavin)	Flavin adenine dinucleotide Flavin mononucleotide	Metabolism of carbohydrates, some amino acids, vitamins B_3, B_6, B_9 Catabolism of fatty acids Antioxidant	Powers (2003)[43]
Vitamin B_3 (niacin)	Nicotinamide adenine dinucleotide Nicotinamide adenine dinucleotide phosphate Niacin	Metabolism of carbohydrates, proteins, blood lipids Neurotransmitter synthesis and hemoglobin synthesis Action on HM74A (GPR109A) receptors Maintenance of genome stability	Oldham & Ivkovic (2012)[10]
Vitamin B_5 (pantothenate)	Coenzyme A	Metabolism of fatty acids, amino acids Synthesis of cholesterol, steroids, acetylcholine	Kelly (2011)[44]
Vitamin B_6 (pyridoxine)	Pyridoxal phosphate	Metabolism of amino acids (major role), release of glucose from glycogen, fatty acid metabolism (minor role) Synthesis of serotonin, GABA, dopamine, hemoglobin Antioxidant	Clayton (2006)[9]
Vitamin B_7 (biotin)	Biotin-dependent carboxylases	Metabolism of lipids, proteins, carbohydrates Gene regulation	Zempleni et al. (2008)[45]
Vitamin B_9 (folic acid)	Tetrahydrofolate	Synthesis of methionine, *S*-adenosyl methionine, all proteins, DNA, RNA, some neurotransmitters	Reynolds (2006)[1]
Vitamin B_{12} (cobalamin)	5′-Deoxyadenosyl-cobalamin Methyl-cobalamin	Synthesis of methionine, *S*-adenosyl methionine, all proteins, DNA, RNA Fatty acid metabolism	Stabler (2013)[41]

Abbreviation: γ-aminobutyric acid.

For example, during folate deficiency, thiamine is poorly absorbed because of the frequent occurrence of diarrhea due to the damaged gastrointestinal mucosa. Likewise, other nutrients and folate itself are poorly absorbed.[48]

At the cellular level, the metabolic interrelationships between B vitamins are myriad and may be influenced by genetic determinants, including some polymorphisms of folate, pyridoxine, and cobalamin-dependent enzymes; for some B vitamins, these have not been rigorously investigated.[49] In particular, dysfunction in thiamine metabolism may lead to impaired pyridoxine metabolism.[50] In addition, folate deficiency in cells may indirectly cause thiamine deficiency, because even though thiamine is present, it cannot be activated to thiamine pyrophosphate, its biologically active form, as a result of deficient dihydrofolate reductase activity.[51] Moreover, several B vitamins are dependent on the two most important biologically active forms of riboflavin, flavin adenine dinucleotide and flavin mononucleotide, for synthesis and homeostasis.[51] For example, the conversion of pyridoxine to its coenzyme form, pyridoxal 5′-phosphate, requires the flavin mononucleotide–dependent enzyme, pyridoxine 5′-phosphate oxidase.[52] Notably, the relationship between riboflavin and pyridoxine levels has clinical relevance, mainly among persons aged 65 years and older, in whom a suboptimal status of these two vitamins is common.[3,53] Indeed, in this population, riboflavin supplementation at physiological concentrations corrects suboptimal status of not only riboflavin, but also pyridoxine, suggesting that riboflavin may be the limiting nutrient in elderly people.[53] Moreover, the conversion of folate to 5-methyltetrahydrofolate is dependent on flavin adenine dinucleotide, as is the synthesis of cobalamin.[54] Therefore, a riboflavin deficiency could result in deficiencies of folate, pyridoxine, and cobalamin.[52]

Other reports from countries with cereal grains fortified with folic acid, such as the United States and Australia, indicate the possibility of clinically relevant interactions between folate status and vitamin B_{12} status.[55–57] In particular, these studies show that healthy seniors with poor vitamin B_{12} status (serum cobalamin concentration <148 pmol/L, or plasma methylmalonic acid [MMA] concentration ≥ 210 nmol/L) suffer cognitive impairment and anemia if exposed to high folate intake (serum folate concentration >59 nmol/L).[55,56] However, other studies in older people with low B_{12} and high folate status, in the setting of voluntary fortification in the United Kingdom, showed no such association.[58] Interestingly, in a different population at risk,

such as healthy young adults with low vitamin B_{12} status, a recent study documented that high serum folate concentrations did not exacerbate the biochemical abnormalities related to vitamin B_{12} deficiency.[59]

There are three essential metabolic pathways in which several B vitamins act in concert as coenzymes, all of which have been extensively investigated for their clinical relevance: one-carbon metabolism, folate–cobalamin interactions, and the pathway for de novo synthesis of niacin congeners (see Appendix S1 in the Supporting Information online).

CLINICAL SPECTRUM OF B VITAMIN DEFICIENCY

In thiamine deficiency, the cardiovascular system is frequently involved, usually as one of two main forms: a common, high-output state characterized by heart failure, orthopnea, pulmonary and peripheral edema, or a less common, low-output state characterized by severe hypotension and an absence of edema.[2] In contrast, in vitamin B_2, B_6, B_{12}, and folate deficiency in adults, hematological complications, chiefly characterized by anemia, are frequently reported.[1,41,43]

Gastrointestinal symptoms, including nausea, vomiting, abdominal pain, and diarrhea, are frequently risk factors for the development of B vitamin deficiencies, particularly of vitamins B_1, B_3, and folate.[60,61] The eyes, mucosae, and skin are frequently involved in deficiency of vitamins B_2, B_3, B_6, B_7, B_{12}, and folate, with possible occurrence of cutaneous and oculo-orogenital lesions.[60,61]

THIAMINE (VITAMIN B_1) DEFICIENCY

Natural sources of thiamine include whole-grain products, brown rice, meat products (especially pork liver), vegetables, fruits, legumes, and seafood.[62] Thiamine is not present in fats, oils, or sugar and is present in minimal amounts in alcoholic beverages.[2] In humans, the microbiota in the large intestine is a significant source of thiamine and thiamine pyrophosphate,[14] but it is unclear how it contributes to host thiamine homeostasis.[14] In adults aged 19 and older, the recommended dietary allowance for thiamine is 1.1 mg/d (female) and 1.2 mg/d (male).[63]

Thiamine deficiency can occur in any condition of unbalanced nutrition that lasts for 2 to 3 weeks. This includes poor nutrition, chronic alcohol misuse, loss of thiamine due to recurrent vomiting or malabsorption, increased thiamine requirements due to chronic diseases, prolonged and excessive carbohydrate intake, and gastrointestinal surgical procedures, including gastrectomy to treat ulcers or neoplasms[64] and bariatric surgery to treat obesity.[2,65,66]

In the brain, at the cellular level, thiamine converted into thiamine pyrophosphate has a key role in several biochemical pathways, particularly in glucose and energy metabolism,[2] as shown schematically in Figure 1. The predisposing factors of thiamine deficiency and the pathophysiology have been discussed in recent reviews.[2,67]

Thiamine deficiency affecting the nervous system may present with peripheral neuropathy or Wernicke's encephalopathy, an acute life-threatening disorder fully responsive to prompt and adequate thiamine replacement. Untreated Wernicke's encephalopathy, however, has an estimated mortality of 20%, and the about 80% of patients who survive develop Korsakoff's syndrome, the chronic irreversible form of Wernicke's encephalopathy that does not remit with thiamine treatment.[2,68]

NEUROPATHY DUE TO THIAMINE DEFICIENCY

Chronic thiamine deficiency usually causes a distal, sensorimotor polyneuropathy, with more involvement in the lower than the upper limbs.[35,68,69] Previous studies described clinical, electrophysiological, and histopathological features of patients with neuropathy due to thiamine deficiency caused by gastrectomy, chronic alcoholism, and dietary imbalance.[70,71] Rarely, weakness that is predominant in the proximal portions of the limbs indicates the simultaneous involvement of skeletal muscles.[72,73] In this myopathy, the occurrence of changes in magnetic resonance imaging (MRI) scans and muscle biopsy has been documented.[73]

The onset of polyneuropathy is usually slow, with bilateral, distal, painful paresthesias known as "burning feet." The typical steppage gait, due to foot drop, may appear next, with variable muscle weakness in the lower limbs. Particularly in children, dysphonia may occur. Rarely, a rapid progression of the neuropathy is clinically reminiscent of Guillain-Barré syndrome, although axonal in nature.[72] Rarely, thiamine deficiency manifests with optic neuropathy and/or a selective impairment of the large proprioceptive sensory fibers without motor impairment, which can present as prominent sensory ataxia.[16]

WERNICKE'S ENCEPHALOPATHY

Subacute thiamine deficiency usually causes Wernicke's encephalopathy, an acute neuropsychiatric syndrome with substantial morbidity and mortality, missed at routine clinical examination in about 60% to 80% of cases.[2] Wernicke's encephalopathy is a medical emergency characterized, in 16% of patients, by acute onset of nystagmus and ophthalmoplegia, mental-status changes, and unsteadiness of stance and gait.[2] About 65% of

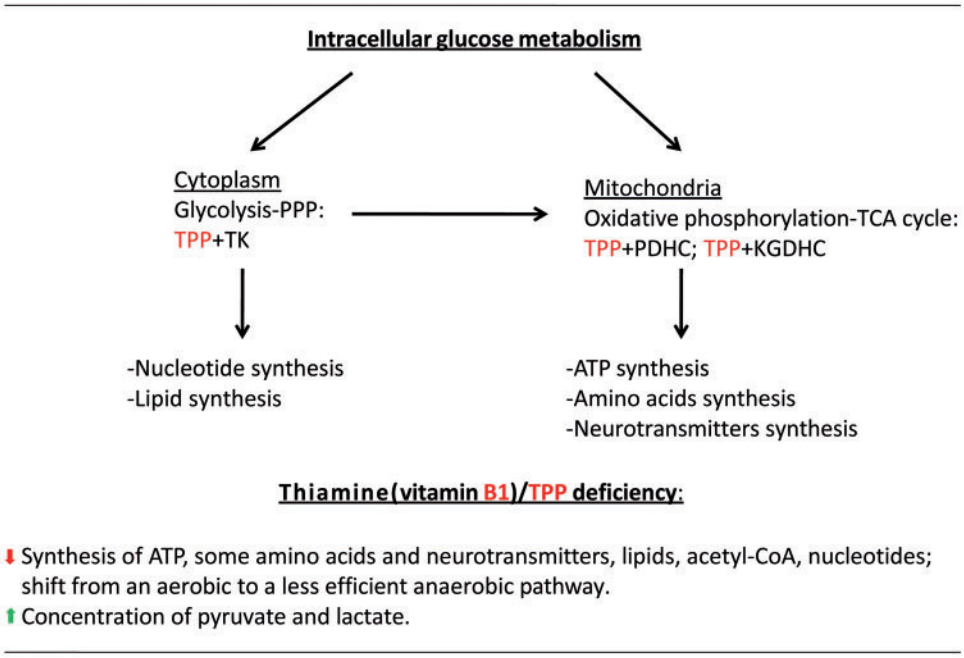

Figure 1 **Schematic representation of the role of thiamine pyrophosphate in intracellular glucose metabolism.** For concentration of pyruvate and lactate, see Chen and Zhong (2013)[145] and Jhala and Hazell (2011).[146] *Abbreviations*: ATP, adenosine triphosphate; CoA, coenzyme A; KGDHC, α-ketoglutarate-dehydrogenase complex; PDHC, pyruvate dehydrogenase complex enzymes; PPP, pentose phosphate pathway; TCA, tricarboxylic acid; TPP, thiamine pyrophosphate; TK, transketolase.

patients show at least one component of this triad at presentation, whereas in 19% of patients this disorder may present with stupor, hypotension and tachycardia, hypothermia, bilateral visual loss and papilledema, epileptic seizures, hearing loss, hallucinations, and behavioral disturbances.[2] In an advanced stage of Wernicke's encephalopathy, patients may exhibit complete ophthalmoplegia, spastic paresis and increased muscular tone, hyperthermia, choreic dyskinesias, and coma.[2] For a thorough discussion of the clinical features of Wernicke's encephalopathy, see a recent review.[2]

KORSAKOFF'S SYNDROME

Korsakoff's syndrome is the chronic form of Wernicke's encephalopathy, caused by structural brain lesions mainly affecting the mammillary bodies, the mammillothalamic tract, and the anterior thalamus.[68,74] Patients show learning impairment, emotional changes, and a chronic, striking loss of working memory, with relatively little loss of reference memory.[2,74]

It has been suggested that Korsakoff's syndrome is most commonly associated with thiamine deficiency in chronic misusers of alcohol.[66,74] However, two recent literature reviews of non-alcohol–related Korsakoff's syndrome indicated that thiamine deficiency per se can cause the full clinical spectrum of Korsakoff's syndrome, including long-term cognitive neurological changes.[75,76] One risk factor for the development of Korsakoff's syndrome may be a genetic predisposition, particularly in individuals with variants of the enzyme transketolase, which has reduced affinity for its cofactor, thiamine pyrophosphate.[77] Other risk factors include the occurrence of repeated subclinical episodes of thiamine deficiency, the combined neurotoxic effects of alcohol misuse and thiamine deficiency, and a partial neuronal response to thiamine replacement therapy because of coexisting deficiencies of other micronutrients, particularly vitamins B_6, B_{12}, folate, and magnesium.[66,74] Notably, about 80% of patients with Korsakoff's syndrome have comorbid thiamine deficiency neuropathy.[74]

DIAGNOSIS OF THIAMINE DEFICIENCY

The various disorders related to overt thiamine deficiency are relatively easy to diagnose clinically, provided a thorough history is taken and a careful clinical examination is performed. In a setting of clinical signs indicative of a possible thiamine deficiency, the dramatic improvement of neurological signs within a few hours after parenteral thiamine administration is practically a diagnostic test, strongly supportive of thiamine deficiency,[2] and can be of aid in cases of insidious acute encephalopathy, acute heart failure of undetermined

nature, and peripheral neuropathy with no other evident cause.[2]

The diagnosis of a subclinical status of thiamine deficiency, in contrast, requires the assessment of thiamine status in whole blood,[66] as some patients with thiamine deficiency may have normal serum/plasma thiamine levels.[66] However, since total thiamine includes free thiamine, total thiamine may be strongly influenced by recent thiamine intake; thus, in certain cases, measurement of thiamine pyrophosphate, which is more specific, or of erythrocyte thiamine transketolase activity may help confirm the diagnosis.[66,78] Moreover, in rare situations usually related to patients with genetic alterations in thiamine transport and metabolism, a normal thiamine status in blood does not coincide with normal levels of thiamine pyrophosphate in neuronal cells or with physiological enzymatic activity.[66,79]

Other paraclinical studies include pyruvate and lactate examination in blood, lumbar puncture, electrophysiological studies, and neuroimaging studies. In thiamine deficiency, concentrations of pyruvate and lactate in blood are usually increased, and these indices may aid diagnosis.[67] The results of cytochemical analysis of cerebrospinal fluid are usually normal.[2] Electroencephalography can show nonspecific slowing of the dominant rhythm,[2] and electrophysiological studies in thiamine-deficiency–related neuropathy show a predominantly motor, axonal neuropathy.[72] Neuroimaging studies are the most valuable methods of confirming a diagnosis of Wernicke's encephalopathy or Korsakoff's syndrome. Typical brain MRI findings of Wernicke's encephalopathy are represented by bilateral symmetric signal intensity alterations in the periventricular regions of the thalami, the mammillary bodies, the periventricular regions of the third ventricle, the periaqueductal region, and the midbrain tectal plate.[2] Of note, in patients with genetic alterations in thiamine transport, the caudate heads are also usually involved.[79] These typical radiologic manifestations respond promptly to thiamine administration.[79] (Figure 2). The lesions are isotense to hypointense to the gray matter on T1-weighted images and hyperintense to gray matter on T2-weighted images.[80] Korsakoff's syndrome can be more accurately diagnosed with 3-dimensional voxel-based morphometry of MRI, which documents parahippocampal, hippocampal, and thalamic atrophy with enlargement of the third ventricle.[81,82]

Management

Abundant data indicate that supraphysiological blood levels of thiamine are not toxic and that, in untreated patients with thiamine deficiency or in patients inappropriately treated with low doses of thiamine, the biochemical abnormalities caused by thiamine deficiency in the brain and cardiovascular system can lead to heart failure, sudden death, and irreversible brain damage.[2,3] Considering these findings, it is critical to immediately treat all patients in whom a thiamine deficiency is suspected with high doses of thiamine. Because the absorption of oral thiamine is erratic, thiamine must be administered parenterally in order to quickly replenish the body's limited stores and to induce a sufficiently high blood concentration of thiamine.[2] However, the optimal dose and duration of thiamine to be administered in the variety of clinical syndromes related to thiamine deficiency are unknown,[2,35] and the information used to guide clinicians is mostly empiric, rather than evidence based.[66,83,84]

In patients with neuropathy, the recommended dose of thiamine is 100 mg intravenously, followed by 100 mg intramuscularly daily for 7 to 14 days.[35,85] Thereafter, administration of oral thiamine, 50 to 100 mg 3 times daily, is suggested until improvement is obvious, continued if necessary for a number of months. In bariatric surgery patients, supplementation should be continued as long as the patient continues to have gastrointestinal complaints.[35,86]

Treatment recommendations for Wernicke's encephalopathy have been determined from one controlled study, several uncontrolled studies, case reports, and review guidelines.[2,66,84,87] Collectively, these reports essentially suggest that the immediate treatment of Wernicke's encephalopathy requires empirical therapy of 200 to 500 mg of thiamine, given parenterally, 3 times per day for 3 days. When an effective response is observed, 200 to 250 mg of thiamine per day, given parenterally, should be continued until clinical improvement ceases. In particular, in order to maximize the therapeutic effect and prevent Korsakoff's syndrome, higher parenteral doses of thiamine should always be used in people with chronic alcohol misuse, in patients with Wernicke's encephalopathy after bariatric surgery, in individuals with congenital defects of thiamine transport and metabolism, and in all patients with signal intensity alterations typical of Wernicke's encephalopathy in brain MRI scans.[35,66,68] In patients with alcohol misuse, and in patients with Wernicke's encephalopathy after bariatric surgery, oral thiamine supplementation should be continued indefinitely at a dosage of 50 to 100 mg 3 times daily.[86]

When a diagnosis of Wernicke's encephalopathy is suspected, parenteral administration of 200 mg of thiamine should always be given before intravenous administration of glucose.[2] Parenteral thiamine, 200 to 250 mg once daily for 3 consecutive days, should also be given to all at-risk subjects admitted to the emergency department.[2] Moreover, deficiencies in other vitamins and

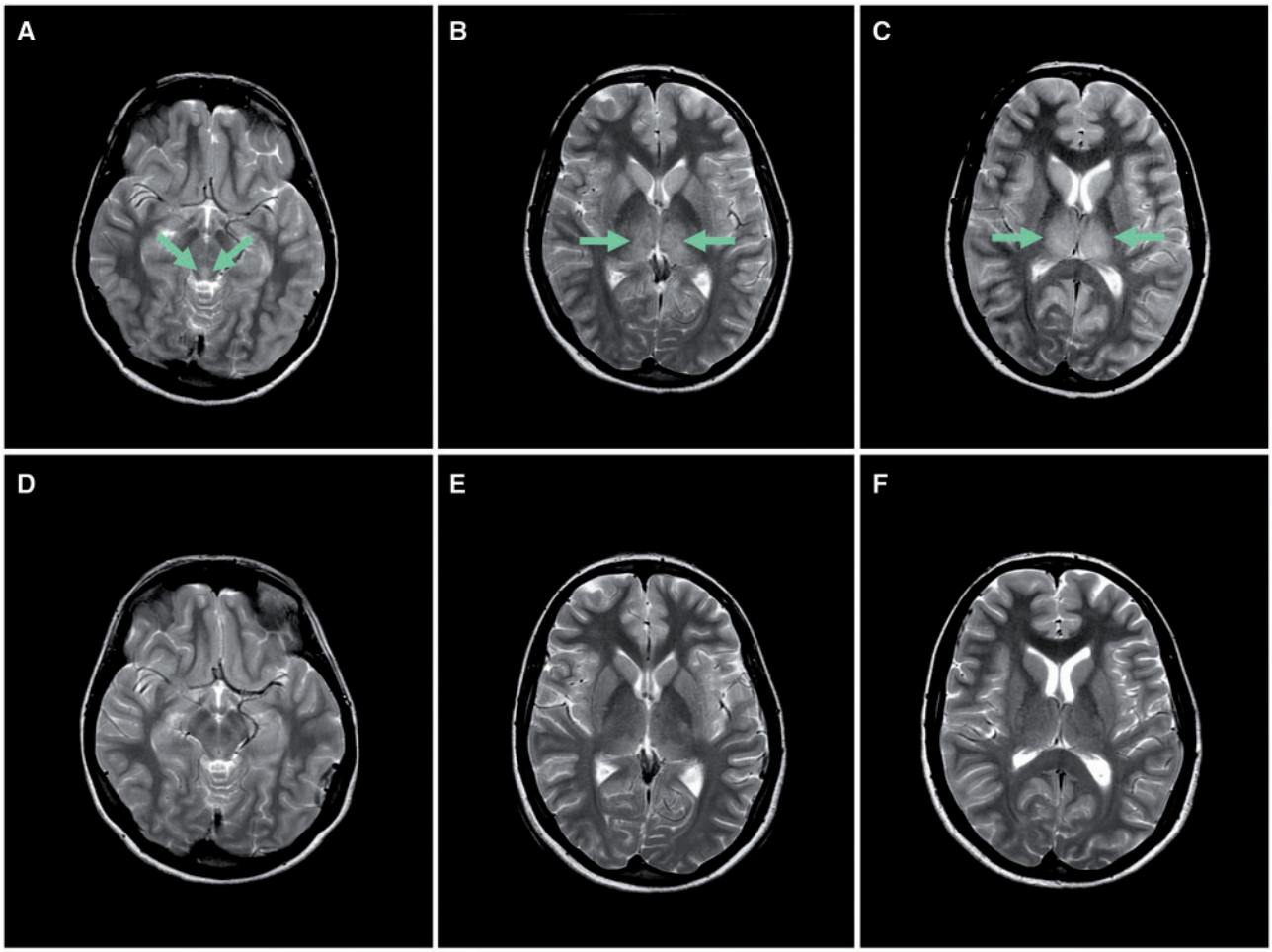

Figure 2 **T2-weighted axial magnetic resonance imaging (MRI) scans of Wernicke's-like encephalopathy.** Symmetrical high-intensity lesions in the thalami and caudate heads (B and C), as well as in the periaqueductal gray matter of the midbrain (A), are evident in a patient with genetic alterations in thiamine transport. Scan performed about 10 days after onset of neurological symptoms. Brain MRI scan after 35 days of thiamine treatment (D–F).

electrolytes should be corrected, especially niacin deficiency, which may induce an encephalopathy indistinguishable from Wernicke's encephalopathy,[88] and magnesium deficiency, because severe deficiency may lead to a refractory response to thiamine.[89]

RIBOFLAVIN (VITAMIN B_2) DEFICIENCY

Riboflavin and its derivatives are found mainly in milk and dairy products, as well as in organ meats, eggs, fatty fish, dark green vegetables, and whole grains.[90]

Isolated riboflavin deficiency is rare.[43] In adults, specific predisposing factors for riboflavin deficiency include the acute or chronic ingestion of boric acid and the chronic use of alcohol, birth control pills, or certain compounds as chlorpromazine, tricyclic antidepressants, and some antimalarial agents, which may impair the intestinal absorption of riboflavin and decrease its bioavailability.[90]

In adults, nonspecific signs or symptoms of riboflavin deficiency include frequent headaches, weakness, mucocutaneous lesions, and normochromic normocytic anemia.[43] Neurological abnormalities due to riboflavin deficiency, such as ataxia and inability to stand, have been well documented in dogs, but rarely reported in humans.[43]

Diagnosis

Riboflavin status is assessed by measurement of red blood cell glutathione reductase activity.[91] An increase in the stimulation of this enzymatic reaction confirms a low level of riboflavin.[91]

Management

Adults with nutritional deficiency of riboflavin should take this vitamin with food, since only about 15% is

absorbed when taken alone. A dosage of 10 to 50 mg daily in divided doses for 3 to 4 weeks is suggested.[43]

NIACIN (VITAMIN B_3) DEFICIENCY

Niacin, which refers to nicotinic acid and nicotinamide, the amide form of nicotinic acid, is found mainly in meat, cereals, dairy products, eggs, and fish.[90] Niacin deficiency is rare in the general population. However, postmortem data from hospitalized patients with alcoholism showed a 27% prevalence of niacin deficiency.[92] Other causes of deficiency include malabsorptive syndromes, frequent dialysis, chronic isoniazid therapy, chronic use of diets rich in the amino acid leucine, which can compete with tryptophan for uptake and foster a niacin deficiency,[69] prolonged use of certain drugs such as levodopa, ethionamide, and 6-marcaptopurine, which may impair the conversion of tryptophan to niacin, and the occurrence of carcinoid syndrome, caused by conversion of tryptophan to 5-OH-tryptophan and then to serotonin by the tumor, with subsequent depletion of body tryptophan stores.[10,61]

Mild niacin/nicotinic acid deficiency can cause episodic vomiting, abdominal pain, constipation, headaches, insomnia, tiredness, glossitis with odynophagia, and a photosensitive pruritic rash on sun-exposed areas of the body, initially intermittently.[61] Chronic deficiency results in pellagra, which means "rough-skin," a disorder characterized by the classic tetrad of dermatitis, dementia, diarrhea and, when pellagra is missed, death.[61] However, dermatologic findings can be absent.[10,61] When present, the photosensitive rash mainly involves the dorsum of the hands and feet and, in a shaped distribution, the anterior neck and chest.[61] The gastrointestinal involvement ultimately leads to intractable, watery diarrhea, with many daily episodes.[61] The term *dementia* indicates a broad spectrum of neuropsychiatric disturbances that range from depression, confusion, and inability to concentrate to the occurrence of hallucinations and delirium.[10,61] Delirium can also manifest as the sole symptom of niacin deficiency.[10]

Notably, in alcoholic pellagra encephalopathy, oppositional hypertonus, myoclonus, cerebellar signs, and ataxia have also been observed.[93] Importantly, suspicion of alcoholic pellagra encephalopathy should be high in patients with alcohol dependence and delirium tremens who fail to improve with escalating doses of benzodiazepines,[10] as well as in those with unexplained persistent mental status changes unresponsive to high doses of parenteral thiamine.[2]

Diagnosis

The diagnosis of niacin deficiency and, in particular, of pellagra is based on clinical observations, and it is strongly supported by the robust improvement of dermatologic and gastrointestinal symptoms within 48 hours after niacin replacement,[10] although cutaneous manifestations may make take several weeks to resolve.[61] Neuropsychiatric symptoms respond to treatment is more variably, as they may resolve within several days or become persistent.[10] Laboratory tests for determination of serum niacin levels and urinary metabolites of niacin are available,[10] but their reliability remains unclear. In pellagra encephalopathy, electroencephalography usually shows nonspecific, diffuse slowing of the dominant rhythm.[92] Brain MRI may show global atrophy.[10,93]

Management

Nicotinamide is preferred to nicotinic acid because of the flushing and headache frequently associated with therapeutic doses of nicotinic acid.[10] The World Health Organization recommends treating pellagra with nicotinamide, either 300 mg/d by mouth, in divided doses, or 100 mg/d parenterally, in divided doses, for 3 to 4 weeks.[10]

PANTOTHENIC ACID (VITAMIN B_5) DEFICIENCY

Pantothenic acid is ubiquitously distributed. Excellent sources include peanut butter, liver, almonds, cheese, and lobster.[90] In humans, the normal microflora of the large intestine also contributes significantly to overall pantothenic acid status.[14] Nutritional pantothenic acid deficiency is very rare in humans. It may occur in severely malnourished patients or in persons who take a metabolic inhibitor of pantothenic acid (e.g., omega-methyl pantothenate).[44] This deficiency commonly presents with fatigue, headache, irritability, restlessness, sleep disturbances, and burning sensations of the hands and feet.[44] Rarely, an ataxic gait may occur.[44]

Diagnosis

Blood concentrations of pantothenic acid do not correlate with pantothenic acid intake or status.[15,44] Urinary pantothenic acid excretion seems a better indicator, with pantothenic acid excretion of less than 1 mg/d considered indicative of a poor status.[44]

Management

Only the dextrorotatory (D) isomer of pantothenic acid possesses biological activity.[44] Because D-pantothenic

acid is relatively unstable, the more stable calcium pantothenate is frequently used in clinical practice.[44] Notably, large doses of oral calcium pantothenate, up to 10 g/d for 6 weeks, have been used in humans, without apparent adverse effects.[44]

PYRIDOXINE (VITAMIN B_6) DEFICIENCY

The term *pyridoxine* is generally used synonymously with vitamin B_6. Pyridoxal and pyridoxamine are two other naturally occurring compounds that have comparable biological activity. The only biologically active form of pyridoxine is pyridoxal 5′-phosphate.[52] Meat, fish, eggs, soybeans, chickpeas, nuts, dairy products, starchy vegetables like potatoes, noncitrus fruits like bananas, and whole-grain cereal products are rich in pyridoxine. Pyridoxine is also produced by the normal microflora of the large intestine.[90]

Vitamin B_6 deficiency most commonly occurs with malnourishment, malabsorption, or alcoholism or as a side effect of medication.[3,12] Alcohol intake antagonizes pyridoxine status through production of acetaldehyde, which competes with pyridoxal 5′-phosphate for binding sites of pyridoxal 5′-phosphate–dependent enzymes. Isoniazid and hydrocortisone interfere with the absorption of pyridoxine. Valproate, carbamazepine, and phenytoin increase the catabolism of pyridoxine. Pyridoxine deficiency has also been associated with other medications like cyclosporine, cycloserine, hydralazine, and penicillamine. Neuropathic symptoms together with pellagra-like dermatitis have been described in association with the use of the B_6 antagonist desoxypyridoxine. Poisoning with gyromitra mushroom can also lead to pyridoxine deficiency. Additional risk factors for pyridoxine deficiency include hyperoxaluria, inflammation, and tissue injury as well as chronic diseases like renal or hepatic disease, human immunodeficiency virus (HIV) infection, sickle cell disease, hereditary sideroblastic anemia, and rheumatoid arthritis.[3,12,90]

Multiple types of seizures, including myoclonic, generalized tonic-clonic, and partial, constitute the main, although rare, manifestation of dietary deficiency of pyridoxine in adults. Such seizures are likely related to an imbalanced production of amine neurotransmitters, such as dopamine, serotonin, glutamate, glycine, and γ-aminobutyric acid, in the brain.[94,95] They do not respond to anticonvulsants but are responsive to pyridoxine supplementation. Moreover, up to 50% of slow isoniazid acetylators (patients in whom metabolic acetylation is slow) treated with isoniazid may develop dose-related peripheral neuropathy due to pyridoxine deficiency,[3,13] and acute isoniazid overdose may rarely lead to repetitive seizures, metabolic acidosis, and coma, all responsive to pyridoxine.[3,12]

Notably, excess consumption of pyridoxine (>1 g/d) has been associated with a predominantly sensory peripheral neuropathy or ganglionopathy[13] that is characterized by sensory ataxia, areflexia, impaired cutaneous and deep sensations, and positive Romberg's sign. The site of the lesion is most likely the dorsal root ganglia.[13]

Diagnosis

Pyridoxine status can be assessed directly by measuring pyroxidine levels in the blood or urine by high-performance liquid chromatography. Because pyridoxine in neutral or alkaline solutions can be inactivated by ultraviolet light, protection from light is essential when measuring pyroxidine levels. Commercial laboratory kits commonly use measurement of plasma pyridoxal 5′-phosphate. A plasma pyridoxal 5′-phosphate concentration of over 20 to 30 nmol/L is considered to indicate adequate status. Indirect diagnostic tests of pyridoxine status include measurement of erythrocyte aminotransferase activity, the methionine load test, and the tryptophan loading test.[3,9,12]

Management

Isoniazid-induced neuropathy is reversible by drug discontinuation or pyridoxine supplementation. Pyridoxine may be supplemented at a dosage of 50 to 100 mg/d to prevent the development of neuropathy.

Neuropathy due to pyridoxine toxicity (following excess consumption) may reverse once the supplementation is withdrawn.[13]

BIOTIN (VITAMIN B_7) DEFICIENCY

Biotin is widely present in meats, vegetables, fruits, milk, cheese, eggs, and marine fish.[90] Humans also obtain biotin from the normal microflora of the large intestine, which synthesizes this nutrient.[14] Overt symptomatic dietary biotin deficiency is rare. In adults, well-documented cases have occurred in association with near-total intravenous feeding without biotin supplementation and with chronic feeding of raw egg white.[45,61] Suboptimal biotin plasma levels have also been documented in chronic misusers of alcohol, in pregnancy women, in patients with malabsorption syndromes, and in subjects on long-term therapy with phenytoin, phenobarbital, or carbamazepine,[14] although the clinical relevance of these findings is uncertain. Clinical features include hair loss, seborrheic dermatitis, periorificial erythema, conjunctivitis, depression, lethargy, muscular pain, involuntary movements, ataxia, dysesthesia, and multiple types of seizures.[7,45,61]

Diagnosis

A dramatic improvement of neurological signs within 24 hours of biotin treatment (e.g., disappearance of involuntary movements or of seizures) is practically a diagnostic test.[7] Biotin status is assessed by quantifying plasma levels, urinary excretion of biotin and its major metabolites, and biotinylated carboxylases in lymphocytes.[45,96] Holo-MCC (3-methylcrotonyl-CoA carboxylase) and holo-PCC (propionyl-CoA carboxylase) in lymphocytes seem to be the most reliable, single markers of biotin status.[96]

MANAGEMENT

The treatment of patients with biotin deficiency is empirical. In most cases, biotin is given orally, at a dosage of 10 to 20 mg/d.[45,61]

FOLATE (VITAMIN B_9) DEFICIENCY

Folate is the naturally occurring form of the vitamin, and folic acid is the synthetic form, used in fortified foods and supplements. Folate is found in vegetables (especially green leafy vegetables), fruits, nuts, beans, peas, dairy products, poultry, liver, eggs, seafood, and grain.[90] Acquired pure folate deficiency is rare, as folate status is affected by so many variable factors. Populations at increased risk of folate deficiency include people with alcoholism, adolescents, and pregnant women.[3,97] Folate deficiency may also occur in patients on restricted diets, such as those used to manage phenylketonuria, and in patients with small bowel disorders associated with malabsorption. Folate absorption may be decreased in conditions associated with reduced gastric secretions, such as gastric surgery, atrophic gastritis, acid-suppressive therapy, and acid neutralization by treatment of pancreatic insufficiency. Drugs such as aminopterin, methotrexate, pyrimethamine, trimethoprim, and triamterene act as folate antagonists and can induce folate deficiency by inhibiting dihydrofolate reductase. The mechanism by which some older anticonvulsants, some antituberculosis drugs, sulfasalazine, and oral contraceptives cause folate deficiency is uncertain.[97] Additional causes of folate deficiency include genetic defects of folate metabolism, which can be related either to defective transport of folate through various cells or to defective intracellular utilization of folate due to certain enzyme deficiencies.[97] These disorders are often associated with severe central neurological dysfunction in children.[97] In adults, a deficiency of the enzyme methylenetetrahydrofolate reductase (MTHFR), caused by alterations in the *MTHFR* gene, can cause moderately elevated levels of homocysteine in plasma, which may be associated with increased risk of thromboembolic disease and stroke.[98,99]

Clinical manifestations of folate deficiency are myeloneuropathy, neuropathy, and megaloblastic anemia.[1,97] In folate deficiency, as in cobalamin deficiency, hematological manifestations do not correlate with neurological manifestations.[97,100] In particular, subacute combined degeneration of the spinal cord is typically caused by cobalamin deficiency,[1,3] but a few cases caused by folate deficiency have been reported.[101,102] In cases caused by folate deficiency, the slowly progressive clinical course is a unique characteristic feature, and neurological deficits reportedly respond well to folic acid, but not cobalamin, supplementation.[101,102]

The clinical features of folate-deficiency neuropathy are those of a slowly progressive, prevalent sensory polyneuropathy,[100] which may be caused to a very small extent by indirect thiamine deficiency.[103] Of note, neuropathic features of folate deficiency are significantly different from both those of thiamine deficiency and those of alcoholic neuropathy, in terms of the initial symptoms, mode of progression, type of neuropathy, and modality of sensory impairment.[70,100] These findings are of particular relevance for diagnosis of these neuropathies in people with chronic alcohol misuse, in whom deficiency of multiple B vitamins may coexist with direct alcohol neurotoxicity.[70,100] Frequently, the clinical manifestations of folate deficiency are indistinguishable from those of cobalamin deficiency because of their interaction in one-carbon metabolic pathways (Figure 3).[3,97] Folate deficiency has also been associated with affective disorders, particularly depression.[1,97] Moreover, it is worth mentioning the relationship between periconceptional folate deficiency, whether maternal or paternal, and an increasing risk of congenital abnormalities, particularly neural tube defects, i.e., anencephaly and spina bifida, cardiovascular malformations, cleft lip and palate, urogenital abnormalities, and limb reductions.[4] Putative underlying mechanisms involve a deregulation of epigenetic mechanisms related to folate deficiency, with cellular changes in *S*-adenosyl methionine levels, altered DNA methylation, and histone modification, all of which can influence gene transcription (Figure 3).[4,5] Based on these studies, currently more than 70 countries practice folic acid fortification of cereal-grain products to prevent neural tube defects.[102,104] However, many countries, including Italy, other European nations, and East Asian countries, have not yet instituted mandatory folic acid fortification.[100,104]

Diagnosis

Because serum folate fluctuates daily and does not correlate with tissue stores, diagnosis of folate deficiency is

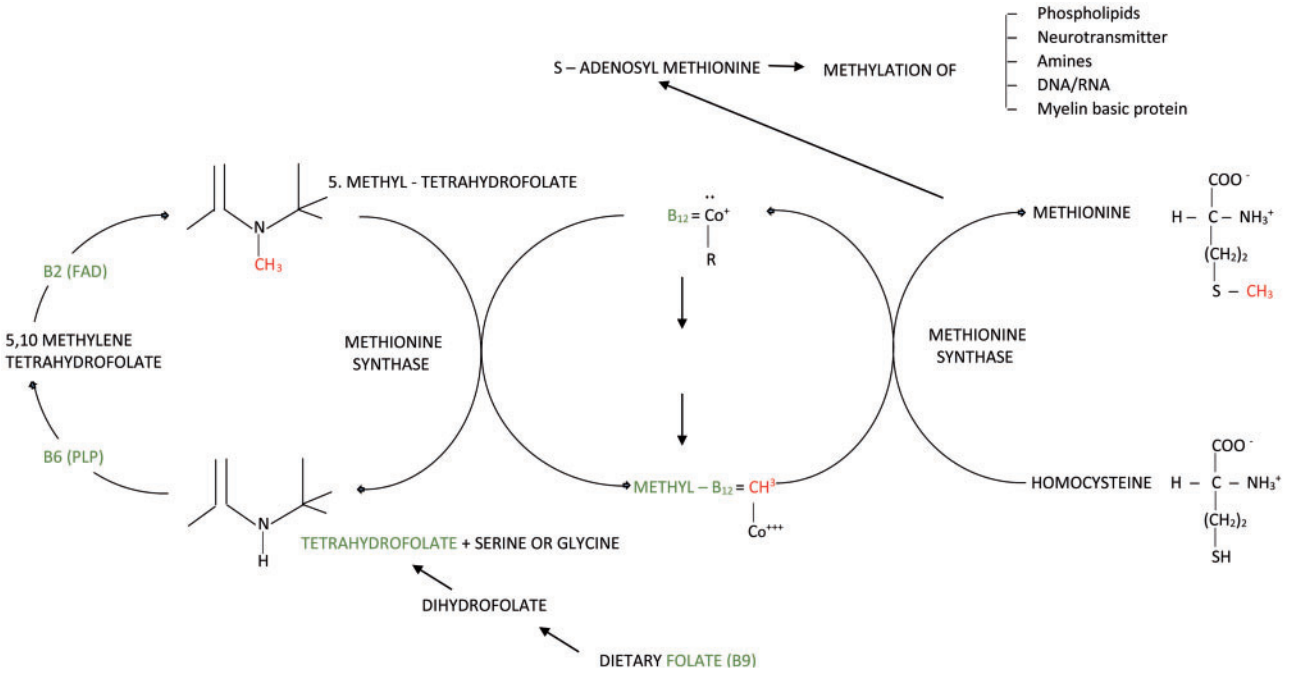

Figure 3 **Simplified scheme of remethylation and folate cycles and the main methylation reactions characterized in the central nervous system.** *Abbreviations*: B2/FAD: vitamin B_2/flavin adenine dinucleotide; B6/PLP: vitamin B_6/pyridoxal 5′-phosphate (see references S1–S3 in the Supporting Information online).

preferentially determined through measurement of folate in red blood cells.[105] Plasma homocysteine levels are often elevated in many patients with clinically significant folate deficiency, as in the case of cobalamin deficiency.[97]

Management

It is recommended that, for prophylaxis against neural tube defects, all women of childbearing age receive 0.4 mg of folic acid daily periconceptionally (1 mo before and 2 mo after). Women on antiepileptic therapy, who are at high risk for neural tube defects, should receive 4 to 5 mg of folic acid daily periconceptionally (at least 1 mo before and 3 mo after).[106]

With documented folate deficiency, an oral dose of 1 mg 3 times a day may be followed by a maintenance dose of 1 mg per day.[3] Daily doses as high as 20 mg may be needed in patients with malabsorption.[3] Coexisting cobalamin deficiency should be ruled out before instituting folate therapy. Even with high doses, toxicity due to folic acid is rare. Plasma homocysteine levels are useful for monitoring response to therapy; they decreases within a few days of instituting folate therapy but do not respond to inappropriate vitamin B_{12} therapy.[97]

COBALAMIN (VITAMIN B_{12}) DEFICIENCY

Vitamin B_{12} refers to a specific group of cobalt-containing corrinoids with biological activity in humans. This group is also referred to as cobalamins. The main cobalamins in humans are adenosylcobalamin, methylcobalamin, and hydroxocobalamin. The form of cobalamin in food is hydroxocobalamin. Cyanocobalamin is a synthetic pharmaceutical agent that must be converted to adenosylcobalamin or methylcobalamin to become metabolically active. Vitamin B_{12} is synthesized solely by microorganisms and is generally not present in plant foods. Meats, eggs, and milk are the major dietary sources.[90] An acidic environment in the stomach is required for cobalamin to be released from food proteins. Vitamin B_{12} deficiency is particularly common in the elderly and is due to achlorhydria-induced food-cobalamin malabsorption.[107–109] Acid reduction therapy may also contribute to cobalamin deficiency.[107–109] Food-cobalamin malabsorption is insidious in onset and is rarely associated with overt clinically significant deficiency. There has been recent concern that low cobalamin levels in the elderly might cause nervous system damage, but studies specifically in the elderly have not consistently demonstrated improvements in neurological function following therapy. This concern has led to the development of the controversial concept of subclinical or subtle cobalamin deficiency.[12,13] Many patients with clinically expressed cobalamin deficiency have intrinsic factor–related malabsorption, such as that seen in pernicious anemia.[41] Pernicious anemia is an autoimmune gastritis resulting from the destruction of gastric parietal cells. This leads

to a lack of intrinsic factor and impaired binding of ingested cobalamin.[110]

Cobalamin deficiency is commonly seen in vegetarians/vegans[29,30] and postoperatively in gastric surgery patients.[39] Other causes of cobalamin deficiency include conditions associated with malabsorption, such as ileal disease or resection, intestinal tuberculosis or lymphoma, celiac disease, Whipple disease, inflammatory bowel disease, radiation enteritis, graft-vs-host disease, pancreatic disease, and tropical sprue.[111] Jejunal bacterial overgrowth can also result in cobalamin malabsorption. The high acidity associated with the Zollinger-Ellison syndrome causes inactivation of pancreatic trypsin and prevents cobalamin release from haptocorrins. Competition for cobalamin secondary to parasitic infestation by the fish tapeworm *Diphyllobothrium latum* may cause cobalamin deficiency. This is not uncommon in Finland and Russia. Prolonged use of drugs like metformin may also cause cobalamin deficiency.[3,11] Vitamin B_{12} deficiency has also been reported in association with oral therapy with the multitargeted tyrosine kinase inhibitor sunitinib[112] and in HIV-infected patients with neurological symptoms, but the precise clinical significance of this is unclear. In these patients, the low vitamin B_{12} levels seen are frequently not accompanied by elevated homocysteine or MMA levels. In AIDS-associated myelopathy, the vitamin B_{12}- and folate-dependent transmethylation pathway is depressed, and cerebrospinal fluid and serum levels of *S*-adenosyl methionine are reduced.[113]

Nitrous oxide (N_2O, "laughing gas") is a commonly used inhalational anesthetic that has been abused because of its euphoriant properties. Nitrous oxide irreversibly oxidizes the cobalt core of vitamin B_{12} and renders methylcobalamin inactive.[11] Clinical manifestations of vitamin B_{12} deficiency appear relatively rapidly with nitrous oxide toxicity because the metabolism is blocked at the cellular level. Postoperative neurological dysfunction can be seen with nitrous oxide exposure during routine anesthesia if subclinical cobalamin deficiency is present.[114] Nitrous oxide toxicity due to inhalant abuse has been reported among dentists, other medical personnel, and university students.[11] The clinical settings and the pathophysiology of cobalamin deficiency have been examined in a recent review.[11]

Clinical features

Clinical manifestations of cobalamin deficiency are myelopathy, neuropathy, glossitis, and megaloblastic anemia. Neurological signs or symptoms may be the earliest and sole manifestation of the deficiency,[11,41] and the severity of hematological and neurological manifestations in a patient may be inversely related. Neurological features of myelopathy, commonly referred as "subacute combined degeneration," include a spastic paraparesis, extensor plantar response, and impaired perception of position and vibration. Accompanying peripheral nerve damage usually manifests with painful paresthesias in both legs, frequently accompanied by varying degrees of ataxia. Rarely, optic nerve involvement may be present. Clinical clues to possible cobalamin deficiency in a patient with polyneuropathy include a relatively sudden onset of symptoms, clinical signs suggestive of an associated myelopathy, onset of symptoms in the hands, and concomitant involvement of upper and lower limbs.[11,41]

Neuropsychiatric manifestations include decreased memory, personality change, psychosis, emotional lability, and, rarely, delirium or coma. Concomitant encephalopathy may obscure coexisting myelopathy.

Unusual, reported neurological manifestations possibly related to cobalamin deficiency include cerebellar ataxia, orthostatic tremor, myoclonus, ophthalmoplegia, catatonia, vocal cord paralysis, a syringomyelia-like distribution of motor and sensory deficits, and autonomic dysfunction.[11,13] Vitamin B_{12} deficiency in children often presents with nonspecific manifestations, such as delayed motor skills, irritability, lethargy, hypotonia, weakness, and failure to thrive.[115,116] In some cases, there may be brain imaging evidence of severe white matter abnormalities consistent with demyelination and brain atrophy.[116] An important effect of vitamin B_{12} and/or folate deficiency is elevation of total plasma homocysteine, which increases the risk of arterial thrombosis, deep vein thrombosis, retinal vein thrombosis, and cerebral venous sinus thrombosis and quadruples the risk of stroke in atrial fibrillation.[117]

Diagnosis

Determination of serum cobalamin is the mainstay for evaluating cobalamin status, although it lacks specificity and sensitivity for diagnosis of cobalamin deficiency (Table 4).[11,41,118] Levels of serum MMA, holotranscobalamin, and plasma total homocysteine are also useful. The specificity of MMA and holotranscobalamin is superior to that of homocysteine. More precisely, since using serum cobalamin levels to diagnose the metabolic adequacy of vitamin B_{12} is extremely insensitive, a diagnosis based on serum cobalamin requires confirmatory testing: levels of holotranscobalamin, homocysteine in folate-replete subjects, or MMA should be determined in patients with serum cobalamin levels in the lower half (or more) of the reference range. Indeed, approximately 20% of elderly persons, as well as 30% of vascular patients above age 70, have metabolic vitamin B_{12} deficiency, and most of these will be missed if serum

Table 4 **Common causes, other than cobalamin deficiency, of abnormal cobalamin, methylmalonic acid (MMA), and homocysteine (Hcy) blood levels, according to Kumar (2014),[11] Stabler (2013),[41] and Carmel (2011)[118]**

	Causes of increased levels	Causes of decreased levels
Cobalamin	Increased haptocorrin concentrations (seen in renal failure, liver disease, and myeloproliferative disorders like polycythemia vera, chronic myelogenous leukemia, chronic myelofibrosis) Intestinal bacterial overgrowth (measurement of biochemically inert B_{12} analogs)	Idiopathic Pregnancy Haptocorrin deficiency (cause of low cobalamin levels in sickle cell disease) Folate deficiency HIV and myeloma (abnormalities in cobalamin binding proteins) Medications: radionuclide isotope studies, anticonvulsants, oral contraceptives
MMA	Infancy, pregnancy Renal insufficiency, volume contraction Inborn errors of metabolism	Antibiotic-related reductions in bowel flora
Hcy	Renal insufficiency, volume contraction Folate or B_6 deficiency Hypothyroidism, renal transplant, leukemia, psoriasis, alcohol misuse Inappropriate sample collection and processing (levels increase if blood is left at room temperature for hours after collection) Medications: isoniazid, colestipol, niacin, L-dopa, diuretics Inborn errors of metabolism	Medications: estrogens, tamoxifen, statins

Abbreviations: HIV, human immunodeficiency virus.

levels of vitamin B_{12} in the normal range are used to determine B_{12} status. Indeed, the serum vitamin B_{12} level below which levels of MMA or total homocysteine rise is approximately 350 to 400 pmol/L, which is above the median for most elderly populations.[119,120] A limitation of MMA as a specific marker of cobalamin deficiency is that MMA increases in renal dysfunction.[119] Measuring MMA and homocysteine is also useful in patients with nitrous oxide toxicity or certain inherited disorders of cobalamin metabolism. In these conditions, cobalamin-dependent pathways are impaired, despite normal cobalamin levels.[11]

In recent years, normal or falsely high values of cobalamin have been reported in many patients with pernicious anemia.[11,41,121] Such results may be attributable to failure of the competitive-binding luminescence assay to inactivate serum intrinsic factor antibodies. Assay failure rates as high as 35% have been reported.[121]

Recently, holotranscobalamin concentration and transcobalamin saturation (total transcobalamin) have been proposed as potentially useful alternative indicators of cobalamin status.[122,123] Their levels appear to fall before those of cobalamin as measured by standard methods. Measurement of serum total transcobalamin may also circumvent the problem of interference from intrinsic factor autoantibodies that characterizes the competitive-binding luminescence assay. However, there is no test for serum total transcobalamin available for clinical use.[11] Inherited cobalamin malabsorption may be studied by genetic testing.[124]

Electrophysiological abnormalities include nerve conduction studies suggestive of sensorimotor axonopathy as well as abnormalities on somatosensory evoked potentials, visual evoked potentials, and motor evoked potentials.[11] Magnetic resonance imaging abnormalities in cobalamin deficiency include a signal change in the posterior and lateral columns (Figure 4) and, less commonly, in subcortical white matter.[11]

Management

The goals of treatment are to reverse the signs/symptoms of deficiency, replenish body stores, ascertain the cause of deficiency, and monitor response to therapy.[3,11,41] With normal cobalamin absorption, oral administration of 3 to 5 µg of cobalamin may suffice. Patients with cobalamin deficiency due to achlorhydria-induced food-bound cobalamin malabsorption show normal absorption of crystalline cobalamin but are unable to digest and absorb the vitamin in food due to achlorhydria. In such patients, 50 to 100 µg cobalamin given orally is often adequate. More recent studies have shown blunted metabolic responses in elderly persons with subclinical deficiency until oral doses reached 500 µg or more.[125] The more common situation is one of impaired absorption, when parenteral therapy (intramuscular or subcutaneous) is required. A short course of daily or weekly therapy is often followed by weekly and then monthly maintenance therapy. A common regimen is 1000-µg intramuscular injections for 5 to 7 days, followed by weekly injections until clear improvement is shown and then monthly 500- to 1000-µg intramuscular injections. If the oral dose is large enough (1000–2000 µg), even patients with an

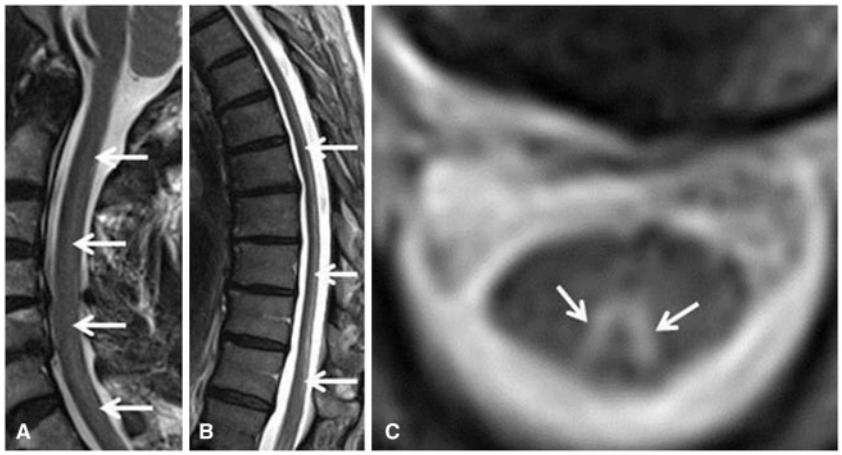

Figure 4 **Sagittal (A and B) and axial (C) T2-weighted magnetic resonance imaging scan from a patient with myelopathy related to vitamin B_{12} deficiency.** Increased signal can be seen in the paramedian aspect of the dorsal cervical (A and C) and thoracic (B) cord (arrows).

absorption defect, including pernicious anemia, may respond to oral cobalamin therapy.[125]

Intramuscular cobalamin should be also given to patients with acute nitrous oxide poisoning and to individuals with a borderline cobalamin level who are expected to receive nitrous oxide anesthesia; in the latter, therapy should be given several weeks before surgery.[126]

Neurological manifestations usually resolve completely within 6 months.[3,11] Hematological derangements, however, respond completely within a few weeks. Normalization of MMA and homocysteine occurs in 10 to 14 days.[11]

B VITAMIN DEFICIENCY AND NEUROLOGICAL DISORDERS

Several studies indicate a possible relationship between status of B vitamins, especially vitamins B_{12}, B_6, B_1, and folate, and many subtypes of cerebrovascular disease, cognitive functions in all ages of life, and certain chronic neurodegenerative disorders that affect the central nervous system, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.[3,6,17,127,128] Moreover, mainly in the neonatal period and early infancy, B vitamin deficiency, especially of vitamins B_1, B_3, B_6, B_7, B_{12}, and folate, may be an uncommon cause of either epileptic seizures or epilepsy (recurrent unprovoked seizures).[8] This latter topic has been recently reviewed elsewhere.[8]

McCully's hypothesis that a main risk factor for arteriosclerosis in the general population was B vitamin deficiency and the consequent hyperhomocysteinemia,[129] together with clinical trials showing that supplementation with vitamins B_6, B_{12}, and folic acid, alone or in combination, significantly lowers plasma homocysteine,[130–132] served as the basis for many studies designed to ascertain if B vitamin supplementation effectively protects against cerebrovascular disease.[133] Collectively, these studies, of uneven quality and design, have frequently reported equivocal or conflicting results.[130–133] Recently, an update of a Cochrane review of 12 randomized controlled trials found no evidence to suggest that homocysteine-lowering interventions in the form of vitamin B_6, vitamin B_{12}, or folic acid supplementation should be used for preventing myocardial infarction, stroke, or death by any cause.[133] In contrast, a more recent meta-analysis of 14 randomized controlled trials found that B vitamin supplementation for lowering of plasma homocysteine significantly reduced stroke events, especially in subjects with 3 or more years of follow-up and without a history of cerebral folate fortification or chronic kidney disease.[130] Moreover, a detailed analysis of the results of the Hope-2 trial, the VISP (Vitamin Intervention for Stroke Prevention) trial, and the SU.FOL.OM3 study suggests that B vitamin therapy to lower plasma homocysteine does reduce the risk of stroke, even if it does not reduce the risk of myocardial infarction.[134–138] The different response of stroke and myocardial infarction to B vitamin therapy may be related to their different pathophysiological mechanisms.[127]

Furthermore, in a recent substudy of the VITATOPS (VITAmins TO Prevent Stroke) trial, a placebo-controlled interventional MRI study on the effects of daily administration of vitamins B_{12} and B_6 and folic acid in stroke patients, B vitamin supplementation was associated with a significant reduction in white matter hyperintensities volume change in a subanalysis of patients with MRI evidence of severe cerebral small vessel disease at baseline.[139] Interestingly, in another group of patients from the same trial, B vitamins in absence of

antiplatelet therapy showed a significant benefit in the secondary prevention of major vascular events.[140] If validated, this latter finding indicates a potential role of B vitamins in the prevention of ischemic events in high-risk individuals with allergy, drug intolerance, or lack of indication for antiplatelet therapy.[140] Moreover, recent findings indicate that, among hypertensive adults without a history of stroke or myocardial infarction, the combined use of enalapril and folic acid, compared with enalapril alone, significantly reduces the risk of first stroke.[141]

In summary, the relationship between homocysteine plasma levels, B vitamin supplementation, and the many subtypes of cerebrovascular disease requires further well-designed studies, as it appears to be more complex than is commonly understood. Such studies could help clarify, among other things, essential information such as the best time to start treatment and the optimal doses of B vitamins to be used in clinical trials, especially in elderly patients, in patients with impaired renal function, and in individuals with peculiar genetic determinants, such as polymorphisms of *MTHFR* and variants of transcobalamin II.[134]

In 1992, it was suggested that elevated plasma levels of total homocysteine also might play a role in the etiology of Alzheimer's disease.[131,132] Subsequent studies showed a definite link between vascular dementia and Alzheimer's disease.[131] The widespread acceptance of the B vitamins/homocysteine theory fueled a large amount of research aimed at documenting a role of B vitamin status in age-related cognitive impairment and decline. The conclusion, however, as discussed extensively in several reviews[141,142] and a recent meta-analysis,[141] is that, although B vitamin supplementation may significantly lower plasma homocysteine levels, consistent demonstration of benefits in intervention trials has been elusive, possibly because most intervention trials do not select subjects on the basis of nutrient status and/or intake.[141–143] Relevant to this, studies suggest that supplementation may protect against cognitive decline when serum folate is less than 12 nmol/L,[143] although there is insufficient literature to define a level for vitamin B_{12}.[143]

There are still relevant, unresolved issues to be clarified in future well-planned studies. These include the role of chronically low plasma levels of vitamin B_{12}, vitamin B_6, or folate on speed of deterioration of specific cognitive functions in the elderly population; the effect of physiological and supraphysiological folate plasma levels on memory function and processing speed, including in relation to homocysteine plasma concentrations; and the biological relevance of the complex biochemical interactions between B vitamins, especially the interaction between folate and vitamin B_{12}.[1,3]

Many B vitamins, especially B_1, B_3, B_6, B_{12}, and folate, are also implicated in the regulation of specific biochemical pathways involved in the pathophysiology of chronic neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, mainly as enzymatic cofactors. Thus, altering the supply of these vitamins through diet can influence lifespan and the rate of neurodegeneration.[144–146] Moreover, an altered vitamin B_1 metabolism may play a role in the perturbed cerebral glucose metabolism found in Alzheimer's disease,[144] with secondary induction of oxidative stress and further accumulation of β-amyloid peptides in the brain.[145] In addition, recent studies highlight a possible relationship between dysfunction in vitamin B_1 metabolism and Parkinson's disease.[17]

Notably, the cholinergic neurons in the brain seem particularly susceptible to diverse neurodegenerative conditions, including Alzheimer's disease and Parkinson's disease, which implies an altered glucose metabolism and acetyl coenzyme A (acetyl-CoA) deficits.[145] Indeed, glucose-derived pyruvate is a principal source of acetyl-CoA in all brain cells, via the pyruvate dehydrogenase complex enzymatic reaction, which is vitamin B_1 dependent (Figure 1). A deficient supply of this common intermediate of several metabolic pathways is likely to be more harmful for cholinergic neurons than for other types of neurons and glial cells because of the additional consumption of acetyl-CoA during acetylcholinergic neurotransmission.[144] However, it remains unclear whether the impaired utilization of glucose in the brain and the disturbed hippocampal/cortical acetylcholine synthesis in Alzheimer's disease are consequences of neurodegeneration or primary biochemical disturbances.[144]

Moreover, since hyperhomocysteinemia is a major risk factor for Alzheimer's disease,[131] it has been also suggested that lowering of total homocysteine plasma concentrations through adequate B vitamin supplementation might partly counteract neurodegeneration and brain atrophy in this pathology.[131] Importantly, recent randomized controlled studies in elderly subjects with mild cognitive impairment and, thus, with increased risk of dementia, have shown that high-dose treatment with vitamin B_6, vitamin B_{12}, and folic acid for plasma homocysteine lowering over 2 years can slow both the rate of atrophy of specific brain regions highly vulnerable to underlying pathological processes, such as the medial temporal lobes (which play a key role in cognitive functions), and cognitive and clinical decline,[18] especially in those with high plasma homocysteine concentrations, above the median of 11 μmol/L.[18] In particular, participants in the B-vitamin supplementation group showed a statistically lower total plasma

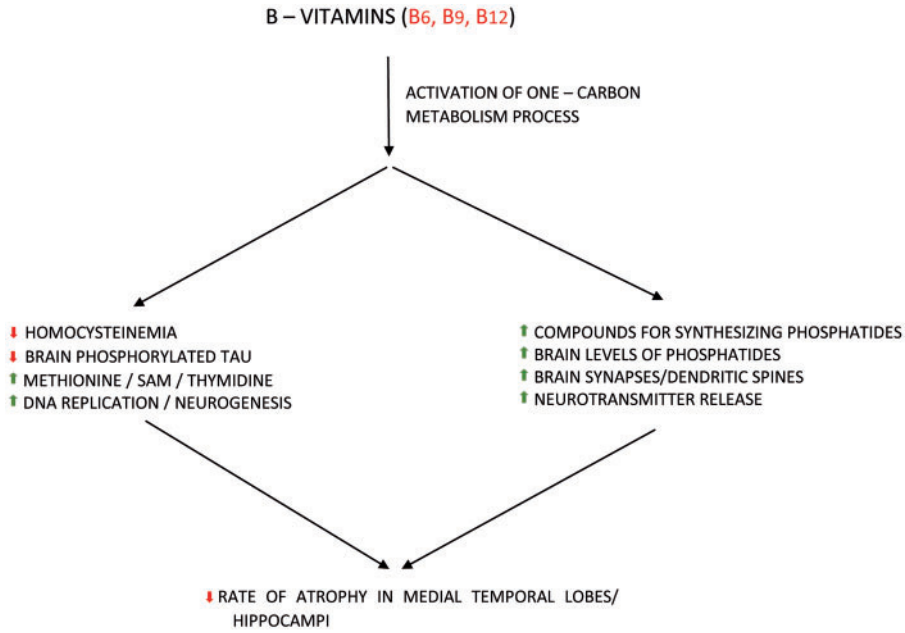

Figure 5 **Hypothetical mechanisms underlying B-vitamin lowering of the rate of medial temporal lobe atrophy in patients with mild cognitive impairment.** *Abbreviation*: SAM, *S*-adenosyl methionine.

homocysteine level, resulting in a decrease in gray matter atrophy and a concomitant slowing of cognitive decline.[18]

The pathogenesis of the B vitamin–related slowing of the rate of brain atrophy in patients with mild cognitive impairment is unknown. Purported mechanisms include a decreased brain level of phosphorylated tau and neurofibrillary tangles in specific brain regions, secondary to plasma homocysteine lowering,[145] and the activation of the one-carbon metabolism process by vitamin B_{12} and folate, with a likely, consequent increase in synthesis of methionine, *S*-adenosyl methionine, thymidine and thus DNA replication, which ultimately could foster adult neurogenesis in medial temporal lobes/hippocampi of these subjects, and cognitive improvement (Figure 5).[145]

Another potential mechanism may implicate the correction by B vitamins of an aberrant lipid metabolism, which seems to play a pathophysiological role in mild cognitive impairment and Alzheimer's disease.[147–151] Specifically, vitamins B_6, B_{12}, and folate as cofactors might enhance both the synthesis and the brain levels of phosphatides, choline, and acetylcholine, which are abnormally low in mild cognitive impairment, by facilitating methylation reactions. Ultimately, this may lead to some recovery of the disturbed organization of brain synaptic networks in cognitively impaired patients, possibly slowing of the rate of atrophy in specific brain areas and improving cognitive performance (Figure 5).[147,149] However, claims that B vitamin supplementation for lowering of plasma homocysteine can prevent cognitive aging within 2 to 3 years of treatment[8,152] were not supported by a large controlled study and recent meta-analysis.[153,154]

Many studies in several model organisms have suggested a role for vitamin B_3 in altered tryptophan metabolism and in many age-related disorders, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease.[155] To date, however, evidence for a role of this pathway in humans is only correlative.[155]

CONCLUSION

Taken together, these findings indicate that subclinical or overt B vitamin deficiency, with frequent involvement both of the central and peripheral nervous system at all stages of life, is a global health concern, especially in selected populations at risk and in certain clinical settings.

Clinicians should pay particular attention to the possible occurrence of several deficiencies associated with significant morbidity and mortality: folate deficiency in women who become pregnant after bariatric surgery; rapid thiamine depletion and Wernicke's encephalopathy in both adults and children in a myriad of clinical settings; and niacin deficiency in people with alcoholism who have prolonged delirium tremens.

Clinicians should avoid the administration of folic acid in the presence of subclinical vitamin B_{12} deficiency, particularly in elderly adults, and of vitamin B_6 in absence of niacin in individuals at risk for niacin deficiency.

Additional efforts are required to develop powerful and reliable biomarkers and assays useful in clinical practice for assessing the deficiency of all B vitamins. Further well planned studies are needed to validate the possibility that some B vitamins given alone or in combination for years, particularly vitamins B_1, B_6, B_{12}, and folic acid, may partly counteract neurodegeneration and the rate of brain atrophy in patients with Alzheimer's disease and Parkinson's disease. While challenging, clinical trials aimed at preventing diseases related to altered B vitamin status by treating at-risk persons with B vitamins before they develop symptoms, could be especially useful.

Many more studies are required to define the anatomical distribution of B vitamins in the human brain (cell bodies and/or fiber systems) in order to understand the neural networks by which B vitamins may modulate epileptogenesis, behavior, mood, and cognitive processing.

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SUPPORTING INFORMATION

The following Supporting Information is available through the online version of this article at the publisher's website.

Appendix S1 Description of the one-carbon metabolism process

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