
Neurological Manifestations Of Vitamin B-12 Deficiency

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Abstract

Vitamin B-12 deficiency is a common problem encountered in developing countries of the world. In Europe and North America it is frequently encountered in the elderly and in people whose diets are compromised such as alcoholics. Recent data has shown that cobalamin deficiency may occur in 5% to 40% of the general population. The prevalence as stated earlier is higher in the elderly and in nursing home residents. Vitamin B-12 deficiency may take decades to develop and patients may be asymptomatic or may present with a wide spectrum of hematological and neuropsychiatric manifestations. The history of research in Vitamin B-12 deficiency is fascinating and the noble prize has been awarded twice to investigators involved in it.

HISTORY

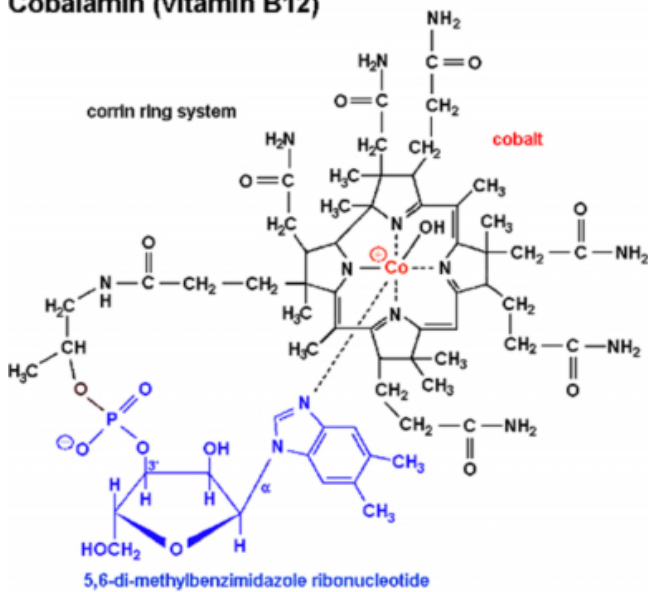
Pernicious anemia is the most common cause of vitamin B-12 deficiency. It was first described by Thomas Addison in 1849 and the anemia associated with it is also called Addison-Biermer disease. The anemia was linked to the stomach by Austin Flint in 1860 when he suggested that degenerative disease of the glandular tubuli of the stomach was the cause of idiopathic Addisonian anemia. Russell (1898) first reported three patients with subacute combined degeneration of spinal cord and delineated the clinical findings of their spinal cord syndrome. Minot, Murphy, Whipple and Castle wrote seminal papers and demonstrated that a factor present in the liver (extrinsic factor) could treat the anemia. This factor was later isolated as vitamin B-12 by Folker and Todd. The constant association of sub acute combined degeneration of spinal cord with pernicious anemia was stressed by the likes of Billings (1902); Bramwell (1915); Woltman (1918); Hurst and Bell (1922) and Greenfield and O'Flynn among others. Pleiffer, 1915; Woltman, 1918; Hamilton and Nixon, 1921; McAlpine, 1929; Hyland and Farquharson, 1936; Davidson, 1931; Zimmerman, 1941; Adams and Kubik, 1944; Foster, 1945; Spillane, 1947; and Victor and Lear, 1956; were among the first to comment on the neuropathological changes associated with pernicious anemia. Bickel (1914), Adams and Kubik (1944) reported on the association of optic atrophy and vitamin B-12 deficiency. Bickel found degeneration of the papillomacular bundle in a case of Vitamin B-12 deficiency.

STRUCTURE

Vitamin B-12 refers to any of the biologically active forms related to cyanocobalamin. The vitamin was first isolated in 1948. It is a complex molecule composed of a cobalt atom contained in a corrin ring, a tetrapyrrole structure similar to heme but with a cobalt atom rather than iron at its center. Humans are completely dependent on dietary sources for cobalamin. Animal proteins such as red meat, poultry, eggs and dairy products are rich sources of Vitamin B-12; deficiency is thus common in strict vegetarians (vegans). Ovolactovegetarians and lacto vegetarians may obtain adequate amounts of the vitamin. Cyanocobalamin is stored in the liver and total body stores are of the order of 2 to 10 mg. The recommended daily allowance (RDA) is 2.4 micrograms/day in adults and 2.6 micrograms/day in pregnant and lactating women. As the vitamin is highly conserved via the enterohepatic circulation and the liver stores about 3 mg of it, it takes 5 to 10 years for cobalamin deficiency to manifest itself in a previously healthy adult who suddenly stops taking the vitamin in his diet.

Figure 1

Cobalamin (vitamin B12)



ABSORPTION

The vitamin after ingestion is absorbed via a complex mechanism. The acidic Ph of the stomach cleaves cobalamin from other dietary protein. The free cobalamin then binds to the salivary R binder and the complex then travels to the upper small intestine. In the duodenum and upper jejunum, pancreatic enzymes (in the presence of an alkaline pH) lyse the R-protein-cobalamin complex. B-12 then binds to intrinsic factor, a 50-kd glycoprotein secreted by the gastric parietal cells. The IF-cobalamin complex is then absorbed through endocytosis in the terminal ileum. Up to 1% of free cobalamin is absorbed passively in the terminal ileum. Thus mega doses of oral vitamin B-12 may be appropriate in the treatment of pernicious anemia in a reliable patient. Secretion of intrinsic factor (IF) parallels that of hydrochloric acid, thus achlorhydria leads to cobalamin deficiency via reduced IF secretion. Once cyanocobalamin is internalized into the ileum, IF is removed from the complex and the vitamin gets bound to transport proteins namely transcobalamin I, II and III and is transported via the portal blood stream to the liver and other body tissues. Though transcobalamin II is the most important cobalamin transporter, about 70% of the serum cobalamin is bound by haptocorrins. In pernicious anemia, a condition which is associated with chronic atrophic gastritis, an autoimmune process leads to the destruction of the gastric parietal cells and thus an absence of intrinsic factor. As parietal cells secrete hydrogen ions in addition to intrinsic factor, patients with pernicious anemia have gastric achlorohydrria.

PATHOPHYSIOLOGY OF NEUROLOGICAL MANIFESTATIONS

Cyanocobalamin mediates two important enzymatic reactions in humans. The first is the conversion of methylmalonyl-coenzyme A to succinyl-coenzyme A and the second is the conversion of homocysteine to methionine. Deficiency of cyanocobalamin thus leads to accumulation of methylmalonyl-CoA and homocysteine in the serum and these can be used as surrogate markers of vitamin B-12 deficiency. Methyl-cobalamin is the cofactor for methionine synthesis in the methylation of homocysteine to methionine. Methyltetrahydrofolate is the methyl group donor. This reaction is necessary for de novo synthesis of DNA and thus when disrupted affects rapidly dividing cells of the bone marrow (resulting in anemia) and those of the gastrointestinal tract. The failure of methionine synthesis due to cobalamin deficiency may lead to an accumulation of methyltetrahydrofolate, trapping the folate in a chemical form unavailable for purine synthesis, this is the so called “folate trap hypothesis”.

The exact mechanism of neurological damage in B-12 deficiency is still not fully elucidated. Impaired methionine synthesis may lead to depletion of S-adenosylmethionine which is required for the synthesis of myelin phospholipids. The second hypothesis is that the generation of odd-chained fatty acids, resulting from a deficit of succinyl-CoA may get incorporated into the myelin resulting in neurological syndrome of Vitamin B-12 deficiency.

ETIOLOGY

Protean conditions can result in cyanocobalamin deficiency. These include pernicious anemia (absence or deficiency of IF), various malabsorption syndromes (bacterial overgrowth, blind loop, post ileal resection, Crohn's disease, fish tapeworm, chronic infections like HIV, drugs causing mucosal defects) and more rarer congenital conditions like transcobalamin deficiency.

Table 1: Causes of vitamin b-12 deficiency

1. Pernicious anemia (lack of IF due to immune mediated destruction of gastric parietal cells)
2. Nutritional deficiency (vegans, elderly, alcoholics, HIV positive, breast fed infants of vegetarian mothers)
3. Type B atrophic gastritis (associated with helicobacter pylori infection)

4. Pathology of distal ileum (distal ileal resection, inflammatory bowel disease like Crohn's disease, ileocaecal tuberculosis, Whipple's disease, tropical sprue)
5. Surgical gastrectomy
6. Colonization of small bowel with bacteria or intestinal parasites like *Diphyllobothrium latum* (tapeworm)
7. Nitrous oxide inhalation (functional deficiency)
8. Congenital syndrome (Imerslund-Grasbeck syndrome)

NEUROLOGICAL MANIFESTATIONS

Vitamin B-12 deficiency may be entirely asymptomatic or present with protean hematological and neuropsychiatric manifestations. Here we shall limit our discussion to the neuropsychiatric manifestations of vitamin B-12 deficiency.

Table 2: Neurological manifestations of vitamin b12 deficiency cns manifestations

1. Dementia
2. Depression
3. Acute psychosis, reversible manic and schizophreniform states (Megaloblastic madness)
4. Cerebrovascular disease (homocystenemia is an independent risk factor for stroke)

SPINAL CORD MANIFESTATIONS

1. Myelopathy (Sub acute combined degeneration of spinal cord), ataxia, spasticity and abnormal gait

PNS MANIFESTATIONS

1. Neuropathy
 - a. motor-sensory polyneuropathy (parasthesias, numbness and weakness)
 - b. mononeuropathy (optic or olfactory)
 - c. autonomic neuropathy (impotence, urinary or fecal incontinence)
3. Myeloneuropathy (combined myelopathy and neuropathy)

Let us now consider these manifestations in more detail.

CNS MANIFESTATIONS

DEMENTIA AND ACUTE PSYCHOSIS (MEGALOBlastic MADNESS)

Neuropsychiatric manifestations such as memory loss, depression, hypomania, paranoid psychosis with auditory and visual hallucinations the so called megaloblastic madness have been described with vitamin B-12 deficiency. Patients may present with violent behavior or more subtle personality changes. They may also present with vague complaints typical of aging such as fatigue, generalized weakness and loss of memory. Cognitive testing may reveal frank dementia. These complaints may be attributed to aging or psychiatric illness unless a high index of suspicion is entertained and a test for vitamin B-12 deficiency is carried out. It is still not clear if mild or moderate B12 deficiency can cause dementia and whether supplementation of the diet with B12 can prevent or delay the onset of dementias like Alzheimer's disease. Patients who are demented usually show little to no cognitive improvement with B12 supplementation.

CEREBROVASCULAR DISEASE

Homocysteine is an atherogenic and thrombophilic agent, thus an increase in the plasma homocysteine represents an independent risk factor both coronary artery disease and cerebrovascular disease as well as peripheral vascular disease. It is one of the risk factors for cerebrovascular disease in the young. Deficiency of vitamin B-12 inhibits the conversion of homocysteine to methionine. Homocysteine plays an important role in cross linking of collagen and thus its excess in the vascular walls may predispose to both arterial and venous thrombosis. Occlusion of coronary, renal and cerebral arteries with attendant infarction has been reported as early as first decade of life. Patients may present with dislocated optic lenses (usually downward and medially). The presence of homocystenemia may act synergistically with other risk factors like hypertension and smoking thus increasing the risk for strokes. Cobalamin deficiency thus might be the cause of an otherwise unexplained ischemic stroke or cranial artery dissection.

SPINAL CORD MANIFESTATIONS

SUBACUTE COMBINED DEGENERATION OF SPINAL CORD

The term sub acute combined degeneration of spinal cord is used to describe the pathological process seen in vitamin B12 deficiency; macroscopically the cord is shrunken in the

anteroposterior diameter while microscopically there are multifocal vacuolated and demyelinating lesions in the white matter and in the posterior and lateral columns. The large myelinated fibers are predominantly affected with the earliest change been swelling of the myelin sheath. The process starts in the posterior columns of the upper thoracic cord and the lesions spread laterally as well as longitudinally to involve the cervical segments. Secondary axonal degeneration occurs as the disease advances leading to fixed neurological deficits. The myelopathy of vitamin B-12 deficiency is virtually indistinguishable from the vacuolar myelopathy of AIDS. Clinically this myelopathy presents with paraesthesias in the hands and feet with early loss of vibration and position sense leading to a progressive disturbance with gait. Ankle jerks are lost early on in the process due to a superimposed peripheral neuropathy and this might be an important diagnostic clue to the clinician. Loss of vibration or position sense is always found and may be the first to appear, whereas other modalities of sensation may be affected in advanced disease. In mildly affected cases the activity of the knee and ankle jerks may be either increased or diminished but in severely affected patients these reflexes are always decreased or absent. Extensor plantar responses may also be present. Myelopathic signs tend to be symmetric and reflect the predominant involvement of posterior and lateral columns of the spinal cord. Macrocytic anemia is an inconsistent finding in patients with vitamin b-12 myelopathy, thus macrocytosis and hyper segmented polymorphonuclear cells may or may not be seen on bone marrow examination and peripheral smear. The findings of a low serum B-12 concentration, elevated levels of homocysteine and methylmalonic acid and a positive Schilling's test may aid in diagnosis.

PERIPHERAL NEUROPATHY

The most frequent manifestations of peripheral neuropathy are paresthesias and numbness. The paresthesias usually first occur in the lower extremities. At this early stage there might be no objective signs on the neurological examination. As posterior column disease may give rise to exactly the same signs and symptoms it is difficult to distinguish the early signs of myelopathy from that of peripheral neuropathy .So a patient presenting with depressed ankle jerks, position and joint sense abnormalities, impaired vibration sense and blunting of pin-prick perception may be erroneously diagnosed to have a neuropathy rather than a myelopathy of the posterior columns. Pathological studies have documented a demyelinating neuropathy in some and shown an axonal or mixed picture in others.

OPTIC NEUROPATHY

Optic neuropathy is a rare manifestation of cobalamin deficiency. Patients present with complaints of diminished visual acuity. The optic neuropathy in cobalamin deficiency is of retrobulbar type and cannot be distinguished from other nutritional neuropathy such as tobacco and alcohol amblyopia. . Visual field examination by perimetry demonstrates a central or cecocentral scotoma. The cyanide component of cyanocobalamin has been suggested to be the cause of neuropathy though this has not been conclusively proven. In any case elderly patients presenting with optic neuropathy and cobalamin deficiency should be encouraged to quit smoking and reduce their intake of alcohol to prevent further optic nerve damage.

NEUROPATHOLOGICAL FEATURES

Gross Findings-In long standing cases the posterior and lateral funiculi of spinal cord are translucent (pale) and sclerotic indicative of advanced gliosis. Often the cross-sectional area of the spinal cord is reduced due to tissue loss and glial scarring.

Microscopic findings-The earliest change seen in the spinal cord is swelling of the myelin sheaths often to many times the original diameter. The fibers with the largest diameters i.e., the thickest myelin sheaths are the ones which are preferentially affected. The swollen individual myelinated fibers give a vacuolated sieve-like appearance to stained cross-sections of the spinal cord. Abundant macrophage activity leads to breakdown of the myelin sheaths. Some astrocytic activation and proliferation may be evident in early lesions but is not a prominent feature. These changes by themselves are not specific since they may be seen in other diseases which cause degeneration of the spinal cord white matter; however in the myelopathy of B-12 deficiency it is the topographical distribution of the swollen fibers in a multifocal, partially asymmetrical manner which gives the spinal cord its characteristic appearance.

DIAGNOSING VITAMIN B-12 DEFICIENCY

The work up to diagnose cyanocobalamin deficiency should begin with a thorough evaluation of a peripheral smear to diagnose the type of anemia. Cyanocobalamin deficiency characteristically produces a megaloblastic picture with macro-ovalocytosis and hypersegmented neutrophils (polymorphs). The mean corpuscular volume (MCV) is greater than 100 fl and at least one neutrophil should have six or more lobes. Leukopenia, thrombocytopenia, increased lactic acid dehydrogenase and increased bilirubin all reflect

ineffective hematopoiesis. Serum vitamin B-12 level should be measured (normal between 200-900 pg/ml). If it is in the low normal range and the index of suspicion is high serum methyl-malonic acid and homocysteine levels can be measured and these will be found to be elevated. Elevated serum gastrin levels with achlorohydria points towards pernicious anemia as the cause of vitamin B-12 deficiency. Serum antibodies to intrinsic factor and anti-parietal cell antibodies can be measured too. Low holotranscobalamin II level is a sensitive indicator of vitamin B-12 deficiency though currently the test is available only in research centers. Shilling's test helps to rule out cyanocobalamin deficiency due to intrinsic factor deficiency. In this test radio labeled cobalamin is given by mouth after the patient's intrahepatic stores have been saturated by an intramuscular injection of unlabeled cobalamin. The excretion of radio labeled cobalamin is measured in the urine. If this test is abnormal the test is repeated with radio labeled cobalamin bound to intrinsic factor given orally. If the patient has a deficiency of intrinsic factor (pernicious anemia) the absorption will be normal. Magnetic resonance imaging may show T-2 weighted hyperintensities involving the posterior columns especially in the cervical region and EMG may show evidence of motor and sensory axonopathy.

TREATMENT

The treatment of cobalamin deficiency is relatively straight forward now. Before 1948 whole liver and later refined liver extract was used. Either hydroxy-cobalamin or cyano-cobalamin can be used for treatment. In Japan methyl-cobalamin is used for treatment. We prefer to treat patients with 1000 micrograms of vitamin B-12 intramuscularly daily for one week, weekly for one month and then monthly for the rest of the patient's life. Daily oral supplementation with mega doses of vitamin B-12 may suffice in patients who are reliable. Oral therapy is unpredictable and patients tend to comply poorly once they have achieved clinical improvement. It should be emphasized to the patients and the attendants the importance of life-long treatment, otherwise relapse may occur. If iron deficiency is present it must also be treated. Supplementation of the diet with vitamin B-12 may be another viable and low cost option to prevent this devastating illness and its consequences.

RECOMMENDED READING

1. Herbert V. Vitamin B12--an overview. In: Herbert V, ed. Vitamin B12 deficiency. London: Royal Society of Medicine Press, 1999:1-81

2. Wynn M, Wynn A. The danger of B12 deficiency in the elderly. *Nutr Health* 1998;12:215-26
3. Dharmarajan TS, Norkus EP. Vitamin B12 deficiency in the elderly--population-based research. In: Herbert V, ed (1), pp 27-34
4. Carmel R. Cobalamin, the stomach, and aging. *Am J Clin Nutr* 1997;66(4):750-9
5. Stabler SP, Lindenbaum J, Allen RH. Vitamin B-12 deficiency in the elderly: current dilemmas. *Am J Clin Nutr* 1997;66(4):741-9
6. Ho C, Kauwell GP, Bailey LB. Practitioners' guide to meeting the vitamin B-12 recommended dietary allowance for people aged 51 years and older. *J Am Diet Assoc* 1999;99(6):725-7
7. Dharmarajan TS, Ugalino JT, Kanagala M, et al. Vitamin B12 status in hospitalized elderly from nursing homes and the community. *J Am Med Dir Assoc* 2000;1:21-4
8. Russell RM, Rasmussen H, Lichtenstein AH. Modified Food Guide Pyramid for people over seventy years of age. *J Nutr* 1999;129(3):751-3
9. Herbert V. Staging vitamin B-12 (cobalamin) status in vegetarians. *Am J Clin Nutr* 1994;59(5 Suppl):1213-22S
10. Herbert V, Das KC. Folic acid and vitamin B12. In: Shils ME, Olson JA, Shike M, eds. *Modern nutrition in health and disease*. 8th ed. Philadelphia: Lea & Febiger, 1994;402-25
11. Schjonsby H. Vitamin B12 absorption and malabsorption. *Gut* 1989;30(12):1686-91
12. Snow CF. Laboratory diagnosis of Vitamin B12 and folate deficiency. *Arch Intern Med* 1999;159:1289-98
13. Hussein WI, Green R, Jacobsen DW, et al. Normalization of hyperhomocysteinemia with L-thyroxine in hypothyroidism. *Ann Intern Med* 1999;131(5):348-51
14. Stabler SP. Screening the older population for cobalamin (vitamin B12) deficiency. *J Am Geriatr Soc* 1995;43(11):1290-7
15. Pruthi RK, Tefferi A. Pernicious anemia revisited. *Mayo Clin Proc* 1994;69(2):144-50
16. Green R, Kinsella LJ. Current concepts in the diagnosis of cobalamin deficiency. *Neurology* 1995;45(8):1435-40

17. Marcuard SP, Albernaz L, Khazanie PG. Omeprazole therapy causes malabsorption of cyanocobalamin (vitamin B12). *Ann Intern Med* 1994;120(3):211-5
18. Holloway KL, Alberico AM. Postoperative myeloneuropathy: a preventable complication in patients with B12 deficiency. *J Neurosurg* 1990;72(5):732-6
19. Dharmarajan TS, Koshy A, Sipalay M, et al. The need to screen: a case in point. In: Herbert V, ed (1), pp 9-13
20. Carrazana E. The neurological manifestations of vitamin B12 deficiency. In: Herbert V, ed (1), pp 21-6
21. Lindenbaum J, Heaton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. *N Eng J Med* 1988;318(26):1720-8
22. Johnson LE. Vitamin nutrition in the elderly. In: Morley JE, Glick Z, Rubenstein LZ, eds. *Geriatric nutrition: a comprehensive review*. 2nd ed. New York: Raven Press, 1995:79-105
23. Dharmarajan TS, Norkus EP. An algorithmic approach to the screening of vitamin B12 status and the treatment of identified deficiency. In: Herbert V, ed (1), pp 49-52
24. Carmel R. Introduction: beyond megaloblastic anemia. *Semin Hematol* 1999;36(1):1-2
25. Swain R. An update of vitamin B12 metabolism and deficiency states. *J Fam Pract* 1995;41(6):595-600
26. Elia M. Oral or parenteral therapy for B12 deficiency. *Lancet* 1998;352(9142):1721-2
27. Norkus EP, Patel B, Dharmarajan TS. Does regular multivitamin (MVT) use prevent Vitamin B12 deficiency in community elderly? (Abstr) *J Am Coll Nutr* 1999;18:535
28. Reynolds EH. Neurological aspects of folate and vitamin B12 metabolism. *Clin Haematol*.1976 Oct;5(3):661-96
29. Abramsky O. Common and uncommon neurological manifestations as presenting symptoms of vitamin B-12 deficiency. *J Am Geriatr Soc*.1972 Feb;20(2):93-6
30. Bassi SS, Bulundwe KK, Greeff GP, Labuscagne JH, Gledhill RF. MRI of the spinal cord in myelopathy complicating vitamin B-12 deficiency : two additional cases and a review of the literature. *Neuroradiology*. 1999 April;41(4):271-74
31. Pittcock SJ, Payne TA, Harper CM. Reversible myelopathy in a 34-year-old man with vitamin B12 deficiency. *Mayo Clin Proc*. 2002 Mar;77(3):291-4
32. McNeely JK, Buczulinski B, Rosner DR. Severe neurological impairment in an infant after nitrous oxide inhalation. *Anesthesiology*.2000 Dec;93(6):1549-50
33. Prabhakar S, Syal P, Singh P, Lal V, Khandelwal N, Das CP. Non-compressive myelopathy: clinical and radiological study. *Neurol India*.1999 Dec;47(4):294-9
34. Halliday AW, Vukelja SJ. Neurological manifestations of vitamin B-12 deficiency in a military hospital. *Mil Med*. 1991 Apr;156 (4):201-4
35. Chiew IS, Goh KL, Loh TG. Vitamin B-12 neuropathy in the absence of anemia-case report. *Singapore Med J*.1989 Apr;30(2):221-2
36. Kinsella LJ, Green R. Anesthesia paresthetica: nitrous oxide-induced cobalamin deficiency. *Neurology* 1995 Aug; 45(8):1608-10.
37. Lindenbaum J, Heaton EB, Savage DG, Brust JC, Garrett TJ, Podell ER, Marcell PD, Stabler SP, Allen RH. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. *N Engl J Med*. 1998 Jun30;318(26):1720-8

References

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