Vitamin B12 deficiency

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Introduction

This article includes discussion of vitamin B12 deficiency, cobalamin deficiency, and Addison-Biermer disease. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

B12 deficiency may cause an extraordinary variety of progressive neurologic syndromes. In this article, the author describes the well-established manifestations of B12 deficiency as well as more controversial associations with macular degeneration, cerebrovascular disease, and dementia. In addition, although severe B12 deficiency has long been known to cause severe developmental delay, this update includes emerging information suggesting that a relative B12 deficiency may cause a common metabolic syndrome in infancy that is potentially linked to subtle developmental problems.

Key points

- B12 deficiency should be suspected in any patient with otherwise unexplained peripheral neuropathy, myelopathy, optic neuropathy, dementia, ataxia, movement disorder, or psychiatric disturbance.
- Serum B12 level should be determined in any patient with suspected B12 deficiency; abnormal blood cell indices are neither sensitive nor specific for B12 deficiency.
- In cases of borderline low B12 levels, or when B12 deficiency is strongly suspected despite reported normal levels from an automated assay, elevated serum methylmalonic acid and homocysteine levels may confirm a physiological deficiency.
- Daily, high-dose oral B12 supplementation appears as effective as parenteral therapy, and is substantially less costly. A brief parenteral course of therapy may still be needed for patients with significant neurologic signs of B12 deficiency.
- Modest elevations in serum methylmalonic acid and homocysteine levels are common in breastfed infants and may represent a physiologically significant B12 deficiency.

Historical note and terminology

Improvements in histological technique in the late 19th century led to the recognition of pernicious anemia, also called Addison-Biermer disease, as a distinct diagnostic entity with hematologic, gastrointestinal, and neurologic features (Chanarin 2000). Osler, among many others, provided harrowing accounts of the then mysterious and lethal progressive condition (Osler and Bell 1877; Gardner and Osler 1877). The first accurate description of spinal cord pathology associated with certain types of anemia was by Ludwig Lichtheim (Lichtheim 1887). Russell and colleagues coined the term "subacute combined degeneration of the spinal cord" in their definitive study of the neuropathological abnormalities commonly associated with pernicious anemia (Russell et al 1900). In 1926, Minot, Murphy, and Whipple showed that a factor present in calf liver could rapidly restore red blood cell counts in pernicious anemia, and in 1934, they were awarded the Nobel Prize for this discovery. Later efforts by Folker and Todd led to the isolation of the active anti-anemic factor in liver, vitamin B12. Kass has written an excellent short history of the early research on B12 deficiency, a field in which the Nobel Prize has twice been awarded (Kass 1976).

In general, the term "vitamin B12" refers to any of the biologically active molecules related to cyanocobalamin, the form of vitamin B12 originally isolated from the liver.

Clinical manifestations

Presentation and course

Vitamin B12 deficiency typically presents with either hematologic or neurologic signs. A curious feature of the condition is that the hematologic and neurologic signs are frequently dissociated. In fact, in 1 large series the severity of the neurologic deficits correlated inversely with the degree of anemia and macrocytosis (Healton et al 1991). Neurologic deficits are common in vitamin B12 deficiency. In the series of Healton and colleagues, 39% of patients with deficiency had neurologic manifestations, and in almost 80% of these cases, the neurologic symptoms were the sole or dominant manifestation of the deficiency (Healton et al 1991).

Neurologic manifestations. Well recognized neurologic manifestations include peripheral polyneuropathy, myelopathy, optic neuropathy, psychiatric disturbances, and dementia.

Subacute combined degeneration of the spinal cord. This syndrome is so named because it may cause progressive degeneration of both the corticospinal and dorsal column tracts of the spinal cord. Typically, the neurologic syndrome evolves over a period of several months, although in a substantial number of patients the disease takes a more chronic course. The most common early sign is paresthesias, which usually first occurs in the lower extremities. At this early stage there may be no objective abnormalities on the neurologic exam. Later, signs and symptoms of a myelopathy involving the dorsal and lateral columns combined with a peripheral neuropathy may develop. Impaired vibration and joint position sense are found on exam. The patient may be ataxic. Weakness is less common. Spasticity occurred in only 5% of cases in Healton and colleagues' series (Healton et al 1991). Incontinence of bladder or bowel, impotence, or orthostatic hypotension is only infrequently caused by B12 deficiency. These deficits do not necessarily evolve in a stereotyped pattern.

Peripheral polyneuropathy. Vitamin B12 deficiency is a frequently recognized cause of distal symmetric polyneuropathy, and it should be screened for in all patients presenting with polyneuropathy. Although commonly encountered in primary care, vitamin B12 deficiency may also be identified in patients previously deemed as having an idiopathic neuropathy seeking evaluation in a tertiary care center (Farhad et al 2015). Electrodiagnostically, vitamin B12 deficiency causes an axonal neuropathy. Despite the causative relationship between B12 deficiency and neuropathy, baseline B12 levels do not appear to correlate to electrophysiologic markers such as amplitude of responses on nerve conduction studies or nerve conduction velocity (Miles et al 2016).

Uncommon neurologic manifestations. Rarely, B12 deficiency will manifest as a movement disorder, such as parkinsonism, focal dystonia, chorea, or blepharospasm (Pacchetti et al 2002; Ahn et al 2004; Edvardsson and Persson 2010; Sharrief et al 2012). Rarer still are reports of seizures in B12 deficiency (Dogan et al 2012; Naha et al 2012). Several small studies suggest that dysautonomic syndromes, such as orthostatic hypotension, postural orthostatic tachycardia syndrome (POTS), and syncope are associated with B12 deficiency and may be improved by B12 therapy (Beitzke et al 2002; Moore et al 2004; Oner et al 2014). However, dramatic dysautonomia does not appear to be a prominent manifestation of deficiency.

Ophthalmologic manifestations. An unusual but well-documented manifestation of cobalamin deficiency is optic neuropathy. This may present as a subacutely progressive decrease in visual acuity with a cecocentral scotoma (ie, a scotoma obscuring central vision and enlarging the blind spot). B12 deficiency may present with a maculopathy similar to age-related macular degeneration, and it is possible that a relative deficiency may also play a role in age-related macular degeneration (AMD), the most common cause of blindness or low vision in older adults (Doan and Chao 2014). An epidemiological study found an increased risk of AMD in people with B12 deficiency and a reduced risk of AMD in those taking B12 supplements (Gopinath et al 2013). A prospective trial found a modest but meaningful reduction in the incidence of AMD in those treated with a combination of B vitamins, including B12 (Christen et al 2009).

Dementia and neuropsychiatric manifestations. Severe B12 deficiency causes psychiatric and cognitive disturbances in some patients. The abnormalities are not specific and can range from depression or mild memory impairment to global dementia. Usually, these occur along with other neurologic deficits such as a myelopathy or neuropathy. It is uncertain whether mild or moderate B12 deficiency can cause dementia.

Many epidemiological investigations find an association between lower levels of B12 or folate (or elevated blood homocysteine and methylmalonic acid, which are indicators of folate or B12 deficiency) and Alzheimer disease or other

forms of cognitive impairment (Clarke 1998; Wang 2001; Starr et al 2005; Kang et al 2006; Koike et al 2008; Kwok et al 2011). A community-based study of elderly persons similarly showed that serum indices of relative B12 levels were associated with increased risk of progressive brain atrophy over 5 years (Vogiatzoglou et al 2008). Some studies in rodent models of Alzheimer disease demonstrate that both B-vitamin deficiency and hyperhomocysteinemia can increase levels of the amyloid forming peptides A-beta 1-40 and A-beta 1-42, increase levels of beta amyloid plaque, and cause cognitive impairment (Pacheco-Quinto et al 2006; Zhang et al 2009; Zhuo and Pratico 2010).

Despite the suggestive epidemiological and experimental data, no prospective trial has demonstrated that supplementation of the diet with B12 or folate can prevent or delay the onset of Alzheimer disease or other dementia. The cognitive performance of patients with mild or moderate B12 deficiency and dementia usually does not improve with B12 supplementation (Carmel et al 1995; Cunha et al 1995; Kwok et al 1998; Stott et al 2005; Eussen et al 2006; Balk 2007). The VITALS trial randomly assigned 409 patients with clinically diagnosed Alzheimer disease (MMSE scores between 14 and 26) and normal B12, folate, and total homocysteine levels to daily B vitamin supplementation (B12 1 mg, B6 25 mg, folate 5 mg) or placebo, and followed the patients for 18 months (Aisen et al 2008). No effect on the rate of decline of cognitive function was observed.

Modest and inconclusive beneficial effects of B12 supplementation were observed in 2 trials. In an Australian study of the effect of B12, folate, and other randomized interventions on cognitive function in a group of subjects at increased risk for depression, an improvement in some memory tests was observed in those randomized to B12 and folate supplementation (Walker et al 2012). A British group has found that B12 and folate supplementation reduced the rate of brain atrophy in persons with mild cognitive impairment, and this effect was particularly pronounced in those subjects with higher levels of homocysteine at baseline (Smith et al 2010; Douaud et al 2013). The effect on tests of cognition was not reported in detail.

The discrepancy between, on the one hand, repeated findings of an association between indices of relative B12 deficiency and cognitive impairment and, on the other hand, the lack of substantial benefit in therapeutic trials of B vitamin supplementation, is not understood. Most clinical trials have been of relatively short duration, so it is possible that more substantial benefits would be seen with more prolonged therapy (Health Quality Ontario 2013).

Uncommonly, B12 deficiency will present with prominent psychiatric manifestations. Psychosis has been reported several times (Dogan et al 2012).

B vitamins and cerebrovascular disease. Observational studies have found a direct relation between mild or moderately elevated serum homocysteine levels and the risk of both coronary artery and cerebrovascular thrombosis (Verhoef et al 1994; Yoo et al 1998; Remacha 2011). Mild to moderate elevations in homocysteine may also be associated with increased risk for cranial artery dissections (Gallai et al 2001). Cobalamin deficiency, which elevates plasma homocysteine, might, thus, be a cause of otherwise unexplained ischemic stroke or cranial artery dissection (Penix 1998; Whyte et al 2012). Total homocysteine levels are inversely related to the levels of both folate and cobalamin consumed in the diet (Siri et al 1998), but in countries where grain products are fortified with folate, B12 intake may be the major determinant of homocysteine levels (Green and Miller 2005). Thus, cobalamin deficiency might increase the risk of cerebral and myocardial infarction by increasing serum homocysteine levels.

Despite these observational studies, the prospective, blinded, and placebo-controlled VISP, NORVIT, HOPE-2, WAFACS, VITATOPS, and SEARCH trials have all failed to show a significant benefit of high dose B vitamin (including cobalamin) supplementation for preventing thrombotic vascular events or death (Toole et al 2004; Bonaa et al 2006; Lonn et al 2006; Albert et al 2008; Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine Collaborative Group et al 2010; VITATOPS Trial Study Group 2010). These 6 large studies were similar in design. All examined the effect of combined folate and B12 supplementation (most with B6 as well) on the rate of thrombotic vascular events in high-risk subjects. Subjects were recruited from patients with nondisabling cerebral infarction (VISP); myocardial infarction (NORVIT); cerebrovascular, peripheral vascular, or coronary disease or diabetes (HOPE-2); or female health professionals with known cardiovascular disease or vascular disease risk factors (WAFACS), recent stroke or transient ischemic attack (VITATOPS), or myocardial infarctions (SEARCH). Subjects were followed for 24 (VISP), 40 (NORVIT), 60 (HOPE-2), 88 (WAFACS), 41 (VITATOPS), or 80 months (SEARCH). No study demonstrated a significant reduction in the rate of coronary events or stroke. The dose of B12 used in the VISP and NORVIT trials and issues with the design of the VISP trial might have obscured a small but still meaningful benefit to B12 supplementation (Spence 2006). More recently, metaanalysis of patients from 2 large trials revealed that patients with normal kidney function may benefit from B12 supplementation for stroke prevention, whereas patients with impaired

kidney function may not (Spence et al 2017).

Pediatric B12 deficiency. Cobalamin deficiency may occur in infants whose mothers are cobalamin deficient or in those with rare inherited conditions such as Imerslund-Grasbeck syndrome (see Etiology section). Severe cobalamin deficiency in infancy presents as developmental regression. A severe neuropathy may result in "floppy infant" syndrome (Renault et al 1999). Infantile spasms and West syndrome (developmental delay, infantile spasms, and hypsarrhythmia) have been reported (Erol et al 2007; Malbora et al 2014). A number of reports describe myoclonus, tremor, or seizures emerging on initiation of B12 therapy in severely deficient infants. These conditions improve with continued B12 treatment (Grattan-Smith et al 1997; Grech et al 2001; Ozer et al 2001; Benbir et al 2007; Ozdemir et al 2010). However, infants and children who have experienced B12 deficiency may be left with long-term neurologic impairment (von Schenck et al 1997; Yavuz 2008).

A metabolic profile of elevated methylmalonic acid and homocysteine serum levels is common in exclusively breastfed infants, even in wealthy western countries (Greibe et al 2013). This profile typically emerges in the first few months of life. There is debate as to the cause of this profile, but a study demonstrates that B12 supplementation of the infant normalizes this profile, suggesting that B12 deficiency contributes (Bjorke-Monsen et al 2008). Infants with this metabolic profile and with subtle and common signs of delay in motor development clinically improve with B12 supplementation (Torsvik et al 2013).

Non-neurologic manifestations. When present, the hematologic manifestations of B12 deficiency include macrocytic anemia, hyper-segmentation of neutrophil nuclei, neutropenia, and megaloblastic changes in the bone marrow. It should be emphasized that the presence of abnormalities in the peripheral blood is an insensitive indicator of even severe and neurologically symptomatic deficiency (Healton et al 1991; Atay et al 2014). Severe deficiency may cause a thrombotic microangiopathy resembling thrombotic thrombocytopenic purport (TTP) (Noel et al 2013). Uncommonly, B12 deficiency presents primarily with prominent gastrointestinal manifestations. These include glossitis (a "beefy red" tongue). In severe cases, a pan-enteropathy is present with diarrhea and malabsorption of nutrients. The skin may become hyperpigmented. Typically, this is seen on the hands and feet, but it can occur anywhere (Marks et al 1985). Rarely, jaundice occurs due to impaired erythropoiesis (Dasari et al 2012).

Prognosis and complications

Left untreated, pernicious anemia and other causes of severe B12 deficiency are fatal. Fatal cases are marked by severe myelopathy, encephalopathy, or anemia. Neurologic symptoms may not reverse with B12 therapy, so prompt recognition and treatment is needed to avoid permanent disability.

Pernicious anemia is also associated with an increased risk of carcinoid tumors and carcinoma of the stomach (Spoelstra-de Man et al 2000). Endoscopic screening for gastric cancer may be warranted in patients diagnosed with pernicious anemia (Annibale et al 2011).

Clinical vignette

A 41-year-old woman was referred for headaches and numbness in the extremities. She first noted tingling paresthesias approximately 9 months earlier, beginning simultaneously in the feet and hands. She had a history of unilateral pounding headaches since adolescence, but these had been occurring more frequently in the past 3 months, about twice a week. Her past history was notable for hypothyroidism; she had been on replacement therapy since age 25 years. The only medication taken was thyroxin 125 µg daily. On examination, the patient appeared depressed and anxious. Cranial nerve and motor examinations were entirely normal. Vibration sense was reduced in the great toes bilaterally, but sensory examination was otherwise normal. There was mild difficulty with tandem walking but the examiner perceived some possible embellishment. Romberg sign was absent. Tendon reflexes were normal. Laboratory data obtained included normal thyroid stimulating hormone and hemoglobin A1c and negative syphilis serology. Hematocrit and mean cell volume were normal. B12 level was 150 pg/ml (radioimmunoassay). Methylmalonic acid was elevated at 3500 nM/L. The patient was given cyanocobalamin 1 mg intramuscularly daily for 5 days (as an outpatient) then maintained on 1 mg intramuscularly monthly. Her paresthesias and mild gait instability resolved within a month of initiating therapy. Vibration sense returned in the toes. Headaches were unchanged by B12 therapy but reduced in frequency after the patient began taking amitriptyline 50 mg nightly.

Biological basis

Etiology and pathogenesis

Disturbances at any step in cobalamin metabolism may result in actual or functional deficiency, but pernicious anemia accounts for greater than 90% of cases of symptomatic B12 deficiency, and most other symptomatic cases are due to other intrinsic factor-related sources of B12 malabsorption (Carmel 2007). Pernicious anemia is the result of an autoimmune gastritis. The principle antigenic target of this gastritis is thought to be the H/K ATPase of gastric parietal cells. It may be that gastric infection with H. pylori triggers the processes leading to autoimmune gastritis responsible for pernicious anemia (Toh et al 2012). The destruction of parietal cells removes the source of both gastric acid and intrinsic factor. The loss of intrinsic factor markedly reduces the efficiency of B12 absorption from food, which eventually leads to physiologically significant B12 deficiency.

Bariatric surgery is increasingly common and may provide an anatomic and physiologic reason for B12 deficiency. Both purely restrictive (eg, banding) and malabsorptive (eg, Roux-en-Y bypass) procedures increase the risk of B12 deficiency, although the malabsorptive procedures are more likely to do so (Gehrer et al 2010). After gastric bypass, vitamin B12 and pyridoxine deficiency appear to be the second most common nutritional deficiencies following thiamine deficiency (Punchai et al 2017). Thirty percent of patients who have had the Roux-en-y gastric bypass procedure may develop B12 deficiency (Malinowski 2006). Gastrectomy for any reason increases the risk of deficiency because parietal cells, the source of intrinsic factor, are removed. Any pathology of the distal ileum may impair absorption of the intrinsic factor-cobalamin complex. Thus, cobalamin deficiency has been reported with regional enteritis, Whipple disease, ileal tuberculosis, tropical sprue, and surgical resection of the distal ileum, among other conditions.

Severe cobalamin deficiency less commonly results from other disturbances. Nutritional deficiency is common in vegans (Krajcovicova-Kudlackova et al 2000; Herrmann et al 2001; Gilsing et al 2010; Pawlak et al 2013). Perhaps the most common cause of low B12 (but not symptomatic deficiency) is the condition known as “food-cobalamin malabsorption,” in which B12 in food is absorbed poorly but the crystalline B12 in vitamin pills is well absorbed (Carmel et al 2001). Food-cobalamin malabsorption is associated with type B atrophic gastritis, a common condition itself associated with *Helicobacter pylori* infection.

Nitrous oxide irreversibly oxidizes the cobalt in cobalamin. Thus, a functional deficiency of cobalamin can be created by the inhalation of nitrous oxide, a common anesthetic agent and recreational drug.

Several inherited conditions can cause actual or functional B12 deficiency. The Imerslund-Grasbeck syndrome is a rare inherited condition characterized by a specific deficiency in cobalamin absorption and proteinuria. The syndrome can be caused by mutations in either of the 2 proteins, “cubulin” and “amnionless,” which are needed for in cobalamin absorption from the ileum. Mutations in the gene for intrinsic factor can also cause hereditary cobalamin deficiency but without proteinuria (Tanner et al 2005; Tanner et al 2012). Various inherited defects in the synthesis of the biologically active forms of B12, adenosylcobalamin and methylcobalamin, from ingested cobalamin substrate are referred to as cobalamin diseases A-H. These usually present in infancy. However, neurologic and psychiatric presentations of cobalamin C disease have been described in adolescents and adults (Roze et al 2003).

Cobalamin is a complex molecule at the core of which is a corrin ring: a tetrapyrrole structurally homologous to heme but with a cobalt atom, rather than iron, at its center (Stryer 1995). Cobalamin is known to participate in only 2 enzymatic reactions in humans. First, it is a cofactor for the conversion of homocysteine to methionine. Second, it is essential for the conversion of methylmalonyl-CoA to succinyl-CoA. In states of cobalamin deficiency, homocysteine and methylmalonic acid levels rise in the blood. How impairment of the 2 cobalamin dependent reactions leads to the particular syndromes associated with deficiency is not completely understood. The hematologic and gastrointestinal abnormalities in cobalamin deficiency are similar to those of isolated folate deficiency and are generally attributable to impairment of DNA synthesis in the rapidly dividing cells of the gastrointestinal tract and bone marrow. Cobalamin is not known to participate in DNA synthesis, but folate, as 5,10-methylene tetrahydrofolate, is essential for the synthesis of purines. The failure of methionine synthesis due to cobalamin deficiency may either (1) lead to an accumulation of 5-methyl-tetrahydrofolate, trapping folate in a chemical form unusable in purine synthesis (the "folate trap" hypothesis) or (2) impair methylation reactions needed to produce formyl-tetrahydrofolate, a precursor to 5,10-methylene tetrahydrofolate. Whatever the mechanism, the impairment of DNA synthesis can be circumvented by the administration of sufficient amounts of exogenous folate. Thus, the hematologic and gastrointestinal effects of

cobalamin deficiency are reversed by folate supplementation.

In contrast, it would appear that the neurologic effects of cobalamin deficiency are due to metabolic disturbances unrelated to purine synthesis because the neurologic deficits may develop independently of the hematologic abnormalities, and folate supplementation will not prevent or reverse these deficits. The exact mechanism of neurologic damage in B12 deficiency remains obscure, but disruption of normal myelin function appears important. One hypothesis is that impaired methionine synthesis leads to a depletion of S-adenosylmethionine, required for the synthesis of myelin phospholipids. Alternatively, accumulated methylmalonate and methylpropionate, precursors of the cobalamin dependent synthesis of succinyl-CoA, may be incorporated abnormally into branched-chain fatty acids, resulting in abnormal myelination (Green and Kinsella 1995).

Humans are completely dependent on dietary sources for cobalamin, with a minimum daily requirement of about 2.5 µg and a recommended intake of 6 µg daily. A typical American diet provides about 20 µg daily. Virtually all dietary cobalamin comes from meat or dairy products. Vegan diets can lead to cobalamin deficiency, and no vegetable product is a reliable source of biologically active cobalamin, although data suggest that the edible seaweed used for wrapping sushi (“mori” or purple laver) may contain significant amounts of biologically active B12 (Watanabe et al 2000; Croft et al 2005). In the absence of any cobalamin absorption, physiologic deficiency may not develop for 2 to 5 years because the liver stores about 3 mg of the vitamin.

Efficient absorption of dietary cobalamin requires several steps. Cobalamin in food is transferred to proteins produced in saliva known as "R binders” (salivary haptocorrins) in the low pH environment of the stomach. The higher pH of the duodenum then promotes the transfer of cobalamin to intrinsic factor, a protein produced by gastric parietal cells. The cobalamin-intrinsic factor complex travels to the ileum, where cells bearing specific receptors take up the complex. In the blood, transcobalamin II is the physiologically important cobalamin transporter, but other proteins, mainly transcobalamin I, bind about 70% of serum cobalamin. In pernicious anemia, a chronic autoimmune gastritis leads to the destruction of parietal cells and an absence of intrinsic factor. Because parietal cells secrete hydrogen ions as well as intrinsic factor, patients with pernicious anemia have gastric achlorhydria. Medications are not an uncommon etiology of vitamin B12 deficiency. Proton pump inhibitors and other acid lowering agents have been implicated, as they cause iatrogenic gastric achlorhydria. A large meta-analysis of studies of patients with proton pump inhibitor or H2-receptor blocking agents showed an odds ratio of 1.68 to develop vitamin B12 deficiency (Jung et al 2015). An additional medication that may drive vitamin B12 deficiency is metformin.

Diabetics on metformin are at risk for B12 deficiency because the drug impairs B12 absorption. The mechanism of this effect is debated (Ting et al 2006; Andres and Federici 2007). Several randomized, placebo-controlled trials indicate that metformin therapy leads to a progressive decline in B12 levels and can cause physiologically significant deficiency (Liu et al 2014). Patients randomized to metformin therapy in the Diabetes Prevention Program Outcome Study were more likely to show vitamin B12 deficiency or borderline B12 levels (Aroda et al 2016). Despite this risk, many patients on metformin are not checked for B12 deficiency, even when they have possible signs of deficiency, such as peripheral neuropathy (Pierce et al 2012).

The relationship between metformin exposure and B12 deficiency remains somewhat ill-defined. A cross-sectional controlled study found no significant mean B12 level difference between diabetic or nondiabetic patients whether they had been treated with metformin or were treatment-naïve (Rodriguez-Gutierrez et al 2017). Further, diabetics on metformin found to have B12 deficiency may be at no higher risk of developing neuropathy (Pan et al 2017). Nonetheless, peripheral polyneuropathy in a diabetic on metformin should not be assumed to be due to diabetes without checking a B12 level. Routine B12 supplementation in patients on metformin therapy is not currently the standard of care (Yan and Khalil 2017).

Conflicting evidence links chronic levodopa therapy in patients with Parkinson disease to an increased risk of symptomatic B12 deficiency, perhaps because carbidopa metabolism through the catechol-O-methyl transferase pathway may deplete B12-dependent cofactors (Rajabally and Martey 2011; Ceravolo et al 2013; Muller et al 2013). Patients receiving continuous enteral levodopa infusions may be particularly at risk (Muller et al 2013; Merola et al 2014). Checking B12 levels may be worthwhile prior to instituting levodopa therapy and periodically in patients under chronic treatment.

The most prominent neuropathological abnormalities in subacute combined degeneration are found in the spinal cord. Early descriptions of the disease emphasized demyelination, but in fact, degeneration of both myelin and axons is

found (Duchen 1992). Glial scarring is generally not prominent, except in cases where symptoms have been longstanding. Cerebral abnormalities are generally mild with scanty areas of perivascular demyelination and fusiform axonal swelling. In the peripheral nervous system, the histopathology is less well characterized. Some have noted a loss of myelinated fibers.

Epidemiology"

The overall incidence or prevalence of symptomatic vitamin B12 deficiency is unknown. A number of studies have documented a high frequency of B12 deficiency in certain groups. The largest such group in the United States is probably the elderly, with rates of laboratory diagnosed deficiency near 15% in some studies.

Both vegans (those whose diets contain no animal products) and vegetarians (diets containing dairy or eggs but no meat) have high rates of B12 deficiency (Herrmann et al 2001; Gilsing et al 2010; Pawlak et al 2013; Rizzo et al 2016). Of particular concern are the breastfed infants of vegetarian or vegan mothers and children on vegetarian or vegan diets (Centers for Disease Control and Prevention 2003). Other groups at high risk include those with HIV infection and AIDS, as well as certain populations outside the United States where malnutrition and intestinal parasitism may play a role (Antony 2003). Persons with Crohn disease, particularly those who have had an ileal resection, are at increased risk of B12 deficiency (Bermejo et al 2013).

Folate supplementation will normalize the blood abnormalities in B12 deficiency and thereby erase the hematologic signs of the condition (see section on Pathogenesis and pathophysiology). However, most patients with neurologic signs of B12 deficiency do not have readily detectable abnormalities of the blood (Healton et al 1991). (The study by Healton and colleagues demonstrating this was done before grain fortification was mandated in the United States.) It is also worth noting that the cost of obtaining a B12 level is about the same as that of an automated complete blood count. Therefore, the clinician needs to be aware of the neurologic signs of B12 deficiency and specifically seek evidence for this diagnosis if it might explain a patient's condition, rather than waiting for evidence of B12 deficiency to turn up on a complete blood count ordered for other purposes.

Prevention

In those at risk (see Epidemiology section for a description of risk groups), B12 deficiency can be prevented through oral supplementation with the vitamin (see Management section). It is particularly important to be alert to possible B12 deficiency in pregnant and breastfeeding women because of the potential for irreversible neurologic injury to the child.

Differential diagnosis

The neurologic manifestations of B12 are not specific, and other causes of subacute to chronic neuropathy, myelopathy, or both will need consideration depending on the clinical scenario. Prominent among conditions causing myelopathy in particular would be multiple sclerosis, HTLV-1 associated myelopathy, Lyme disease, neurosyphilis, and HIV infection. In cases where peripheral neuropathy is the presenting feature, evaluation for common causes, such as impaired glucose metabolism and monoclonal gammopathy, is wise. As described below, nitrous oxide causes a clinical syndrome indistinguishable from other forms of vitamin B12 deficiency. As such, clinicians may wish to obtain history regarding nitrous oxide exposure or abuse. Additionally, the hematologic and gastrointestinal signs of B12 deficiency can be mimicked by folate deficiency (Donnelly and Callaghan 1990; Ravakhah and West 1995). A deficiency of B12 transport in the blood is reported to have caused subacute combined degeneration in the presence of normal B12 levels measured in the serum (Reynolds et al 1993).

Although rare, copper deficiency is increasingly recognized to present with a syndrome very similar to subacute combined degeneration (Kumar et al 2004; Jaiser and Winston 2010). The increasing recognition of copper deficiency may be due to rising rates of bariatric surgery. Upper gastrointestinal surgeries are a major risk factor for this condition. Another cause is excessive consumption of zinc, which until recently was found in high quantities in dental adhesives (Jaiser and Winston 2012).

Diagnostic workup

Evaluation of possible B12 deficiency should begin with measurement of the serum cobalamin level. Usual lower limits of normal are 170 ng/L (111 pM/L) for the radioimmunoassay and 250 ng/L (184 pM/L) for the chemiluminescent assay.

However, neurologically significant deficiency may occur with low normal levels measured in the serum. Serum cobalamin levels do not strictly correlate with physiologic deficiency in part because assays measure total serum cobalamin, yet the transcobalamin II bound fraction (holotranscobalamin II) is physiologically most important. Certain conditions, such as liver disease, can increase serum haptocorrins, thereby increasing total serum cobalamin, even with relatively low levels of cobalamin bound to transcobalamin II (Snow 1999). Holotranscobalamin II levels can be assessed, but this measurement is not yet shown to be superior to the serum cobalamin level as the first step in detecting true B12 deficiency (Goringe et al 2006; Nilsson et al 2004; Valente et al 2011; Carmel 2012).

In cases with borderline serum cobalamin levels, measuring serum homocysteine and methylmalonic acid levels may clarify the situation. Methylmalonic acid is somewhat more sensitive than homocysteine as an indicator of cobalamin deficiency, but some B12 deficient patients will have an isolated elevation of homocysteine (Goringe et al 2006). What levels of methylmalonic acid or homocysteine are definitely pathologic is difficult to define. Traditionally, greater than 3 standard deviations above the mean is considered elevated, but levels less elevated than this will often decline in patients supplemented with cobalamin or folate, perhaps indicating a relative deficiency of these vitamins. The greater than 3 standard deviation cutoff for serum methylmalonic acid is generally around 350 nM/L and for homocysteine is 15 µM/L (20 µM/L in patients over age 60). A practice guideline by the American Academy of Neurology recommends measuring methylmalonic acid or homocysteine levels in patients with unexplained distal symmetric polyneuropathy and low normal B12 levels (England et al 2009). Little evidence of the efficacy of B12 therapy in such patients exists, but a retrospective case series found that 10 of 23 patients with neuropathy, low normal B12, and elevated methylmalonic acid levels improved with B12 supplementation (Nardin et al 2007).

Diagnosis is further complicated by the fact that certain automated assays may indicate false normal, or even elevated, B12 levels in patients with high levels of anti-intrinsic factor antibodies, and such antibodies are found in 70% of patients with pernicious anemia (Carmel 2012; Yang and Cook 2012; Stabler 2013). If a patient's clinical situation strongly suggests B12 deficiency, methylmalonic acid or homocysteine levels should be determined, even if the lab reports a normal or even high B12 level.

Abnormal blood indices are insensitive signs of neurologically significant B12 deficiency (Healton et al 1991). Hypersegmentation of neutrophil nuclei can be a sensitive indicator of B12 or folate deficiency, but this finding is easily missed on routine examination of the blood smear. Megaloblastic changes in the bone marrow are usually seen in B12 deficiency, even in the absence of abnormalities in the indices of circulating erythrocytes.

Cobalamin deficiency should not be assumed to be due to pernicious anemia (autoimmune destruction of parietal cells resulting in intrinsic factor deficiency). The Schilling test was previously used to investigate and clarify the cause of deficiency. This test relied on radiolabeled cobalamin to track defects in absorption. Unfortunately, the Schilling test is currently unavailable in the United States (Carmel 2007). The diagnosis of pernicious anemia can be made if anti-intrinsic factor antibodies are present in the serum (Carmel 2007). This test is specific but lacks the sensitivity of the Schilling test. In practice, B12 supplementation is the appropriate treatment for virtually all forms of B12 deficiency. Nevertheless, it is important to keep in mind that B12 deficiency may be the first sign of otherwise overlooked abnormalities of the gut.

Other tests yield nonspecific abnormalities in B12 deficiency. MRI may show regional hyperintensities in the affected tracts or structures on T2-weighted images, but the sensitivity of MRI for detecting signs of B12 deficiency is low (Jain et al 2014). Typically, these are found in the posterior columns, but abnormalities may be found in the cerebral white matter and rarely in other locations, such as the globus pallidus (Chatterjee et al 1996; Larner et al 1997; Sharrief et al 2012). In a population-based cohort study, the burden of white matter MRI T2 hyperintensities correlated with biochemical indices of relative B12 deficiency, even when these indices were in the widely accepted normal range (de Lau et al 2009). In infants, the scan may show delayed myelination (Grattan-Smith et al 1997). Fine and colleagues, referring to the electrophysiology of patients with B12 deficiency, state that "motor and sensory axonopathy is the physiologic signature of vitamin B12 deficiency in the peripheral nervous system" (Fine et al 1990). In their study of 10 patients, evidence of denervation was greater in sensory axons than motor axons and was more severe distally than proximally. Conduction velocities were normal. They also found abnormal sensory evoked responses with prolonged L3-P27 intervals (indicating slowed conduction between the cauda equina and the somatosensory cortex of the brain). Visual-evoked responses were normal, but others have reported visual-evoked response abnormalities in patients with subacute combined degeneration, even in the absence of visual symptoms (Hennerici 1985).

Management

The neurologic deficits caused by B12 deficiency are not always reversible. Therefore, it is important that if B12 deficiency is thought to be the cause of neurologic deficits, B12 replacement therapy be begun as soon as possible after blood has been taken for diagnostic tests. Traditionally, this initial therapy has consisted of 4 to 7 daily parenteral (usually intramuscular) injections of 1000 µg of cobalamin. The reasoning has been that B12 stores can be repleted faster and more surely by parenteral administration than by the oral route. This initial therapy is then traditionally followed by monthly injections of 1000 µg of cobalamin.

In fact, the pharmacologic superiority of parenteral B12 to oral supplementation with large doses of cobalamin has never been demonstrated. In the absence of intrinsic factor, the gut absorbs about 1% of ingested cobalamin, and this appears to be true even in patients with diseases of the ileum. A number of studies have compared the effect of oral and parenteral cobalamin (Ross et al 1954; Kuzminski et al 1998; Bolaman et al 2003). In these studies, large doses (2 to 3 mg) of daily oral B12 appear equally effective to daily parental cobalamin 1 mg in rapidly restoring cobalamin stores and treating the signs of deficiency. Even in patients with inflammatory bowel diseases such as Crohn disease, oral supplementation of B12 appears effective (Gomollon et al 2017). A study in children found that an oral dose of 1 mg daily was effective in children under 2 years of age, but suggested that 2 mg daily would be indicated for children greater than 6 years of age (Bahadir et al 2014). Oral vitamin B12 replacement is inexpensive and substantially less costly and more convenient for most patients than parenteral therapy (BC Guidelines and Protocols Advisory Committee 2012; Masucci and Goeree 2013).

None of the studies cited above included large numbers of patients with neurologic deficits, although significant improvement occurred in orally treated patients with such deficits. The neurologic deficits included in these studies tended toward mild sensory phenomena rather than severe myelopathic manifestations. In the absence of more data, it would seem prudent to at least initiate therapy with at least 1 intramuscular injection of 1000 µg. This could then be followed by several weeks of very high dose oral therapy (2 mg cobalamin daily). Thereafter, daily doses of 1 mg of cobalamin should maintain adequate body B12 stores, even in cases of pernicious anemia.

Whether oral or parenteral maintenance therapy is chosen, it is crucial that efficacy is monitored initially by clinical improvement. Sustained correction of B12 deficiency should be checked annually by serum B12, methylmalonic acid, or total homocysteine levels (Carmel 2008). Pernicious anemia requires lifelong treatment, and studies have shown substantial rates of noncompliance with B12 supplementation (Carmel 2007).

Special considerations

Pregnancy

Maternal B12 deficiency or borderline deficiency presents 2 major risks to the developing fetus and infant. First, B12 deficiency may increase the risk of neural tube defects (Kirke et al 1993; Ray et al 2007; Thompson et al 2009). Second, neurologic and hematologic manifestations of B12 deficiency may occur in infants breast fed by mothers who have subnormal stores of cobalamin (Grattan-Smith et al 1997; Hinton et al 2010). The placenta avidly procures cobalamin for the fetus so deficiency does not usually manifest until infancy, usually within the first year. B12 deficiency in infants may cause irreversible developmental impairment. Infants of mothers on vegan or vegetarian diets are at significant risk of B12 deficiency unless the mother takes supplementary B12. Two studies found an increased risk of puerperal cerebral venous sinus thrombosis in mothers with hyperhomocysteinemia. These studies were performed in countries where maternal malnutrition is likely more prevalent than it is in the industrialized west. In both studies, a lack of dietary folate, rather than B12 deficiency, seemed to be the cause of the hyperhomocysteinemia (Cantu et al 2004; Nagaraja et al 2008).

Anesthesia

The anesthetic agent nitrous oxide irreversibly inactivates cobalamin. Typical neurologic symptoms of B12 deficiency may develop over a few days or weeks after a single exposure to nitrous oxide in patients with borderline or deficient stores of vitamin B12 (Green and Kinsella 1995). This condition should be promptly treated with parenteral B12 or permanent neurologic damage may occur. Symptoms of B12 deficiency will also develop in some who chronically use nitrous oxide as a recreational drug, even in the absence of B12 deficiency (Layzer et al 1978). A study suggests that nitrous oxide-mediated B12 deficiency may lead to an acute prothrombotic state by elevating homocysteine levels

(Badner et al 2000). Ninety patients undergoing endarterectomy were randomized to anesthesia with or without nitrous oxide. Postoperative homocysteine levels were higher in the patients randomized to nitrous oxide anesthesia, and ischemic signs on the ECG were significantly more frequent in this group. Preoperative vitamin supplementation with B12 can prevent the nitrous oxide-induced elevation in homocysteine levels (Badner et al 2001; Kiasari et al 2014).

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**References especially recommended by the author or editor for general reading.

Former authors

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ICD and OMIM codes

ICD codes

ICD-9:
Subacute combined degeneration of the spinal cord in conditions classified elsewhere: 336.2

Vitamin B12 deficiency: 266.2

ICD-10:
Subacute combined degeneration of spinal cord in diseases classified elsewhere: G32.0
Deficiency of other specified B group vitamins: E53.8

Profile

Age range of presentation

0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

Sex preponderance

male=female

Family history

family history may be obtained

Heredity

heredity may be a factor

Population groups selectively affected

none selectively affected

Occupation groups selectively affected

none selectively affected

Differential diagnosis list

conditions that present with a subacute to chronic neuropathy or myelopathy
multiple sclerosis
HTLV-1 associate myelopathy
Lyme disease
neurosyphilis
HIV
copper deficiency
folate deficiency

Associated disorders

Alcohol-tobacco amblyopia
Cerebral vascular disease
Dementia
Depression
Developmental delay
Folate deficiency
Gastric resection

Glossitis
Imerslund-Grasbeck syndrome
Malabsorption
Megaloblastic anemia
Myelopathy
Optic neuropathy
Pernicious anemia
Polyneuropathy
Regional enteritis
Subacute combined degeneration of the spinal cord

Other topics to consider

Crohn disease: neurologic manifestations
Copper deficiency myeloneuropathy
Folic acid deficiency
Hyperhomocysteinemia
Methylmalonic acidemia
Nutrition and the brain
Nutrition-related peripheral neuropathies
Toxic and nutritional deficiency optic neuropathies

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