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CHALLENGES WITH THE DIAGNOSIS OF VITAMIN B12 DEFICIENCY IN OLDER ADULTS

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Abstract

The incidence of water soluble vitamin B12 deficiency increases with age. Vitamin B12 deficiency, although common, is under-recognized in older adults due to its variable clinical presentation. Subclinical and atypical clinical presentations are also very common in the elderly. Current laboratory parameters to diagnose vitamin B12 deficiency from serum vitamin B12 levels are not sufficiently sensitive. The focus of this article is to discuss the challenges associated with the diagnosis of cobalamin deficiency in older adults.

L'incidence de la carence en eau soluble vitamine B12 augmente avec l'âge. Carence en vitamine B12, bien que commune, est sous-diagnostiquée chez les adultes âgés en raison de sa présentation clinique variable. Présentations cliniques infracliniques et atypiques sont aussi très fréquente chez les personnes âgées. Paramètres courants de laboratoire pour le diagnostic de carence en vitamine B12 de vitamine B12 sérique ne sont pas suffisamment sensibles. L'objectif de cet article est de discuter les défis associés au diagnostic de carence en cobalamine chez les aînés

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Introduction

Vitamin B12 deficiency is a common nutritional deficiency, especially in the older population, which is often missed. Cobalamin (aka vitamin B12) is an essential vitamin which, despite being required for multiple enzymatic physiological processes throughout the body, has its main roles within the bone marrow for cellular DNA synthesis and for the synthesis and maintenance of myelin within both the peripheral and central nervous systems.

Dietary intake is the main source of cobalamin through the consumption of animal products (i.e., meat, dairy produce and eggs). Additional supplementation is obtained from cobalamin and folate enrichment of most available food sources within North America. The current national recommendation for daily cobalamin intake for adults is five micrograms.

Cobalamin deficiency usually arises through three basic pathophysiological processes, which are described in Table 1. Additional miscellaneous causes include the use of certain medications such as proton pump inhibitors (PPIs), histamine receptor antagonists (H2RA) (i.e., ranitidine) and metformin (Table 2). In a study by Reinstatler et al., metformin-induced cobalamin deficiency occurred in 6% of the diabetic subjects who were using metformin.[2]

Table 1. Three pathological processes responsible for the development of cobalamin deficiency

1. Gastrointestinal malabsorption	2. Inadequate nutritional intake	3. Increased cobalamin demand
Pernicious anemia	Vegan	Increased cellular turnover (i.e., hemolysis, leukemia)
Gastritis	Elderly	
Post-gastrectomy/bariatric surgery		
Crohn's disease		
Postileal resection/bypass		
Pancreatic insufficiency		
Medications (metformin, nitrous oxide, H2RA)		

Table 2. Medications that can cause vitamin B12 deficiency[3]

Metformin
H2 Blockers ***– Class effect***
Protein pump inhibitors ***– Class effect***
Protein pump inhibitors ***– Class effect***
Colchicine
Cholestyramine
Anticonvulsants ***– phenobarbital, phenytoin, Pregabalin, Primidone and Topiramate***[4]
Nitrous oxide
Antibiotics – Tetracycline
The prevalence of vitamin B12 deficiency ranges from 3-40%. It has been seen in 12% of elderly subjects in the community and in up to 30-40% in hospitalized and institutionalized elderly populations.[5] A recent observational study in older inpatients showed an increase in the incidence with aging.[6]

Assessment

Clinical

The atypical presentation of vitamin B12 deficiency can make the diagnosis difficult, especially in the older population who will often have a subclinical presentation or borderline serum vitamin B12 levels. As the clinical presentation of cobalamin deficiency is extensive and has been described elsewhere,[7] our review will focus on the neuropsychiatric presentations due to their atypical and more frequent presentation in the geriatric population. Consideration of other potential differentials is also important, including the presence of co-existing nutritional deficiencies (i.e., folate[8] and copper[9]).

Neuropsychiatric symptoms may precede hematologic signs and are often the presenting manifestation of cobalamin deficiency. The neurological syndromes associated with vitamin B12 deficiency can range from myelopathy, neuropathy, neuropsychiatric abnormalities (described below) and less often, optic nerve atrophy. Cerebellar involvement is also possible, usually presenting as a new onset cerebellar ataxia.[10]

Possibly the most common presenting symptom affecting up to one third of all subjects presenting with clinical deficiency, is the development of a sensory neuropathy due to involvement of the dorsal columns. Clinically, this presents as the combination of reduced or absent proprioception and vibration during testing combined with hyporeflexic patellar reflexes and absent ankle jerks. If untreated, continued progression results in the development of the classical myelopathy, i.e., *"Subacute combined degeneration of the spinal cord* (SCD),*"* and its classical presentation of lower extremity spasticity, clonus, hyper-reflexia, posterior column sensory loss and gait ataxia.

Autonomic neuropathy, although unusual, can also develop, resulting in a similar clinical presentation to that for primary autonomic failure,[11] with the primary findings including a clinically significant orthostatic hypotension, impotence, constipation and urinary retention. Nutritional optic neuropathy is also possible, but rarely seen in this population.[12]

One of the common psychiatric manifestations can be a mood disorder (both depression and mania) or psychosis.[13] The association between cobalamin deficiency and depressive symptomatology may be most significant in elderly patients, with literature supporting a significant improvement in symptoms with subsequent supplementation.[14] There may also be a potential association between vitamin B12 deficiency and the development of cognitive decline and dementia.[15]

Laboratory testing

The specific testing for cobalamin deficiency includes the measurement of cobalamin levels and associated metabolite intermediaries (namely homocysteine and methylmalonic acid [MMA]), which are described in more detail below.

A. Serum cobalamin

The direct measurement of serum cobalamin level is a cheap, widely available and well-established test. However, with the development of newer testing techniques comes a lack of standardization and clear reference standards, which ultimately limits interpretation of the test results. Whilst current test specificities are high (97%) for detecting clinical cobalamin deficiency, its sensitivity is much lower, and thus, levels may remain within "normal" limits until a clinically significant deficiency has developed.[16]

The precise concentration at which deficiency is "defined" is debatable however, due to the absence of formal guidelines, variations in measurement, an absence of standardization and natural population variation, which may be most pronounced in the older cohort. Although a cobalamin level of less than 200 pg/mL has been associated with cobalamin deficiency,[17] increasing the lower limit of normal to 300 pg/mL may identify a larger population and improve test sensitivity to 99% (but may decrease specificity – likely not a clinically risky effect given that the treatment is relatively benign).[18] Despite the aforementioned benefits, accuracy can be limited by multiple external influences. Therefore, to maximize test accuracy and reliability, measurement of the serum cobalamin level (as well as red cell folate level) should be drawn with the patient fasted and prior to receiving any blood transfusions.

Falsely low cobalamin measurements have been recorded in the presence of certain drugs (e.g., estrogen[19]) and with certain medical conditions (Table 3). Falsely elevated or falsely normal cobalamin levels have been detected in the presence of renal failure or liver disease (Table 3). The other important consideration regarding cobalamin measurement is that, even in the presence of normal serum cobalamin

levels, tissue cobalamin levels can be low, resulting in the development of a functional cobalamin deficiency.[20] This factor has driven research to develop more accurate measures of cobalamin deficiency.

Table 3. Medical conditions and medications that can interfere with the measurement of cobalamin levels

Medical conditions/medications that can result in a falsely low cobalamin level	Medical conditions that can cause falsely or normal or high serum cobalamin levels[21,22]
Multiple myeloma	Myeloproliferative disorders
Folate deficiency	Renal insufficiency
Oral contraceptives[19]	Liver disease

If elderly subjects have low cobalamin levels and normal methylmalonic acid level and homocysteine levels, then they should not be considered deficient. This profile is seen in 20-40% of older adults.[23] A similar picture is also seen with multiple myeloma subjects, but will return to normal after treatment of multiple myeloma, suggesting the initial low cobalamin value may be due to assay interference.[24]

B. Cobalamin metabolite intermediaries

Whilst measurement of the specific cobalamin metabolic intermediaries (i.e., MMA and homocysteine) is possible it is not routinely employed, and, due to limited availability, is reserved for patients with borderline normal cobalamin levels with a high clinical suspicion of cobalamin and/or combined folate and cobalamin deficiency, the presence of an unexplained clinical presentation, an isolated macrocytosis or where cobalamin and/or folate measurements are thought to be inaccurate. Perhaps the most important utility for their measurement is to aid differentiation between cobalamin and folate deficiency. In the presence of a true cobalamin deficiency, then both MMA and homocysteine should be elevated. By comparison, only homocysteine will be elevated with folate deficiency. However, there is no gold standard for determining cobalamin deficiency and the problems with the tests used are due to an uncertain boundary between cobalamin depletion and disease.[25] Given the lack of standardization of these tests, and the minimal side effect profile seen with cobalamin and folate supplementation, it may be most beneficial to start cobalamin and folate replacement whilst waiting for such results to be available or if the diagnosis is unclear.

Homocysteine

An elevated concentration of total homocysteine is thought to represent a highly sensitive indicator of early (clinical) cobalamin deficiency. The precise test sensitivity and specificity depends on the threshold value for homocysteine with sensitivity ranging from 0.73-0.9 and specificity ranging from 0.38-0.68.[26] Widespread application is limited by its poor specificity, as elevated levels occur in the presence of many non-associated conditions and with certain lifestyle characteristics (i.e., smoking, alcoholism and even coffee consumption). The other important consideration involves the detailed but necessary instructions required for sample collection and analysis, and the extensive length of time required for processing. Together, these drawbacks limit the accuracy and widespread applicability of the test.

By definition, subclinical cobalamin deficiency will not show any clinical features – its diagnosis depends solely on biochemical biomarkers. In the absence of clear diagnostic thresholds, the general consensus is that homocysteine levels greater than 15-25 micromols/L are associated with subclinical cobalamin deficiency, with subclinical being defined as low levels of cobalamin in the absence of clinical features, whilst homocysteine levels greater than 50 micromols/L tend to be associated with clinically evident cobalamin deficiency.[26]

Methylmalonic acid (MMA)

MMA is the end product produced following the breakdown of amino acids to methylmalonyl CoA during the citric acid cycle. In the presence of cobalamin deficiency there is reduced enzymatic activity ultimately resulting in elevated levels of both plasma and urine MMA concentrations. Whilst the clinical significance of this deficiency in adults is not clear, levels greater than three standard deviations above local laboratory references are associated with clinical cobalamin deficiency with a sensitivity of 98% and specificity of 96%. The serum MMA is more specific for vitamin B12 deficiency than the homocysteine test.[27]

Sensitivity and specificity of a test may be assessed via ROC curve analysis, using MMA or an alternative appropriate metabolic marker, to define evidence of metabolic disturbance due to cobalamin deficiency.[28] Combining both MMA and homocysteine results may offer the greatest clinical accuracy for detecting cobalamin deficiency, especially in the presence of normal cobalamin values, and can essentially rule out cobalamin deficiency.[29] Cautious interpretation of the MMA concentration is advised; between 5-25% of the elderly may have increased MMA concentrations without evidence of cobalamin deficiency. Also, false positive results are possible in the setting of decreased renal function.[30]

In older adults with normal cobalamin levels (based on WHO suggested cut-off of less than 150 pM (203 pg/mL[31]) in the Framingham study, when sensitive biomarkers like MMA and homocysteine were used, sensitivity and specificity for diagnosing vitamin B12 deficiency improved.[32]

C: Other potential tests

Direct measurement of tissue cobalamin levels would provide the most accurate reflection of cobalamin stores. Unfortunately, no such tests are available at present. Whilst theoretical possibilities have included either hepatic sampling or red cell cobalamin measurement, such testing is impractical and not widely available. Given the benefits seen with cobalamin replacement and consequences of its deficiency, an argument could be made for providing replacement without invasive testing for laboratory evidence of deficiency.

Measurement of the active metabolite of cobalamin, holotranscobalamin (a complex formed by the attachment of cobalamin to transcobalmin) has been suggested as an alternative test for measuring cobalamin levels.[33] Although this does not directly measure tissue cobalamin levels, it is thought to provide an accurate reflection of the amount of active cobalamin available for cellular use. Whilst it is potentially thought to be a sensitive marker for early cobalamin deficiency, a recent study suggested that it can also be useful to assess the intestinal absorption of vitamin B12 level.[34] However, despite its potential value for detecting cobalamin deficiency it is not routinely available, thus limiting its use to the research setting.

D. Hematological markers for vitamin B12 deficiency

Many of the hematological changes (megalobalstic or macrocytic anemia) that occur with cobalamin deficiency are seen in other conditions, most notably folate deficiency, and thus, combined with their clinically indistinguishable presentations, can make the diagnosis very challenging.[34] In patients with megaloblastic or macrocytic anemia, folate supplementation without checking for vitamin B12 deficiency can result in damage to the nervous system. Should the possibility of folate deficiency be entertained, it is imperative that the cobalamin level is checked prior to folate supplementation or if this is not possible, then combined cobalamin and folate supplementation should be administered.

In a study by Hershko C. et al., 46% of the 83 iron deficient patients with microcytosis proved to have co-existing cobalamin deficiency, suggesting that microcytic anemia can mask co-existing cobalamin deficiency.[35]

Key points

1. *Vitamin B12 deficiency is a common but under-recognized problem amongst older adults.*
2. *Although age-related achlorhydia (i.e., a physiological decline/absence of gastric acidity) is the most common cause for vitamin B12 deficiency in the elderly, less common but reversible causes include the use of certain medications (i.e., metformin, PPIs, histamine receptor antagonists such as ranitidine).*
3. *Atypical presentations in the older population are the rule, with neuropsychiatric manifestations (e.g., sensory neuropathy, depression etc.) being most common.*
4. Although a cobalamin level of less than 200 pg/mL has been associated with cobalamin deficiency,[1] increasing the lower limit of normal to 300 pg/mL may identify a larger population and improve test sensitivity to 99%.
5. Whilst specific testing for increased concentrations of cobalamin metabolites (e.g., homocysteine and methyl malonic acid) may provide greater diagnostic accuracy compared to measurement of serum cobalamin levels alone, the lack of established reference levels can limit their interpretation.
6. Since there is no gold standard test to define cobalamin deficiency, clinical features are important in making the diagnosis. If there is discordance between clinical features of deficiency and test results, in order to avoid neurological damage treatment should not be delayed.

Conclusions

In older adults, vitamin B12 deficiency may go unrecognized because of its subtle and atypical clinical presentation. All the available tests to diagnose vitamin B12 deficiency have significant limitations. Although diagnosis has previously relied upon the assessment of serum cobalamin levels, the use of more specialized tests (i.e., measurement of cobalamin metabolites) may provide greater diagnostic accuracy. In the absence of available metabolite testing or with diagnostic uncertainty and especially in the presence of clinical symptoms, empirical treatment with vitamin B12 is safe, effective and has no associated toxicity. In patients with malabsorption B12 deficiency or pernicious anemia, life-long treatment with injections is preferred. Large oral daily doses (1,000 microgram orally daily) might be an acceptable alternative, since sufficient amounts of vitamin B12 are absorbed by passive diffusion in the small intestine.[36]

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