Late Life Vitamin B12 Deficiency

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KEYWORDS

• Vitamin B12 • Elderly patients • Anemia

KEY POINTS

- Vitamin B12 deficiency can present with a wide array of symptoms, and, if unrecognized, lead to significant morbidity especially with regard to the hematologic and neurologic complications.
- Vitamin B12 is far more prevalent in the elderly population than in the general population.
- In particular, the elderly are at higher risk of vitamin B12 deficiency due to higher incidence of polypharmacy, pernicious anemia and food cobalamin malabsorption.

INTRODUCTION

Vitamin B12 deficiency may present with a wide array of symptoms and, if unrecognized, lead to significant morbidity particularly in terms of the hematologic and neurologic complications. This is of particular concern in the elderly because of its high prevalence with advancing age and the enhanced difficulty of recognizing subtle changes in symptoms and distinguishing those from normal aging.

In general, vitamin B12 is available only through the consumption of animal products, including meat, eggs, and dairy. Once vitamin B12 is consumed, it is bound to R protein present in saliva and gastric secretions. Subsequently, intrinsic factor, which is produced by the parietal cells of the stomach, binds to vitamin B12, until it is reabsorbed by the distal ileum.[1]

Once bioavailable, vitamin B12 is used for purine and pyrimidine synthesis and subsequent formation of DNA; deficiency of vitamin B12 can result in arrest in the S phase of cellular division inhibiting further replication.[2] Metabolically, vitamin B12 is required to synthesize methionine from homocysteine in the methionine cycle and in the conversion of methylmalonyl coenzyme A to succinyl coenzyme A.[3] In these pathways, B12 deficiency leads to increases of methylmalonic acid (MMA) and homocysteine.

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The daily requirement of B12 consumption recommended by the US Food and Drug Administration and the Institute of Medicine is 2.4 μg/d[4] for adults, and 2.0 μg/d after 50 years of age.[4] Typical consumption by the average American exceeds this value.[4] Once consumed it is stored hepatically (with stores as high as 1.5 mg); these stores can supply sufficient vitamin B12 for metabolism for 5 to 10 years before deficiency manifests.[5,6]

The elderly have a higher prevalence of B12 deficiency than the general population.[4] Possible reasons for this include decreased gastrin and subsequent decreased gastric acidity, and the increased use of medications that decrease B12 absorption. However, thus far, the available evidence to support these mechanisms has been conflicting.[4]

COBALAMIN (VITAMIN B12) DEFICIENCY

Vitamin B12 (cobalamin) deficiency in the elderly is likely to be more frequent than commonly appreciated. Data from the Framingham study showed that 12% of community-dwelling elderly were cobalamin deficient.[7] Other studies report that as many as 30% to 40% of sick or institutionalized elderly are cobalamin deficient.[8] In one large series from France, nearly 5% of hospitalized patients between the ages of 65 and 98 years were cobalamin deficient.[1] A study in Georgia in 2010 evaluated the prevalence of B12 deficiency (defined as <258 pmol/L) in patients of various ethnic background aged 80 to 89 and greater than 98 years. Among this geriatric population not receiving vitamin B12 replacement, the centenarians were found to have a higher prevalence of B12 deficiency at 35% versus 23% among octogenarians.[9] The KORA-Age study evaluated 1079 residents in the city of Augsburg, Germany and found that 27% of participants (aged 65–93 years) demonstrated laboratory evidence of vitamin B12 deficiency (defined as <221 pmol/L). The prevalence of B12 deficiency among those participants aged 85 to 93 years was significantly higher, at 38%.[10]

The mechanism accounting for anemia in community-dwelling elderly (those 65 years and older) was examined by Guralnik and associates from data derived in the NHANES III study.[11] In that large dataset, 11% met the WHO criteria for anemia (hemoglobin <12 g/dL for women and <13 g/dL for men). Of these, iron deficiency accounted for 16.6%, whereas B12 deficiency accounted for 5.9%. The combination of folic acid and B12 deficiency added another 2%. Unexplained anemia (See William B. Ershler's article, "Unexplained Anemia in the Elderly," in this issue) accounted for approximately one-third of the observed anemia in the population sampled.

CLINICAL MANIFESTATIONS

The clinical presentation of vitamin B12 deficiency is manifold but primarily presents with neurologic or hematologic abnormalities. The hematologic manifestations can be diverse, including leukopenia, anemia, and thrombocytopenia. The neurologic manifestations often present as distal peripheral neuropathy but can be as severe as subacute combined degeneration of the dorsal columns or cerebellar symptoms.[1] Less common manifestations include glossitis, atrophy of the skin, or seemingly unrelated symptoms such as dementia and venous thrombosis due to hyperhomocysteinemia.[5,12,13]

Adding to the subtlety of the diagnosis, consideration of B12 deficiency in patients who present without anemia is important. For example, Healton and colleagues[14] found that 21% of the 147 B12-deficient patients who had been referred for neurologic symptoms over a 17-year period were not anemic. In another observational cohort

that included 201 patients evaluated at a single institution, nearly half reported neurologic or psychiatric symptoms at the time of diagnosis and 28% had no hematologic abnormalities.[15]

Furthermore, a recent study of 165 Taiwanese patients, median age 76 years, with mild to moderate Alzheimer dementia on cholinesterase inhibitors found an inverse correlation between vitamin B12 levels and progression of dementia.[12] It is hypothesized that vitamin B12 may play a role in dementia as deficiencies are associated with a loss of white matter of the brain and spinal cord. One theory suggests that insufficient B12 leads to defective methylation of myelin basic protein.[12] However, supplementation of vitamin B12 has not yet demonstrated improvement in Alzheimer dementia.[16]

DIAGNOSIS

The evaluation of vitamin B12 deficiency begins with testing a serum vitamin B12 level. Macrocytic anemia supports a suspected diagnosis of B12 deficiency, although it is not essential, as mentioned earlier. Typically, the mean corpuscular volume begins to increase once the vitamin B12 level is <200 ng/L.[3] By contrast, MMA and homocysteine levels are both more sensitive and specific for the diagnosis of B12 deficiency.[3] A Mayo Clinic series of 72 patients found increased MMA levels in a patient with a B12 level of 400 ng/L (295 pmol/L).[3]

According to the study of Andrès and colleagues,[1] the definition of cobalamin deficiency is a serum cobalamin level less than 150 pmol/L on 2 separate occasions or a serum cobalamin level less than 150 pmol/L and a total serum homocysteine level greater than 13 μmol/L, or a methylmalonic acid greater than 0.4 μmol/mL, in the absence of renal failure or folate and B12 deficiency. However, as pointed out by Solomon,[17] there is considerable uncertainty about the diagnostic criteria and probably no single laboratory value is sufficient.

Of note, there is some evidence to suggest that significantly increased titers of intrinsic factor antibodies may result in falsely normal serum cobalamin levels.[18] Therefore, a high index of suspicion should prompt additional testing for vitamin B12 deficiency despite an apparently normal serum level. In addition, there are conditions that have been associated with falsely low B12 levels, including folate deficiency, pregnancy, and transcobalamin deficiencies; these should be considered when diagnosing true deficiency.[3,19]

There is a third assay, the holotranscobalamin, that is more sensitive than a serum vitamin B12 level. In contrast to the serum vitamin B12 assay, which evaluates the combined active and inactive forms of vitamin B12, the holotranscobalamin evaluates the active portion of the vitamin.[19]

ETIOLOGY

There are multiple causes of vitamin B12 deficiency to be considered. Mild B12 deficiency is often caused by drugs that interrupt the normal absorption of vitamin B12, such as metformin, H2 inhibitors, and proton pump inhibitors.[1,2] Of note there is some controversy as to whether metformin results in actual vitamin B12 deficiency or only a low serum vitamin B12 level while not affecting intracellular vitamin B12 levels.[20,21] Similarly, vegan diets may result in vitamin B12 deficiency, although it typically takes several years of compliance with a vegan diet for this to manifest. A more severe B12 deficiency is observed when there is an inability to absorb B12, such as in pernicious anemia or gastrectomy, in which the production of intrinsic factor is diminished, or ileal resection,[2] in which the distal absorption of B12 is affected. Rarer

causes of B12 deficiency include inflammatory diseases of the ileum, pancreatic exocrine deficiency, and *Diphyllobothrium latum* parasitic infection.[1]

In particular, the elderly seem to be at higher risk for pernicious anemia and food cobalamin malabsorption.[1,22] Food cobalamin malabsorption is characterized by the inability to release cobalamin from food or from intestinal transport proteins, particularly in the presence of hypochlorhydria. This syndrome is defined by the presence of cobalamin deficiency despite adequate dietary intake. In this type of malabsorption, the Schilling test,[23] which uses the oral administration of crystallized vitamin B12, will be normal. The cause of food cobalamin malabsorption is predominantly gastric atrophy, which is far more prominent in the elderly. Over 40% of patients who are more than 80 years of age have gastric atrophy, which may or may not be related to *Helicobacter pylori* infection.[1] The causes of B12 deficiency in the elderly (and the approximate frequency with which they occur) are shown in **Box 1**. Other factors that contribute to food cobalamin malabsorption are shown in **Box 2**.

CLINICAL APPLICATION AND TREATMENT

The British Committee for Standards in Hematology has incorporated the aforementioned data into an algorithmic format to assist the practitioner with specific guidelines for the workup and treatment of vitamin B12 deficiency. If a vitamin B12 level is checked for nonspecific symptoms (ie, without clear evidence of neuropathy, glossitis, or anemia), and without significant laboratory abnormalities and results <150 ng/L (110 pmol/L), the patient should undergo investigation and treatment for presumed pernicious anemia. However, if the vitamin B12 level results between 150 and 200 ng/L (110–148 pmol/L) it is reasonable repeat the measure in 1 to 2 months, because the repeated measure is frequently within the normal range, and, under those circumstances, no additional evaluation is recommended. However, if the repeat vitamin B12 level remains less than 200 ng/L, empiric therapy can be considered and subsequent investigation for pernicious anemia with an intrinsic factor antibody is warranted. If the intrinsic factor antibody is negative, the serum vitamin B12 should be evaluated for a third time. If it is more than 200 ng/L, no further investigation is required. However, if the serum B12 level remains between 150 and 200 ng/L the deficiency should be confirmed with MMA, homocysteine, or holotranscobalamin levels. If the deficiency is confirmed with these laboratory tests it is reasonable to consider treatment for antibody-negative pernicious anemia.[19]

By contrast, these same guidelines recommend that all patients with symptoms correlating with a high clinical suspicion (ie, glossitis or neuropathy) or objective laboratory evidence of vitamin B12 deficiency (anemia) and a serum B12 level less

Box 1
Causes of B12 deficiency in older patients

- Food cobalamin malabsorption (60%–70%)
- Pernicious anemia (15%–20%)
- Dietary deficiency (<5%)
- Malabsorption (<5%)
- Hereditary causes (<1%)

Data from Andres E, Loukili NH, Noel E, et al. Vitamin B12 (cobalamin) deficiency in elderly patients. CMAJ 2004;171(3):251–9.

Box 2
Other factors that contribute to malabsorption of vitamin B12 in older people.

- Intestinal microbial proliferation
- Chronic alcoholism
- Gastric reconstruction
- Pancreatic enzyme deficiency
- Sjogren syndrome
- Long-term ingestion of drugs
  - Biguanides
  - Antacids
  - H2 receptor antagonists
  - Proton pump inhibitors

Data from Andres E, Loukili NH, Noel E, et al. Vitamin B12 (cobalamin) deficiency in elderly patients. CMAJ 2004;171(3):251–9.

than 200 ng/L undergo further evaluation for pernicious anemia and begin empiric therapy while these laboratory tests are pending. If, however, a patient has a serum B12 level greater than 200 ng/L, but B12 deficiency is still suspected (given the prevalence of falsely increased serum B12 levels), the suspected diagnosis and cause should be further investigated with a serum MMA, homocysteine, holotranscobalamin level, and intrinsic factor antibody. While these results are pending, empiric therapy should be initiated.[19]

The treatment of vitamin B12 deficiency depends on the cause of the deficiency. For patients with pernicious anemia due to impaired intrinsic factor function or neurologic symptoms, parenteral supplementation with cobalamin injections (1000 μg) several times per week for 1 to 2 weeks, followed by weekly injections for 1 month, is recommended.[2,19,24] A maintenance dose is then provided varying from monthly to bimonthly[2] for patients with neurologic symptoms on presentation, to quarterly for those without initial neurologic symptoms.[19] Interestingly, there is evidence to suggest that oral supplementation is still effective in patients with impaired intrinsic factor function or loss of the terminal ileum when sufficiently high doses of vitamin B12 are provided due to passive diffusion across mucus membranes.[2,19,24–26] In elderly patients, in whom impaired gastric absorption seems to be a predominant cause of vitamin B12 deficiency,[27] oral supplementation at very high doses has been found to be effective at reducing MMA levels. A dose finding trial by Eussen[28] found that daily oral doses of 500 μg were required to lower MMA levels by 33%. Similarly, Andrès and colleagues[22] found that oral vitamin B12 supplementation in 10 patients produced an improvement in vitamin B12 levels and hematologic parameters in most patients treated with 5000 μg of oral vitamin B12 weekly. However, given concerns regarding compliance in the elderly, parenteral administration may be a more effective means to ensure adequate repletion.

SUMMARY

Vitamin B12 deficiency exists at a fairly high prevalence in the elderly population. As the general population ages, clinicians need to be aware of the myriad of ways in which vitamin B12 can present. These can often be iatrogenic (such as polypharmacy and bariatric surgery), autoimmune, or as yet unclear, as in the case of gastric atrophy

and its possible association with *H. pylori*. Furthermore, it is essential to properly investigate the suspected cause of vitamin B12 deficiency, because the type and duration of treatment varies. In elderly patients, clinicians should maintain a high index of suspicion that vitamin B12 deficiency may be the cause of, or contributing to, commonly observed vague symptoms (eg, fatigue, paresthesias, mild gait abnormalities). This is particularly salient given the fairly high prevalence of vitamin B12 deficiency and the relative ease of treatment. In particular, clinicians should be aware of the high prevalence of food cobalamin malabsorption as a common cause, and become comfortable initiating appropriate patient-centered treatment most likely to produce clinical response.

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