Vitamin B_{12} (Cobalamin) Deficiency

Theresa Lowry Lehnen, RGN, GPN, RNP, BSc, MSc, M. Ed, PhD
Clinical Nurse Specialist and Associate Lecturer South East Technological University

Vitamin B_{12} (cobalamin) is a water-soluble vitamin that is derived from animal products such as red meat, eggs and dairy products. Vitamin B_{12} deficiency is a common condition which can present with non-specific clinical features, and in severe cases with neurological or haematological abnormalities. Food-bound cobalamin malabsorption is the most common cause of low serum cobalamin levels, while pernicious anaemia accounts for most severe cases of vitamin B_{12} deficiency.[1] The prevalence of vitamin B_{12} deficiency is approximately 6-12% in adults under 60 years of age, and approximately 17% in all adults with macrocytic anaemia. A deficiency is more common in older people, affecting approximately 1 in 10 people aged 75 and over, and 1 in 20 people aged 65 to 74. [7] Pregnant women, and vegans are also more susceptible to vitamin B_{12} deficiency.[2]

Vitamin B_{12} is required in the body to form red blood cells and DNA, and is also involved in the development and function of brain and nerve cells. It acts as coenzymes for the crucial methyl transfer reaction in converting homocysteine to methionine and the isomerization reaction that occurs in the conversion of L-methylmalonyl-CoA to succinyl-CoA. Vitamin B_{12} is only present naturally in animal products because it is a product of bacteria synthesis, however, many foods are also fortified with synthetic vitamin B_{12}.[3] The RDA of vitamin B_{12} for adults aged 19-64 is 1.5 mcg/day.[4]

Vitamin B_{12} metabolism

Dietary vitamin B_{12} is found in association with food proteins, and released on exposure to the low pH within the gastric lumen to facilitate absorption in the small intestine. Once released, vitamin B_{12} is immediately bound by haptocorrin (transcobalamin I) and remains attached until proteolytic cleavage of the complex in the duodenum, where it binds to intrinsic factor (IF), a second carrier protein, synthesised by the parietal cells of the gastric mucosa. Intrinsic factor is necessary for the uptake of vitamin B_{12} in the terminal ileum. On traversing the brush border, vitamin B_{12} dissociates from IF, and enters the circulation where it binds with transcobalamin II which is responsible for the delivery of cobalamin to peripheral tissues and the liver. Following transport to peripheral tissues, free vitamin B_{12} is generated. In the cytosol, vitamin B_{12} is used as a cofactor by methionine synthase (MS) to react homocysteine with N^5-methyltetrahydrofolate (N^5-MeTHF) to produce methionine and tetrahydrofolate (THF). Synthesis of THF allows the downstream generation of purines and pyrimidines required for DNA and RNA synthesis. Following absorption, large amounts of vitamin B_{12} are stored in the liver. [1]

Aetiology

Vitamin B12 deficiency has 3 primary aetiologies; autoimmune, malabsorption and dietary insufficiency. The complex absorption mechanisms provide various ways by which vitamin B_{12} deficiency can develop. In pernicious anaemia, autoimmune destruction of parietal cells and consequent impairment of intrinsic factor secretion is the cause. Although a well-known cause of vitamin B_{12} insufficiency and associated with severe deficiency, pernicious anaemia accounts for only a minority of cases. Vitamin B_{12} deficiency occurs from poor dietary intake in malnourished patients, such as the elderly, and in people with excess alcohol intake.[1, 8] Prolonged medication use including, metformin, histamine H_2 blocker, anticonvulsants and proton pump inhibitors (PPIs) can also affect how much vitamin B_{12} the body absorbs.[7, 9, 11] Vitamin B_{12} is stored in excess in the liver, decreasing the likelihood of deficiency. However, in cases where vitamin B_{12} cannot be absorbed, for example in dietary insufficiency, malabsorption, or lack of intrinsic factor, hepatic stores are depleted, and deficiency ensues.[6]

Presentation

Lack of vitamin B_{12} affects multiple body systems and is characterised by haematological and neurological effects, ranging from milder manifestations such as fatigue, muscle weakness, sore red tongue, mouth ulcers, disturbed vision and paraesthesia, to severe features like pancytopenia and degeneration of the spinal cord. Vitamin B_{12} deficiency may present with non-specific symptoms, however, it warrants urgent evaluation and treatment when haematological and or neurological features are present. Sequelae of untreated vitamin B_{12} deficiency includes not only permanent neurological symptoms, but also osteoporosis and cardiovascular disease.[2] The substantial hepatic storage of vitamin B_{12} can delay clinical manifestations for up to 10 years after the onset of deficiency. [11]

Diagnosis

A complete medical history and physical examination should be carried out, with an emphasis on gastrointestinal and neurological findings. Vitamin B_{12} deficiency manifests as macrocytic anaemia, and presenting symptoms often include signs of anaemia, such as fatigue and pallor. Jaundice may also be a presenting symptom, due to the increased haemolysis caused by impaired red blood cell formation. Other presenting complaints may include peripheral neuropathy, glossitis, diarrhoea, headaches, and neuropsychiatric disturbances.[6]

A past medical history of coeliac disease or Crohn's disease or any surgical history of gastrectomy or bowel resection, especially resection of the ileum, should increase suspicion for B_{12} deficiency. A thorough dietary history is important to note, especially for patients with a strict vegan diet, which would increase the likelihood of a B_{12} deficiency.[6] A neurologic exam should evaluate for dementia, peripheral neuropathy, ataxia, and a loss of proprioception.[6]

Laboratory tests include a full blood count, serum B_{12} and folate levels. In cases where the diagnosis is still unclear after initial testing, other lab tests, such as MMA and homocysteine

levels, may be required. In patients who are deficient in B_{12}, the FBC would show a decrease in both haemoglobin and haematocrit. Folic acid deficiency also presents as macrocytic anaemia and is often confused with B_{12} deficiency. Serum levels of both B_{12} and folate can help differentiate between the two disease processes. A serum B_{12} above 300 pg/mL is interpreted as normal. Patients with B_{12} levels between 200 and 300 pg/mL are considered borderline, and further enzymatic testing may be helpful in diagnosis. Patients with B_{12} levels below 200 pg/mL are considered deficient. However, a low serum B_{12} level does not determine the aetiology, and if uncertain further testing should be done.[6]

In patients with borderline vitamin B_{12} levels (200 to 300 pg/mL), further enzymatic testing should be performed. B_{12} deficiency results in the accumulation of MMA and homocysteine, therefore, serum levels of both MMA and homocysteine should be elevated in cases of B_{12} deficiency. These values also help to distinguish B_{12} deficiency from folate deficiency, in which homocysteine levels are elevated, but MMA levels are normal. [6]

Once a diagnosis has been confirmed, the aetiology must be addressed. If there is no surgical history, an appropriate GI workup for causes of malabsorption, such as Crohn's or coeliac disease should be carried out. In other cases, a history of adherence to a strict vegan diet may be the source. If both the GI and dietary workup is negative, then the cause is likely to be autoimmune. Blood tests for serum levels of anti-intrinsic factor antibodies may lead to the diagnosis of pernicious anaemia.

Investigation of patients with symptoms of vitamin B_{12} deficiency may also reveal elevated levels of serum cobalamin. An elevation in serum vitamin B_{12} levels may arise from increased oral or parenteral intake, decreased uptake by the liver or kidney, greater release from cells especially hepatocytes, or a rise in the synthesis of the trans-cobalamins by hepatocytes or granulocytes. High serum cobalamin levels are associated with liver disease, malignancy and haematological dyscrasias, and may be positively correlated with risk of mortality. [1]

Treatment

Intramuscular injections of hydroxocobalamin are the mainstay of treatment for vitamin B_{12} deficiency, however, evidence suggests that oral therapy may be as efficacious as parental treatment.[1] For patients with no neurological involvement, the usual regimen is hydroxocobalamin 1 mg on alternate days for two weeks, followed by three-monthly injections of hydroxocobalamin 1 mg. This regimen should be given for life if the condition is due to pernicious anaemia. If the deficiency is due to another cause, then treatment should continue until sustained improvement in haematological indices is seen. In cases where there are neurological features, the same dose is given until no further symptomatic improvement is seen, followed by two-monthly injections.[1]

The *NICE Clinical Knowledge of Summaries* recommends that the intramuscular (IM) route should be used in all deficiency cases where there are neurological symptoms as an acute dose - hydroxocobalamin 1mg on alternate days for two weeks. Usually the IM route is used as maintenance, however, if the deficiency is diet related, not due to lack intrinsic factor, and the patient does not display neurological symptoms, oral OTC supplements (Cyanocobalamin 50-150mcg daily) may be used. Parenteral therapy is preferable for vitamin B_{12} deficient symptomatic patients, however, as it is retained in the body for longer than oral supplements. Malabsorption is frequently a cause of deficiency, and in such cases, oral supplements are unlikely to be effective. [12]

Referral to secondary care is recommended if severe neurological symptoms are present, the patient is pregnant or if there is any uncertainty about the diagnosis. Gastroenterology investigations are warranted if there is suspicion of malabsorption, gastric cancer or coeliac disease. Often, management of underlying conditions, such as provision of antibiotics for bacterial overgrowth, and cessation of causative medications if possible can prove useful.[1]

Patients should be educated about their condition, the importance of vitamin B_{12} supplement adherence, and close follow-up with their primary clinician. Patients on a strict vegan diet should be made aware of the importance of supplementation to prevent B_{12} deficiency. Good dietary source of vitamin B_{12} include eggs, meat, milk and other dairy products, salmon and cod, as well as foods which have been fortified with B_{12} including some soy products, breakfast cereals and breads. All patients with risk factors for the various aetiologies of vitamin B_{12} deficiency should be monitored routinely with laboratory tests. [12]

Complications

Although uncommon, vitamin B12 deficiency can lead to complications, including, heart failure due to anaemia, disabling neurological deficits, temporary infertility, pregnancy complications, risk of gastric cancer and the risk of developing an autoimmune disorder such as type 1 diabetes, myasthenia gravis, Hashimoto disease, or rheumatoid arthritis.[4, 6] Maternal vitamin B_{12} deficiency during pregnancy or while breastfeeding may lead to neural tube defects, developmental delay, failure to thrive, hypotonia, ataxia, and anaemia. Women at high risk or with known deficiency should supplement with vitamin B_{12} during pregnancy or while breastfeeding. [11]

Prognosis

For patients who are promptly treated with vitamin B_{12}, the prognosis is good. Younger patients have better outcomes than older individuals, and the best response is obtained in people with the absence of severe neurological deficits.[6] Understanding the pathophysiology, recognising symptoms, and providing prompt treatment are central to early detection, improved quality of life, and the prevention of complications of vitamin B_{12} deficiency.

References

1. Shipton, M., Thachil, J. (2015). Vitamin B12 deficiency - A 21st century perspective. *Clinical medicine (London, England)*, *15*(2), 145–150.
2. BMJ (2019). Investigating vitamin B12 deficiency. *BMJ* 2019;365: 1865. Available at: https://doi.org/10.1136/bmj.l1865
3. Morris, A., Mohiuddin, S. (2021). Biochemistry Nutrients. In StatPearls Publishing. Available at: https://www.ncbi.nlm.nih.gov/books/NBK554545/
4. HSE (2022). B vitamins and folic acid. Health Service Executive. Available at: https://www2.hse.ie/conditions/vitamins-and-minerals/b-vitamins-and-folic-acid/
5. Nielsen, M., Rasmussen, M., Andersen, C., Nexø, E., Moestrup, S. (2012). Vitamin B_{12} transport from food to the body's cells - A sophisticated, multistep pathway. *Nat Rev Gastroenterol Hepatol* 2012; 9:345–54.
6. Ankar, A., Kumar, A. (2022. Vitamin B12 Deficiency. StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441923/
7. HSE (2022). Vitamin B12 or Folate Deficiency Anaemia. Health Service Executive. Available at: https://www2.hse.ie/conditions/vitamin-b12-or-folate-deficiency-anaemia/
8. Röhrig, G., Gütgemann, I., Kolb, G., Leischker, A. (2018). Clinical hematological symptoms of vitamin B_{12} deficiency in old age: Summarized overview of this year's symposium of the Working Group "Anemia in the Aged" on the annual conference of the German Geriatric Society (DGG) in Frankfurt. Z Gerontol Geriatr. 2018 Jun;51(4):446-452.
9. Freedberg, D., Kim, L., Yang, Y. (2017). The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice from the American Gastroenterological Association. Gastroenterology. 2017 Mar;152(4):706-715.
10. Watson, J., Lee, M., Garcia-Casal, M. (2018). Consequences of Inadequate Intakes of Vitamin A, Vitamin B_{12}, Vitamin D, Calcium, Iron, and Folate in Older Persons. Curr Geriatr Rep. 2018;7(2):103-113.
11. Langan, R., Goodbred, A. (2017). Vitamin B_{12} Deficiency: Recognition and Management. *Am Fam Physician.* 2017 Sep 15;96(6):384-389. Available at: https://www.aafp.org/afp/2017/0915/p384.html
12. NHS (2019). Guideline for the management of Vitamin B12 deficiency. National Health Service. Available at: https://midessexccg.nhs.uk/about-us/the-library/medicines-management/clinical-pathways-and-medication-guidelines-1/chapter-9-nutrition-and-blood-2/3002-vitamin-b12-deficiency-in-adults-september-2018-new/file