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NEUROLOGY OF SYSTEMIC DISEASES (J BILLER, SECTION EDITOR)

Neurology of Nutritional Deficiencies

Kristin L. Miller[1] · Gabriela Trifan[1] · Fernando D. Testai[1]

Abstract

Purpose of Review The goal of this chapter is to educate clinicians on the neurologic manifestations of certain nutritional deficiencies in order to promptly identify and appropriately treat these patients.

Recent Findings Many vitamin and nutritional deficiencies have been described dating back to the early days of neurology and medicine. Some are very rare and thus, there are no randomized controlled studies to assess supplementation or dosage; however, there are reviews of case reports that can assist clinicians in choosing treatments.

Summary While endemic vitamin and nutritional deficiencies may be rarely encountered in many countries, vulnerable populations continue to be at risk for developing neurologic complications. These populations include those with diseases causing malabsorption, the elderly, chronic alcohol users, as well as pregnant mothers with hyperemesis gravidarum to name a few. It is important to recognize syndromes associated with these nutritional deficiencies, as prompt identification and treatment may prevent permanent neurologic damage.

Keywords Vitamin deficiency · B vitamin deficiency · Neurologic symptoms of vitamin deficiencies · Malabsorption vitamin deficiency · Nutritional deficiency

Introduction

A functional nervous system requires an adequate and consistent supply of appropriate nutrients. Worldwide, up to 820 million people are undernourished per the 2019 report by the Food and Agriculture Organization of the United Nations [1•]. While endemic vitamin and nutritional deficiencies may be rarely encountered in many countries, vulnerable populations continue to be at risk for developing neurologic complications. It is important to recognize syndromes associated with nutritional deficiencies, as prompt identification and treatment may prevent permanent neurologic damage. We will discuss common vitamins and nutrients that are particularly important in the central and peripheral nervous system, and the neurologic manifestations seen with their deficiencies.

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✉ Kristin L. Miller
kmille25@uic.edu

[1] Department of Neurology and Rehabilitation, University of Illinois at Chicago College of Medicine, 912 S Wood St, Chicago, IL 60612, USA

Vitamin B1 (Thiamine) Deficiency

Background

Thiamine, also known as vitamin B1 or aneurin, is an essential nutrient present in different foods, including whole grain products, meat, fish, black beans, and eggs. In industrialized countries, breads, cereals, and infant formulas are commonly fortified with thiamine. Thus, endemic thiamine deficiency occurs, predominantly, in low-income, underdeveloped countries. The recommended adult daily allowance (RADA) is 1.2 mg for men, 1.1 mg for women, 1.4 mg during pregnancy, and 1.5 mg for breastfeeding women [2].

Metabolism and Physiologic Function

Most dietary thiamine is in its phosphorylated form. Intestinal phosphatases hydrolyze the phosphate group and free thiamine is absorbed in the jejunum through active transport. Thiamine is stored in very small amounts in the liver and has a short half-life. Thus, people normally require a constant supply from the diet. Thiamine is a critical cofactor for different enzymes, including [3]:

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- *Transketolase*. This is a key enzyme in the pentose monophosphate shunt. In the absence of thiamine, there is a decreased production of pentoses and nicotinamide adenine dinucleotide phosphate (NADP). Pentoses are necessary for the synthesis of nucleic acids and NADP participates of the biosynthesis of fatty acids and antioxidants such as glutathione.
- *Pyruvate dehydrogenase E1*. The pyruvate dehydrogenase is an enzymatic complex formed by three enzymes. One of them, referred to as E1, uses thiamine pyrophosphate as a cofactor. The pyruvate dehydrogenase complex links glycolytic pathway to the Krebs cycle. Thiamine deficiency inhibits E1 and prevents the conversion of pyruvate into acetyl-CoA.
- *Alpha-ketoglutarate dehydrogenase*. This enzyme is part of the Krebs cycle and converts alpha-ketoglutarate into succinyl-CoA. In the absence of thiamine, both the pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase become dysfunctional. Consequently, there is a decreased production of adenosine triphosphate (ATP) and the reduced form of nicotinamide adenine dinucleotide (NADH) leading to energy failure and cellular dysfunction (Fig. 1).

In autopsy studies, patients with Wernicke encephalopathy have proliferative vasculopathy which may present with petechial hemorrhages, particularly in the mammillary bodies. In addition, neuronal cell loss and gliosis can occur in the mammillary bodies, medial dorsal thalamic nuclei, hypothalamus, and around the third ventricle, aqueduct of Sylvius, and floor of the fourth ventricle. Individuals with Korsakoff syndrome have neuronal loss and gliosis of the mammillary bodies and medial dorsal thalamic nuclei similar to Wernicke encephalopathy [4].

Presentation

Thiamine deficiency causes a range of symptoms that may be subtle and easily overlooked (Table 1). In its more severe form, it causes a neurocardiogenic syndrome called *beriberi*. Two forms of beriberi have been described: *dry beriberi* refers to patients that have a length-dependent sensorimotor peripheral neuropathy without cardiac involvement. In contrast, patients with *wet beriberi* have peripheral neuropathy and microvascular dilation leading to edema, arteriovenous shunting, and high-output heart failure. In industrialized countries, thiamine deficiency is commonly associated with chronic

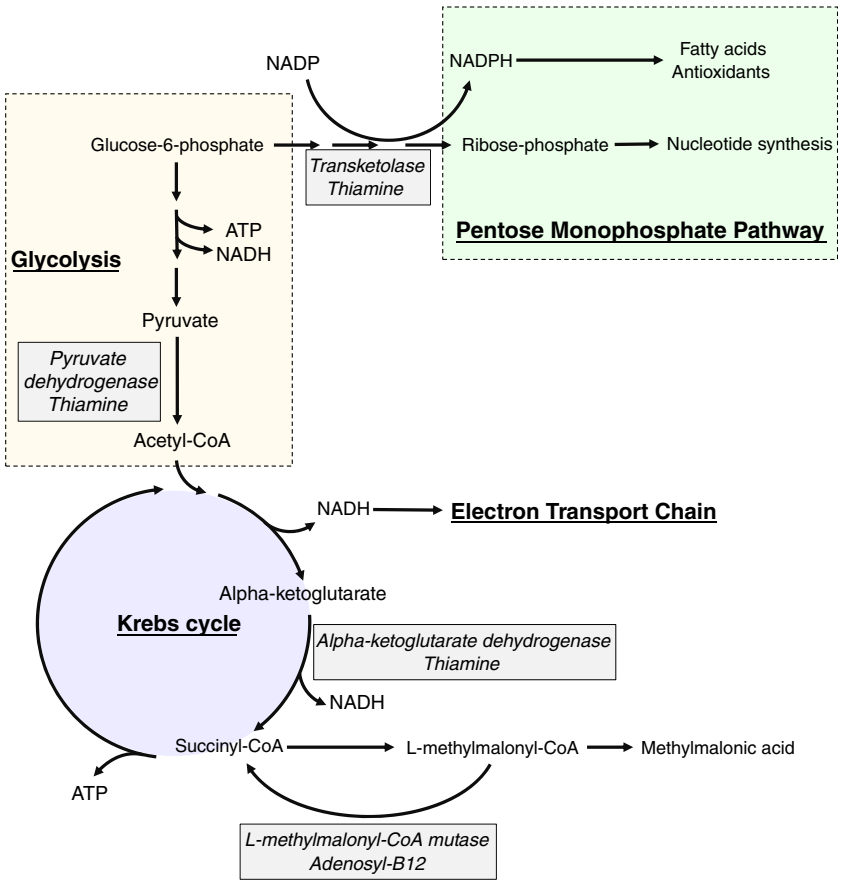

Fig. 1 Sites of action of Vitamin B1 and B12

Table 1 Nutritional factor, clinical features, and causes of deficiency

Nutritional factors	Clinical features	Causes of deficiency
Vitamin B1 (thiamine)	Ophthalmologic - Ophthalmoplegia due to involvement of the III, IV, or VI cranial nerves - Horizontal or vertical nystagmus - Ptosis - Miosis and non-reactive pupils - Retinal hemorrhages (rare) - Papilledema (rare) Ataxia Mental status - Encephalopathy - Amnesia - Stupor or coma - Agitation Peripheral neuropathy - Axonal sensorimotor peripheral neuropathy - Autonomic neuropathy Cardiovascular - Tachycardia - Exertional dyspnea Other - Macrocytosis - Inability to discriminate odors - Hypothermia	Chronic alcoholism Malnutrition and malabsorption Critically ill patients with prolonged intravenous feeding Renal dialysis Acquired immunodeficiency syndrome (AIDS) Magnesium depletion: magnesium is necessary for the conversion of thiamine into active metabolites Diarrhea: Crohn's disease, gluten enteropathy Gastrointestinal procedures (bariatric surgery, primarily gastric bypass) Pregnancy and lactation Elderly
Vitamin B3 (niacin)	Pigmented rash or brown discoloration on exposed skin Headache Gastrointestinal - Stomatitis, gingivitis, glossitis - Diarrhea - Abdominal pain - Vomiting - Anorexia Neuropsychiatric - Encephalopathy that may progress to coma - Irritability, depression, apathy - Memory loss - Myelopathy - Peripheral neuropathy	Alcoholism Malabsorption Secondary to other deficiencies - Vitamin B6 - Vitamin B2 - Iron Carcinoid syndrome Bacterial colonization of the small intestine Inherited conditions (Hartnup syndrome)
Vitamin B6 (pyridoxine)	Neuropsychiatric - Depression - Irritability - Anxiety - Sensorimotor polyneuropathy - Intractable seizures in infants Dermatological - Seborrheic dermatitis - Glossitis - Cheilosis - Conjunctivitis Hematological - Sideroblastic anemia - Weakened immune system - Elevated homocysteine levels	Alcoholism Protein-energy undernutrition Malabsorption - Celiac disease - Crohn's disease - Ulcerative colitis - Inflammatory bowel disease Hemodialysis Medications - Oral contraceptives - Antiseizure medications (carbamazepine, valproic acid, phenytoin) - Isoniazid - Cycloserine - Penicillamine - Hydralazine - Theophylline - L-dopa Increased demands - Chronic liver failure - Pregnancy - Lactation
Vitamin B9 (folic acid, folate)	Neuropsychiatric - Irritability	Alcoholism Malabsorption

Table 1 (continued)

Nutritional factors	Clinical features	Causes of deficiency
	- Encephalopathy	- Inflammatory bowel disease
	- Depression	- Celiac disease
	- Behavioral changes	- Gastric resection
	- Cognitive decline	- Short bowel syndrome
	- Myelopathy	- Tropical sprue
	- Neuropathy	- Amyloidosis
	- Seizures (during infancy)	- Mesenteric ischemia
	- Neural tube defects (during embryogenesis)	Impaired folate metabolism
	Gastrointestinal	- Methotrexate
	- Diarrhea	- Antiseizure medications
	- Glossitis (smooth red tongue)	- Antimalarials
	- Ageusia	Increased folic demands
	Hematological	- Chronic hemolytic anemia
	- Macrocytosis or megaloblastic anemia	- Sickle cell disease
	- Pancytopenia	- Pregnancy
	Other	- Lactation
	- Macrocytosis or megaloblastic anemia	
	- Weakness, tiredness, headache	
	- Headache	
	- Palpitation	
	- Pallor of mucous membrane	
	- Changes in skin, hair, and fingernail pigmentation	
Vitamin B12 (cobalamin)	Mental status	Dietary deficiency (veganism)
	- Confusion	Malabsorption
	- Cognitive decline	- Pernicious anemia
	Neurologic	- Gastric achlorhydria
	- Paresthesia and numbness in the feet	- Gastric resection
	- Lhermitte symptoms	- Chronic pancreatic disease
	- Anosmia	- Competition for intraluminal vitamin B12
	- Reduced visual acuity	(bacterial overgrowth or cobalamin-metabolizing
	- Impaired taste	fish tapeworm
	- Decreased manual dexterity	(*Diphyllobothrium latum*) infestation
	- Lower limb weakness	- Medications that affect the absorption of B12
	- Impotence	(proton pump inhibitors, H2 blockers, metformin)
	- Incontinence	- Terminal ileum disease
	- Orthostatic hypotension	- Crohn's disease
	- Hyperreflexia with clonus	- Resection
	- Extensor plantar responses	Nitrous oxide exposure: anesthesia
	- Ataxia (broad-base)	Increased requirements: pregnancy
	- Cerebellar (due to spinocerebellar degeneration)	Genetic: defect of methylmalonyl CoA mutase.
	- Sensory (due to degeneration of the posterior columns)	Immune disorders
	Psychiatric	- Graves' disease
	- Depression	- Systemic lupus erythematosus
	- Hallucination	
	- Psychosis (called megaloblastic madness)	
	- Behavioral changes	
	- Paranoia	
	Other	
	- Macrocytosis or megaloblastic anemia	
	- Weakness, tiredness	
	- Headache	
	- Diarrhea and bowel disturbances	
	- Pallor of mucous membrane	
	- Glossitis	
	- Premature graying of hair	
Vitamin D	Musculoskeletal	Lack of sun exposure
	- Proximal muscle weakness	Malnutrition
	- Low bone mineral density	Malabsorption
	- Myalgias	- Inflammatory bowel disease
	Autoimmune system	- Celiac disease
	- Increased cancer risk	- Pancreatitis
	- Increased risk of type 1 diabetes and multiple sclerosis	- Gastric bypass

Table 1 (continued)

Nutritional factors	Clinical features	Causes of deficiency
	- Higher risk for severe tuberculosis Neurologic - Increased risk of depression - Increased risk of mental illness (schizophrenia) Other - Increased risk of preeclampsia	Medications - Glucocorticoids - Rifampin - Antiseizure medications (phenobarbital, carbamazepine, phenytoin) Increase demands - Hepatic and renal failure - Pregnancy - Lactation - Dark skin pigmentation - Elderly - Obesity
Vitamin E	Eyes - Retinitis pigmentosa Hematologic - Acanthocytosis - Hemolytic anemia Neurologic - Cerebellar ataxia - Sensory ataxia with large fiber neuropathy - Hyporeflexia - Extensor plantar reflexes	Malabsorption - Chronic cholestasis - Pancreatic insufficiency - Celiac disease - Crohn's disease - Cystic fibrosis - Short bowel syndrome - Bowel resection Insufficient intake - Total parenteral nutrition - Anorexia - Alcoholism Inherited conditions - Ataxia with vitamin E deficiency - Homozygous hypobetalipoproteinemia - Abetalipoproteinemia - Chylomicron retention disease
Marchiafava-Bignami disease	Altered mental state - Confusion, disorientation - Delirium - Unconsciousness - Impaired memory Seizures Apraxia Behavioral changes Dysconjugate gaze Ataxia Corticospinal tract signs Delirium tremens Sensory neuropathy	Chronic alcohol abuse Severe malnutrition - Anorexia Malabsorption

alcoholism where it manifests clinically with Wernicke-Korsakoff syndrome. *Wernicke* refers to the triad of encephalopathy, gait ataxia, and ophthalmologic manifestations. These include nystagmus and ophthalmoparesis. *Korsakoff*, on the other hand, refers to a chronic amnestic disorder characterized by anterograde and retrograde amnesia with confabulation. The term *thiamine deficiency disorder* is nonspecific and describes the broad spectrum of overlapping manifestations related to thiamine deficiency [5, 6].

Causes and Diagnosis

Non-endemic thiamine deficiency is associated with chronic alcoholism and different medical conditions which cause malnutrition and/or malabsorption (Table 1). Thiamine levels can be ascertained by measuring the activity of transketolase in erythrocytes; however, this test has been largely replaced by the direct measurement of thiamine levels in serum. Magnesium is necessary for the conversion of thiamine to active metabolites. Thus, it is important to assess magnesium levels in patients with suspected thiamine deficiency [7].

Treatment

This includes the correction of the underlying cause of the deficiency and the supplementation with thiamine 100 to 200 mg intravenously daily for 7 days, particularly in

alcoholics who may have impairment of intestinal absorption. The recommended oral maintenance dose is 10 to 50 mg daily until the patient is no longer at risk. In addition, if depleted, magnesium should be replaced. The prognosis of thiamine deficiency depends of the severity of the disease and the prompt initiation of treatment. Left untreated, the mortality rate is 10 to 20%. Gaze paralysis typically improves within hours or days after the initiation of treatment. In comparison, the recovery of the amnestic symptoms occurs slowly over 1 year and may be incomplete. It has been estimated that up to 60% of the patients have residual nystagmus or ataxia and 80% have persistent memory loss [7].

Vitamin B3 (Niacin) Deficiency

Background

The term niacin is a generic name for nicotinamide, nicotinic acid, and other associated biologically active derivatives. Niacin is a water-soluble vitamin that is naturally present in red meat as well as liver, poultry, fish, milk, legumes, seeds, and yeast products. Its deficiency leads to a systemic disorder called *pellagra*. This is characterized by dermatitis, diarrhea, and progressive encephalopathy which may result in dementia, coma, and death. Niacin is also present in multivitamins and supplements containing B complex vitamins. The RADA of niacin is 16 mg for men, 14 mg for female, 18 mg during pregnancy, and 17 mg for breastfeeding women [2].

Metabolism and Physiologic Function

Niacin can be synthesized from tryptophan present in dietary proteins. In addition, niacin derivatives in foods are converted to nicotinamide and absorbed primarily in the small intestine and, to some degree, the stomach. Once absorbed, niacin is transported to different tissues where it is transformed into its main metabolically active derivatives: nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Red blood cells uptake some of the niacin excess and serve as a circulating reserve pool. In addition, niacin can also be stored in the liver. The excess of niacin is eliminated in urine as nicotinic acid or nicotinamide.

NAD and NADP and their reduced forms, NADH and NADPH, participate in redox reactions and have an active role protecting cells against the toxic effect of reactive oxygen species. By carrying electrons from one reaction to another, they also link different vital biochemical pathways. NAD, in particular, is reduced to NADH in several catabolic pathways, including glycolysis, Krebs cycle, and β-oxidation. NADH is then oxidized by the electron transport chain in the mitochondria where it generates ATP (Fig. 1). NADH also participates in several anabolic pathways, including gluconeogenesis, and other vital functions, such DNA repair, gene expression, and cell-to-cell communication. NADP, in comparison, is largely used in anabolic reactions including the synthesis of lipids and pentoses which are necessary for the production of nucleotides (Fig. 1) [8•].

Presentation

The deficiency of niacin leads to *pellagra* which is also known as the disease of the four D's because of the occurrence of diarrhea, dermatitis, dementia, and death. On clinical examination, patients develop diffuse erythematous skin lesions that may be painful and most typically localize to sun-exposed areas. In the acute phase, the dermatitis may present with bullae and is called *wet pellagra*. As the skin lesions evolve into chronicity, they thicken and become hyperpigmented. Patients may experience nonspecific gastrointestinal manifestations, including nausea, vomiting, diarrhea, and abdominal discomfort (Table 1). Neuropsychiatric disorders may develop in the absence of dermatologic and gastrointestinal involvement. These include neurocognitive impairment and progressive encephalopathy. Left untreated, pellagra can lead to coma and death [9].

Causes and Diagnosis

The incidence of pellagra decreased significantly with the supplementation of bread and cereals with niacin. However, endemic pellagra may occur in communities with diets limited in protein and heavily based on the consumption of corn, which lacks both niacin and tryptophan. Similar to other vitamins, non-endemic niacin deficiency can be seen in association with alcoholism and malabsorption (Table 1). Niacin deficiency can also occur when the conversion of tryptophan to niacin is reduced, as happens in patients with decreased levels of riboflavin (vitamin B2), pyridoxine (vitamin B6), or iron. Though uncommon, the bioavailability of tryptophan can also be compromised in carcinoid syndrome where tryptophan is routed to the production of serotonin, bacterial colonization of the small intestine which enhances the metabolism of tryptophan, or Hartnup disease. This condition, also known as *pellagra-like dermatosis*, is an autosomal recessive disorder caused by the impaired cellular transport of neutral amino acids, particularly tryptophan. Consequently, the absorption of tryptophan in the intestine is reduced and its excretion in urine is increased.

The diagnosis of niacin deficiency is based on the determination of niacin status in the context of clinical manifestations consistent with the diagnosis of pellagra. Niacin, NAD, NADP, and tryptophan levels can be measured in the serum, but these are not reliable indicators of niacin status. The most sensitive indicator of niacin status is the 24-h urinary excretion

of two niacin metabolites, N1-methyl-nicotinamide and N1-methyl-2-pyridone-5-carboxamide [2].

Treatment

The recommended treatment of pellagra involves the use of nicotinamide at a dose of 300 mg daily divided in three doses for 3 to 4 weeks. Parenteral treatment is typically reserved for severe cases. Since pellagra can coexist with other B vitamin deficiencies, it is recommended to also treat patients with B complex or yeast products. Of note, niacin supplementation is effective for the treatment of different dyslipidemias. The use of oral nicotinic acid, particularly in doses beyond the nutritional needs, activates the dermal Langerhans cells and causes vasodilation of the small subcutaneous vessels leading to skin flushing. In comparison, nicotinamide does not produce this effect [10].

Vitamin B6 (Pyridoxine) Deficiency

Background

Vitamin B6, also called pyridoxine, is a water-soluble vitamin and one of the eight types of vitamins that forms the B complex. Dietary intake is the sole source of vitamin B6, as this vitamin is not synthetized in the body. Pyridoxine is easily available through diet, being found in high amounts in chickpeas, vegetable oil spread, beef liver, yellowfin tuna, other meats, grains, and some fruits and vegetables (avocado, carrots, potato, and spinach). It is absorbed in the jejunum and metabolized to its active form in the liver. The RADA is 0.1 mg for children under 6 months, 1.7 mg for adults over 50, and 1.9 mg during pregnancy [2].

Metabolism and Physiological Function

Vitamin B6 contains six chemically related substances: pyridoxamine, pyridoxine, pyridoxal, and their corresponding phosphorylated derivatives. Pyridoxal 5-phosphate (PLP) is the most biologically active form. Vitamin B6 plays a crucial role in cellular metabolism and it is involved in more than 140 different metabolic reactions in the cell, including protein folding, amino acid biosynthesis and degradation, hemoglobin production, inflammation, and neurotransmitter biosynthesis [11•]. Intake of vitamin B6, alone or with folic acid and vitamin B12, has been linked to decreased cardiovascular risk by lowering homocysteine levels in the body, improvement in short-term memory in older adults, and lower risk of colorectal cancer; these findings have not been validated in larger clinical trials [12–14].

Presentation

Vitamin B6 deficiency can manifests with sideroblastic anemia, dermatitis, confusion, developmental delay, impaired immunity, or intractable seizures (Table 1). A rare genetic disorder caused by a genetic mutation in the ALDH7A1 gene inactivates PLP and causes pyridoxine-dependent epilepsy [15]. PLP is a cofactor in the synthesis of γ-aminobutyric acid (GABA) from glutamate and its deficiency in adults can manifest as seizures. Both vitamin B6 deficiency and toxicity can lead to a sensory or sensorimotor polyneuropathy [16, 17].

Causes and Diagnosis

Vitamin B6 is readily available in diet and sole deficiencies are rare. Acquired vitamin B6 deficiency is seen in patients with renal failure, malabsorption syndromes, chronic alcohol use, the elderly, during pregnancy, or with use of certain medications (Table 1). The most common cause of neuropathy-related vitamin B6 deficiency is the use of isoniazid for tuberculosis treatment, which can be prevented by using vitamin B6 supplementation at a dose of 50 mg daily, during isoniazid treatment [18]. Inherited vitamin B6 deficiency is seen with homocystinuria [2]. Toxicity is seen with doses higher than 2 g/day or with smaller doses when used for a prolonged period of time. Diagnosis of vitamin B6 deficiency or toxicity is based on measuring serum blood levels or urine levels. Normal vitamin B6 levels in serum are between 5 to 50 μg/L. Electromyography and nerve conduction studies (EMG/NCS) can show abnormal quantitative sensory studies [16].

Treatment

The recommended upper limit for vitamin B6 daily intake is 100 mg/day. Higher doses up to 30 mg/kg/day are needed in pyridoxine-dependent epilepsy. When peripheral neuropathy from B6 toxicity is suspected, cessation of vitamin B6 supplementation can lead to resolution of symptoms within 6 months [19].

Folate (Folic Acid or Vitamin B9) Deficiency

Background

Folate is an essential water-soluble vitamin that is present in fruits and fruit juices, nuts, seafood, meat, poultry, dairy products, and grains. Beef liver, black-eyes peas, asparagus, and green leafy vegetables, particularly spinach, Brussels sprouts, and lettuce, are among the foods with the highest levels of folate. In addition, many breads, flours, pasta, cereals, and other grain products are enriched in the synthetic form of

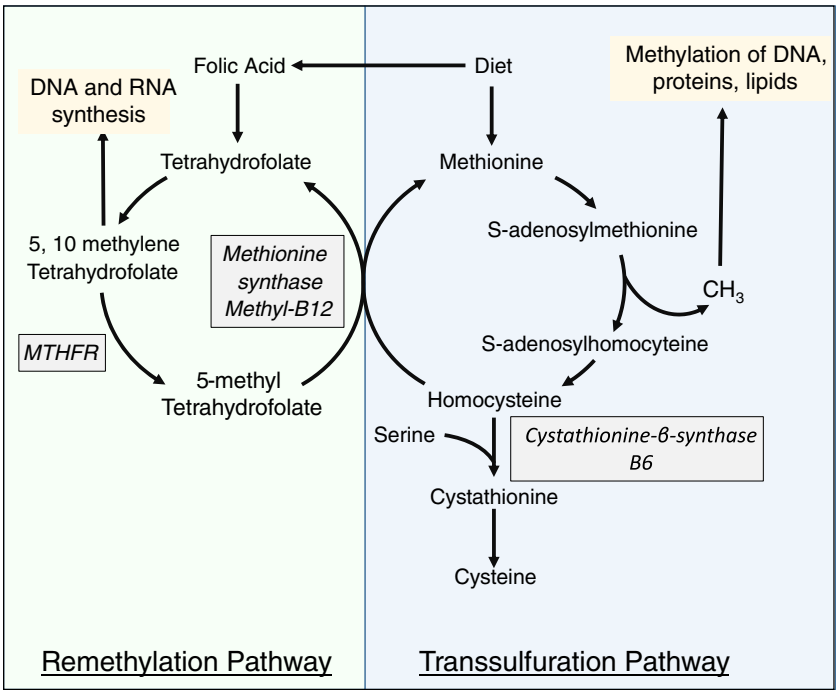

Fig. 2 Metabolism of homocysteine and methionine. MTHFR: methylenetetrahydrofolate reductase.

folate called folic acid or vitamin B9. The RADA is 400 mcg for men and women, 500 mcg during lactation, and 600 mcg during pregnancy [2].

Metabolism and Physiologic Function

Folate is thermolabile and can be easily destroyed during cooking. Dietary folate exists predominantly as polyglutamate and is hydrolyzed to monoglutamate in the intestine. Monoglutamyl-folate is absorbed in the jejunum by both active and passive transport mechanisms. Folate circulates in the blood mainly as 5-methyl-tetrahydrofolate (THF), which is transported into the cells by carrier- or receptor-mediated transporters. Folate participates in the conversion of homocysteine to methionine. In normal circumstances, dietary methionine is metabolized subsequently to s-adenosylmethionine, s-adenosylhomocysteine, and homocysteine; homocysteine enters the transsulfuration pathway where it is converted to cysteine by the vitamin B6-dependent enzyme, cystathionine-β-synthase. Alternatively, homocysteine can enter the remethylation pathway. In this case, the methionine synthase, using 5-methyl-THF and methylcobalamin (or methyl-B12) as cofactors, metabolizes homocysteine to methionine (Fig. 2) [20]. In distinction to vitamin B12, however, folate does not participate of the metabolism of methylmalonic acid. Folate is involved in the synthesis of DNA and RNA as well as the metabolism of amino acids (Fig. 2). In addition, folate participates of genomic and nongenomic methylation processes, which have an effect in cell differentiation, growth, and repair [21].

Presentation

In addition to its negative effect on DNA synthesis and methylation, folate deficiency, similar to vitamin B12 deficiency, is associated with increased levels of homocysteine and reduced levels of methionine and s-adenosylmethionine, which is another important methyl donor. Defective DNA methylation is associated with neural tube defects; thus, folate deficiency during the first trimester of the pregnancy increases the risk of spina bifida and anencephaly. Furthermore, owing to its active role in DNA synthesis, the deficit of folate affects tissues with rapid cell turnover, including the bone marrow and the gastrointestinal system. These manifest clinically with hematologic abnormalities, including macrocytosis, megaloblastic anemia, or pancytopenia, and gastrointestinal manifestations. Vitamin B12 and folate deficiencies have some similarities. Approximately two-thirds of patients develop neurologic manifestations and one-quarter have neurocognitive decline. Based on observational studies, peripheral neuropathy is more common in vitamin B12 deficiency and depression is more common in folate deficiency. Subacute combined degeneration appears to be rare in folate deficiency. Importantly, one-third of the patients with megaloblastic anemia do not have neuropsychiatric symptoms. Conversely, approximately a fifth of the patients with neuropsychiatric disorders do not have hematologic abnormalities [22]. Elevated homocysteine levels, as occurs in vitamin B12 and folate deficiency, have been associated with accelerated atherosclerosis, which increases the risk of cardiovascular events and stroke.

Causes and Diagnosis

Table 1 depicts the most common causes of folate deficiency. Antiseizure medications, particularly phenobarbital, phenytoin, valproic acid, and carbamazepine, as well as methotrexate, sulfasalazine, and trimethoprim can decrease the bioavailability of folate [20]. In addition, the dysfunction of methionine synthase, as occurs in cases of vitamin B12 deficiency, blocks the utilization of 5-methyl-TFH and leads to increased plasma levels of folate which is eliminated in urine [21]. Furthermore, some genetic polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene result in an enzyme with impaired ability to convert folate to its active form 5-methyl-THF leading to increased homocysteine levels.

The diagnosis of folate deficiency is based on the measurement of folate levels in serum. It should be noted that red blood cells are enriched in folate and hemolysis can spuriously increase folate levels. In addition, levels may fluctuate with fasting status, use of alcohol, and during pregnancy. In this context, it has been suggested that red blood cell-folate levels are a better surrogate maker of tissue content of folate and a more accurate indicator of folate status. However, comparative studies demonstrated that serum folate levels are equivalent to red blood cell-folate levels. In addition, there are substantial variations in the red blood cell-folate assay. Thus, serum folate is considered the test of choice to determine folate status [23]. Hematologic studies may demonstrate the presence of megaloblastic anemia or macrocytosis. Low folate increases the levels of homocysteine. In comparison to vitamin B12 deficiency, however, the lack of folate does not affect the serum levels of methylmalonic acid.

Treatment

The treatment of folate deficiency is based on the correction of the underlying cause and the supplementation of folate. The dose of folate depends on the cause of the deficiency. In cases of dietary insufficiency, pregnancy, or use of antiepileptics, the recommended dose is 5 mg of folic acid daily for 4 months or until the end of pregnancy. In malabsorptive states, the recommended dose is 15 mg for 4 months. The prophylactic dose for patients with chronic hemolysis and those on dialysis is 5 mg daily to weekly, depending on the diet and estimated rate of hemolysis [23].

Vitamin B12 (Cobalamin) Deficiency

Background

Vitamin B12, or cobalamin, is a cobalt-containing water-soluble vitamin that is present in animal products, including meat, fish, eggs, milk products, and poultry. Vitamin B12 is generally not present in plant derivatives but is enriched in cereals and dietary supplements. The RADA is 2.4 mcg for adults, 2.6 mcg for pregnant women, and 2.8 mcg for breastfeeding women [2].

Metabolism and Physiologic Function

Vitamin B12 is released from food by the acidic environment of the stomach and the effect of gastric proteases. Vitamin B12 binds intrinsic factor produced by parietal cells and the complex vitamin B12-intrinsic factor is absorbed in the terminal ileal mucosa by receptor-mediated endocytosis. Once in the circulation, vitamin B12 binds to transcobalamin II. The complex vitamin B12-transcobalamin II undergoes lysosomal degradation and the released vitamin B12 is converted to its two active metabolites: methylcobalamin and adenosylcobalamin. Methylcobalamin is a cofactor of the *methionine synthase* and its deficiency leads to elevated levels of homocysteine and decreased levels of methionine and tetrahydrofolate (THF). Methionine is then transformed into s-adenosylmethionine, which participates of the methylation of myelin sheaths, DNA, RNA, and lipids. THF, on the other hand, is necessary for the synthesis of purines and pyrimidines (Fig. 2). Adenosylcobalamin is a cofactor of the *L-methylmalonyl-CoA mutase* and its deficiency leads to increased levels of methylmalonic acid (Fig. 1). The accumulation of methylmalonic acid and its precursor, propionic acid, lead to the production of abnormal fatty acids, particularly odd-number fatty acids, which are incorporated into the myelin sheath.

Presentation

Approximately one-quarter of the patients with vitamin B12 deficiency have non-neurologic symptoms resulting from the abnormal synthesis of DNA. The most commonly affected tissues are those with rapid cell turnover, including the bone marrow and gastrointestinal mucosa. Clinically, patients develop megaloblastic anemia, sore tongue, diarrhea, and constitutional symptoms. In comparison, three-quarters of the patient have neuropsychiatric manifestations. These include depression, hallucinations (including frank psychosis also known as megaloblastic madness), paranoia, personality changes, confusion, and cognitive impairment of different degrees. Peripherally, patients may exhibit a predominantly sensory axonal neuropathy with or without demyelination. One of the most pathognomonic features of vitamin B12 deficiency, though not the most common, is the development of subacute combined degeneration. This is a vacuolar myelopathy that affects, primarily, the posterior columns and the lateral corticospinal tracts and results in myelopathic features with ataxia and sensory loss to vibration and proprioception [24]. Approximately 10% of the patients have foci of spongy

degeneration of the optic nerves and optic chiasm leading to optic neuropathy. Other features include white matter changes and degeneration of small unmyelinated axons resulting in autonomic neuropathy [25, 26].

Causes and Diagnosis

Table 1 depicts the most common causes of vitamin B12 deficiency. Laboratory analyses may show megaloblastic anemia or pancytopenia with neutrophil hypersegmentation. However, the hematologic workup can also be normal, even in the presence of neuropsychiatric symptoms. Serologic studies typically show decreased levels of vitamin B12 and elevated levels of methylmalonic acid and homocysteine. It should be pointed out that elevated levels of methylmalonic acid can also be found in renal failure and dehydration. Similarly, elevated homocysteine levels may be found in chronic renal disease, vitamin B6 deficiency, inborn errors of metabolism (including cystathionine beta-synthase, Fig. 2), hypothyroidism, and folate deficiency. Nitrous oxide, normally utilized in anesthesia, can irreversibly modify the cobalt core of cobalamins. These patients may present with normal vitamin B12 levels and elevated homocysteine and methylmalonic acid levels. Thus, normal vitamin B12 levels do not necessarily exclude the possibility of vitamin B12 deficiency at the tissue level. Additional studies may identify the cause of vitamin B12 deficiency. For example, patients with pernicious anemia have elevated anti-intrinsic factor antibody titers, and those with autoimmune gastritis have, in addition, anti-parietal cell antibodies. Furthermore, the presence of elevated serum gastrin levels should raise the question of gastric achlorhydria. The Schilling test, which is no longer available in many institutions, confirms if the vitamin B12 deficiency is due to malabsorption and the possible cause of the deficiency. In this test, patients receive an oral dose of radioactive vitamin B12 which is then measured in urine. The absence of radioactive vitamin B12 in urine indicates lack of absorption at the intestinal level. Then, the study is repeated with intrinsic factor. The presence of vitamin B12 in urine after supplementation with intrinsic factor is suggestive of pernicious anemia [27]. Nerve conduction studies show reduced or absent sensory potentials with decreased conduction velocity characteristic of peripheral neuropathy. The presence of spontaneous fibrillation potentials in electromyography is suggestive of muscle denervation. In addition, MRI of the brain may show bilateral white matter changes in the temporal, parietal, and occipital lobes. MRI of the spine may show increased T2 signal abnormalities in the posterior columns of the spinal cord consistent of swelling and degeneration. These changes are typically seen in the lower cervical and upper thoracic spinal segments extending into the brainstem [28].

Treatment

The treatment is based on the removal or correction of the underlying cause of vitamin B12 deficiency and supplementation with hydroxocobalamin or cyanocobalamin 100 to 1000 mcg intramuscularly daily for 5 days followed by 100 to 1000 mcg intramuscularly each month [29]. Almost 1% of all vitamin B12 ingested orally is absorbed by passive diffusion. Thus, oral supplementation with 1000 mcg per day is sufficient to meet the average daily requirements of vitamin B12 [30••, 23]. It should be pointed out that the supplementation with folate may correct the hematologic defect delaying the diagnosis of vitamin B12 deficiency and allowing the progression of the neuropsychiatric manifestations [22].

Vitamin D Deficiency

Vitamin D is a fat-soluble vitamin that is primarily synthesized in the skin during exposure to solar ultraviolet B radiation (UVB). It can also be absorbed through diet and supplements. There are two bioequivalent forms of vitamin D which are called vitamin D3, or cholecalciferol, and vitamin D2, or ergocalciferol. Vitamin D2 and vitamin D3 are also present in plant-based diets (mushrooms, yeast, soy) and animal-based protein diets (fish oil, eggs, liver, butter), respectively. Vitamin D is essential in maintaining circulating concentrations of calcium and phosphorous. Thus, vitamin D deficiency presents with skeletal and myopathic manifestations. Multiple studies have linked vitamin D deficiency to non-skeletal processes, including cardiovascular health, depression, cancer, and immune system disorders. From a neurologic stand point, vitamin D deficiency has been associated with migraines, development and disease activity in multiple sclerosis, and seizure control (Table 1). However, whether vitamin D deficiency has an active role in the pathogenesis of these diseases or is a bystander of uncertain significance is still under active investigation [31].

Vitamin E Deficiency

Background

Vitamin E is a fat-soluble vitamin within a family of tocopherols (α, β, γ, and δ) and tocoretinols. α-tocopherol is the most biologically active form in humans and thus vitamin E and α-tocopherol are used synonymously [32]. Dietary intake is the sole source of vitamin E, as this vitamin is not synthetized in the body. Dietary sources of vitamin E include vegetable oils, leafy vegetables, fruits, meats, nuts, and cereals. The RADA of vitamin E is 15 mg per the United

States National Academy of Sciences Food and Nutrition Board [32, 33].

Metabolism and Physiologic Function

The tocopherols are synthesized and stored in plant leaves and seeds; in the human body, it is stored in adipose tissue. As it is a fat-soluble vitamin, vitamin E requires pancreatic enzymes and bile salts to aide in gastrointestinal (GI) absorption in the form of micelles. Chylomicrons transport vitamin E to the liver via the lymphatic system, where vitamin E is incorporated into lipoproteins (usually in very low-density lipoprotein) via α-tocopherol transfer protein (α-TTP) and then secreted into the plasma [34]. Vitamin E is a natural antioxidant and free radical scavenger and, as such, it is thought to protect cellular membranes from lipid peroxidation [35].

Presentation

Vitamin E deficiency in the nervous system presents with a spinocerebellar syndrome and peripheral neuropathy (Table 1) [36]. Differential diagnosis should include diseases that can present with similar findings, including but not limited to posterior fossa tumors, paraneoplastic or drug-related cerebellar degeneration, vitamin B12 deficiency, alcohol abuse, multisystem atrophy cerebellar type, cerebellitis, or hereditary cerebellar atrophy.

Causes and Diagnosis

It is unclear how vitamin E deficiency causes neurologic disease. Neurologic disease was originally thought to be a result of oxidative damage that occurs at low or absent levels of vitamin E; however, the clinical presentation can be heterogeneous and some have argued that the improvement of symptoms with vitamin E replacement does not support this theory [32, 37]. Others have hypothesized that the lack of regulatory functions of vitamin E may be the more likely cause.

As there are many different dietary sources, vitamin E deficiency is rarely caused by dietary restrictions. Instead, it is more commonly associated with conditions causing severe malabsorption and in certain inherited conditions (Table 1) [38–41]. For example, in the genetic syndrome of ataxia with vitamin E deficiency (AVED), absorption of vitamin E is not impacted; however, the ability to store it is [39]. The overall incidence of vitamin E deficiency is unknown but considered rare.

Diagnosis can be made based on serum vitamin E levels; however, this is dependent on the concentration of serum lipids and so may not be an accurate representation [42]. In patients with normal serum lipids, a vitamin E level less than 5 mg/l (0.5 mg/dl) is considered deficient. For patients with elevated serum lipid levels, the effective vitamin E concentration can be calculated by dividing the serum α-tocopherol by the sum of total cholesterol and triglycerides. A normal value is greater than 0.8 [42]. In most patients presenting with neurologic manifestations of vitamin E deficiency, levels are typically undetectable. Supportive studies can include somatosensory evoked potentials that may show a central delay, or nerve conduction studies with an axonal neuropathy.

Treatment

Ultimately, treatment should focus on diagnosing and correcting the underlying cause of the vitamin E deficiency as well as supplementation. Replacement of vitamin E can be oral or intramuscular, and the dose can vary based on the cause of the deficiency [36]. The conversion between different forms of vitamin E is the following: 1 mg of α-tocopherol = 1.49 IU "natural source" D-α-tocopherol = 2.22 IU "all-racemic" DL-α-tocopherol; the doses following are in the form of D-α-tocopherol. For cases caused by malabsorption or cholestasis, 200 to 3600 IU/kg/day is recommended. However, for cases of severe malabsorption, fat-soluble vitamin E replacement may be ineffective and instead larger oral doses or intramuscular administration of a water miscible form (DL-α-tocopherol glycol) may be required. For cases caused by abetalipoproteinemia, 100 to 200 IU/kg/day is recommended. For cystic fibrosis, lower doses of 5 to 10 IU/kg/day are recommended. For cases of ataxia with vitamin E deficiency (AVED), 800 to 3600 IU/kg/day are recommended. Response to treatment is variable and depends on the cause of the deficiency as well as the stage at which the disease is identified [43].

Marchiafava-Bignami Disease

Background

Marchiafava-Bignami disease is a progressive neurologic disorder of selective demyelination of the corpus callosum. It is a very rare disease and current prevalence is unknown. When first described it was lethal, but more recent cases have shown non-fatal outcomes [44].

Metabolism and Physiologic Function

The exact mechanism of the disease is unknown, but it is considered to be of a toxic or nutritional etiology. Histologic studies have demonstrated macrophage infiltration of the affected areas with demyelination and gliosis, primarily affecting the third and fourth layer of the frontal and temporal cortex [45]. Axons tend to be preserved.

Presentation

The hallmark of the neurologic presentation of Marchiafava-Bignami disease is cognitive impairment, though there may be varying degrees and courses of cognitive impairment at presentation (Table 1) [46]. Seizures can be seen and apraxias in the non-dominant hand due to interhemispheric disconnection from corpus callosum demyelination and necrosis have been described [47]. As patients often have a history of alcoholism and malnutrition, other alcohol-related manifestations can also be seen, including behavioral changes, dysconjugate gaze, ataxia, delirium tremens, and sensory neuropathy.

The differential diagnosis should include other vitamin deficiencies commonly seen with alcohol consumption or malabsorption, like thiamine (vitamin B1) and vitamin B12. Neurodegenerative disorders, like Alzheimer's disease and corticobasal syndrome, should also be considered with a more protracted time course. For a more rapid progression, stroke, prion disease, or encephalitis should be considered. Other demyelinating disorders, like multiple sclerosis affecting the corpus callosum, should be considered.

Causes and Diagnosis

Marchiafava-Bignami disease has been strongly associated with chronic alcohol abuse and was initially described in malnourished Italians who drank large amounts of red wine. It can occur rarely in the absence of alcohol use, for example in patients that are severely malnourished [44]. The diagnosis is one based primarily on exclusion of other possible causes of presenting symptoms. On magnetic resonance imaging, symmetric demyelination of the body of the corpus callosum is most commonly seen, though the entire corpus callosum can be involved. Other structures may also be involved, including the optic chiasm, cerebellar peduncles, pons, and deep white matter. Chronically, these areas undergo necrosis and cavitation [46, 47].

Treatment

There are no randomized controlled trials assessing treatment for Marchiafava-Bignami disease given its rarity. Vitamin supplementation with thiamine, vitamin B6, vitamin B12, and folate is typically given. In a review of case reports, early treatment with thiamine significantly reduced the risk of a poor outcome [48••]. The dose of thiamine should be the same as used for Wernicke's disease and should continue for as long as recovery is seen. Some case reports have also described using corticosteroids to reduce edema and suppress demyelination; however, in a meta-analysis, this did not show benefit [48••]. Other possible symptoms on presentation, like seizures, should be controlled. The course of the disease is variable and seems to be dependent on the extent of corpus callosum involvement, with more extensive corpus callosum lesions portending a poor prognosis [46].

Conclusion

There are multiple different causes of nutritional deficiencies, but common ones include diseases of malabsorption and malnutrition. The neurologic presentations of these nutritional deficiencies are varied, but it is vital to recognize the underlying deficiency in order to begin prompt treatment. While there are few randomized controlled trials for many of the treatments of these nutritional deficiencies, expert opinion over years of trial and error have shown that rapid identification and treatment of the deficiency portends better outcomes.

Compliance with Ethical Standards

Conflict of Interest Kristin L. Miller, Gabriela Trifan, and Fernando D. Testai each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• The state of food security and nutrition in the world. Rome: Food and Agriculture Organization of the United Nations; 2019. **This study reports on the current state of food insecurity and nutritional deficiencies across the world today.**
2. Dietary Reference Intakes for thiamine, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington, DC: Institute of Medicine; 1998.
3. Said H. Thiamine. In: Coates PM, Betz JM, Blackman MR, Cragg GM, Levine M, Moss J, et al., editors. Encyclopedia of dietary supplements. 2nd ed. Informa Healthcare: London and New York; 2010. p. 748–53.
4. Osiezagha K, Ali S, Freeman C, Barker NC, Jabeen S, Maitra S, et al. Thiamine deficiency and delirium. Innov Clin Neurosci. 2013;10(4):26–32.
5. Thomson AD, Marshall EJ. The natural history and pathophysiology of Wernicke's encephalopathy and Korsakoff's psychosis. Alcohol Alcoholism (Oxford, Oxfordshire). 2006;41(2):151–8.
6. Wiley KD, Gupta M. Vitamin B1 Thiamine Deficiency (Beriberi). StatPearls 2019.
7. Galvin R, Brathen G, Ivashynka A, Hillbom M, Tanasescu R, Leone MA, et al. EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. Eur J Neurol. 2010;17(12):1408–18. https://doi.org/10.1111/j.1468-1331.2010.03153.x.
8.• Gasperi V, Sibilano M, Savini I, Catani MV. Niacin in the central nervous system: an update of biological aspects and clinical

applications. Int J Mol Sci. 2019;20(4). https://doi.org/10.3390/ijms20040974 **This is a current review of the role of niacin in the central nervous system**.

9. Hegyi J, Schwartz RA, Hegyi V. Pellagra: dermatitis, dementia, and diarrhea. Int J Dermatol. 2004;43(1):1–5.
10. Pellagra and its prevention and control in major emergencies. World Health Organization, United Nations High Commissions for Refugees 2000.
11.• Parra M, Stahl S, Hellmann H. Vitamin B(6) and its role in cell metabolism and physiology. Cells. 2018;7(7). https://doi.org/10.3390/cells7070084 **This is a current review on vitamin B6 metabolism.**
12. Larsson SC, Orsini N, Wolk A. Vitamin B6 and risk of colorectal cancer: a meta-analysis of prospective studies. JAMA. 2010;303(11):1077–83. https://doi.org/10.1001/jama.2010.263.
13. Jia K, Wang R, Tian J. Vitamin B6 intake and the risk of colorectal cancer: a meta-analysis of prospective cohort studies. Nutr Cancer. 2017;69(5):723–31. https://doi.org/10.1080/01635581.2017.1324633.
14. Ebbing M, Bonaa KH, Arnesen E, Ueland PM, Nordrehaug JE, Rasmussen K, et al. Combined analyses and extended follow-up of two randomized controlled homocysteine-lowering B-vitamin trials. J Intern Med. 2010;268(4):367–82. https://doi.org/10.1111/j.1365-2796.2010.02259.x.
15. Pena IA, MacKenzie A, Van Karnebeek CDM. Current knowledge for pyridoxine-dependent epilepsy: a 2016 update. Expert Rev Endocrinol Metab. 2017;12(1):5–20. https://doi.org/10.1080/17446651.2017.1273107.
16. Scott K, Zeris S, Kothari MJ. Elevated B6 levels and peripheral neuropathies. Electromyogr Clin Neurophysiol. 2008;48(5):219–23.
17. Vrolijk MF, Opperhuizen A, Jansen E, Hageman GJ, Bast A, Haenen G. The vitamin B6 paradox: supplementation with high concentrations of pyridoxine leads to decreased vitamin B6 function. Toxicol in Vitro. 2017;44:206–12. https://doi.org/10.1016/j.tiv.2017.07.009.
18. Rasul CH, Das SC. Vitamin B6 supplementation with isoniazid therapy. Trop Dr. 2000;30(1):55–6. https://doi.org/10.1177/004947550003000136.
19. Dalton K, Dalton MJ. Characteristics of pyridoxine overdose neuropathy syndrome. Acta Neurol Scand. 1987;76(1):8–11. https://doi.org/10.1111/j.1600-0404.1987.tb03536.x.
20. Khan KM, Jialal I. Folic acid (folate) deficiency. StatPearls. Treasure Island (FL): StatPearls Publishing LLC; 2019.
21. Blom HJ, Smulders Y. Overview of homocysteine and folate metabolism. With special references to cardiovascular disease and neural tube defects. J Inherit Metab Dis. 2011;34(1):75–81. https://doi.org/10.1007/s10545-010-9177-4.
22. Reynolds E. Vitamin B12, folic acid, and the nervous system. Lancet Neurol. 2006;5(11):949–60.
23. Devalia V, Hamilton MS, Molloy AM. British Committee for Standards in H. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol. 2014;166(4):496–513. https://doi.org/10.1111/bjh.12959.
24. Kumar N. Neurologic aspects of cobalamin (B12) deficiency. Handb Clin Neurol. 2014;120:915–26. https://doi.org/10.1016/B978-0-7020-4087-0.00060-7.
25. Clarke R, Birks J, Nexo E, Ueland PM, Schneede J, Scott J, et al. Low vitamin B-12 status and risk of cognitive decline in older adults. Am J Clin Nutr. 2007;86(5):1384–91.
26. Andres E, Federici L, Affenberger S, Vidal-Alaball J, Loukili NH, Zimmer J, et al. B12 deficiency: a look beyond pernicious anemia. J Fam Pract. 2007;56(7):537–42.
27. Zittoun J, Zittoun R. Modern clinical testing strategies in cobalamin and folate deficiency. Semin Hematol. 1999;36(1):35–46.
28. Klee GG. Cobalamin and folate evaluation: measurement of methylmalonic acid and homocysteine vs vitamin B(12) and folate. Clin Chem. 2000;46(8 Pt 2):1277–83.
29. Carmel R. How I treat cobalamin (vitamin B12) deficiency. Blood. 2008;112(6):2214–21. https://doi.org/10.1182/blood-2008-03-040253.
30.•• Wang H, Li L, Qin LL, Song Y, Vidal-Alaball J, Liu TH. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database Syst Rev. 2018;3:CD004655. https://doi.org/10.1002/14651858.CD004655.pub3 **This is a current systematic review evaluating the evidence for oral versus intramuscular vitamin B12 supplementation for deficiency.**
31. Giustina A, Adler RA, Binkley N, Bouillon R, Ebeling PR, Lazaretti-Castro M, et al. Controversies in vitamin D: summary statement from an international conference. J Clin Endocrinol Metab. 2019;104(2):234–40. https://doi.org/10.1210/jc.2018-01414.
32. Frey R, Brody T. Vitamin E Deficiency. American Society for Clinical Investigation; 2011.
33. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington (DC): Institute of Medicine 2000.
34. Manor D, Morley S. The a-Tocopherol Transfer Protein. Vitamins & Hormones. 2007;76:45-65. https://doi.org/10.1016/S0083-6729(07)76003-X.
35. Ricciarelli R, Argellati F, Pronzato MA, Domenicotti C. Vitamin E and neurodegenerative diseases. Mol Asp Med. 2007;28(5):591–606. https://doi.org/10.1016/j.mam.2007.01.004.
36. Kumar N. Nutritional Neuropathies. The Gale Encyclopedia of Neurological Disorders: E-O. 2017;25(1):900–6.
37. Azzi A. Molecular aspects of medicine. Mol Asp Med. 1978;61:92–103.
38. Phillips JR, Angulo P, Petterson T, Lindor KD. Fat-soluble vitamin levels in patients with primary biliary cirrhosis. Am J Gastroenterol. 2001;96(9):2745. https://doi.org/10.1111/j.1572-0241.2001.04134.x.
39. Genetics Home Reference: TTPA gene. National Institutes of Health. 2019. Available from: https://ghr.nlm.nih.gov/gene/TTPA. Accessed: August 30, 2019.
40. Musunuru K, Pirruccello JP, Do R, Peloso GM, Guiducci C, Sougnez C, et al. Exome sequencing, ANGPTL3 mutations, and familial combined hypolipidemia. N Engl J Med. 2010;363(23):2220–7. https://doi.org/10.1056/NEJMoa1002926.
41. Peretti N, Sassolas A, Roy CC, Deslandres C, Charcosset M, Castagnetti J, et al. Guidelines for the diagnosis and management of chylomicron retention disease based on a review of the literature and the experience of two centers. Orphanet J Rare Dis. 2010;5(1):24. https://doi.org/10.1186/1750-1172-5-24.
42. Horwitt MK, Harvey CC, Dahm JCH, Searcy MT. Relationship between tocopherol and serum lipid levels for determination of nutritional adequacy. Ann N Y Acad Sci. 1972;203(1 Vitamin E and):223–36. https://doi.org/10.1111/j.1749-6632.1972.tb27878.x.
43. Gabsi S, Gouider-Khouja N, Belal S, Fki M, Kefi M, Turki I, et al. Effect of vitamin E supplementation in patients with ataxia with vitamin E deficiency. Eur J Neurol. 2001;8(5):477–81. https://doi.org/10.1046/j.1468-1331.2001.00273.x.
44. Bachar M, Fatakhov E, Banerjee C, Todnem N. Rapidly resolving nonalcoholic Marchiafava-Bignami disease in the setting of malnourishment after gastric bypass surgery. J Investig Med High Impact Case Re. 2018;6:2324709618784318. https://doi.org/10.1177/2324709618784318.
45. Bano S, Mehra S, Yadav SN, Chaudhary V. Marchiafava-Bignami disease: role of neuroimaging in the diagnosis and management of acute disease. Neurol India. 2009;57(5):649–52.

46. Heinrich A, Runge U, Khaw AV. Clinicoradiologic subtypes of Marchiafava-Bignami disease. J Neurol. 2004;251(9):1050–9. https://doi.org/10.1007/s00415-004-0566-1.
47. Berek K, Wagner M, Chemelli AP, Aichner F, Benke T. Hemispheric disconnection in Marchiafava-Bignami disease: clinical, neuropsychological and MRI findings. J Neurol Sci. 1994;123(1-2):2–5. https://doi.org/10.1016/0022-510X(94)90195-3.
48.•• Hillbom M, Saloheimo P, Fujioka S, Wszolek ZK, Juvela S, Leone MA. Diagnosis and management of Marchiafava–Bignami disease: a review of CT/MRI confirmed cases. J Neurol Neurosurg Psychiatry. 2014;85(2):168–73. https://doi.org/10.1136/jnnp-2013-305979 **This is a comprehensive review of imaging-confirmed cases of Marchiafava-Bignami disease and the management approaches taken**.