Vitamin B12 and its Importance For Survival

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ABSTRACT

Vitamin B12, vitamin B12 or vitamin B-12, also called cobalamin, is a water-soluble vitamin with a key role in the normal functioning of the brain and central nervous system, and for the formation of blood. It is one of the eight vitamins essential for the body.. It is normally involved in the metabolism of every cell of the human body, especially affecting DNA synthesis and regulation, but also fatty acid metabolism and amino acid metabolism. Neither fungi, plants, nor animals (including humans) are capable of producing vitamin B12. Only bacteria and archaea have the enzymes required for its synthesis, although many foods are a natural source of B12 because of bacterial symbiosis. The vitamin is the largest and most structurally complicated vitamin and can be produced industrially only through bacterial fermentation-synthesis. Vitamin B12 consists of a class of chemically related compounds (vitamers), all of which have vitamin activity. It contains the biochemically rare element cobalt sitting in the center of a planar tetra-pyrrole ring called a corrin ring. Biosynthesis of the basic structure of the vitamin is accomplished only by bacteria and archaea (which usually produce hydroxycobalamin, but conversion between different forms of the vitamin can be accomplished in the human body. A common semi-synthetic form of the vitamin is cyanocobalamin, which does not occur in nature but is produced from bacterial hydroxocobalamin. Because of its stability and lower production cost, this form is then used in many pharmaceuticals and supplements as well as a food additive. In the body it is converted to the human physiological forms methylcobalamin or deoxy cobalamin, leaving behind the cyanide ion, albeit in a minimal concentration More recently, hydroxocobalamin, methylcobalamin, and adenosylcobalamin can be found in more expensive pharmacological products and food supplements. Their extra utility is currently debated. Vitamin B12 was discovered from its relationship to disease pernicious anemia, which is an autoimmune disease in which parietal cells of the stomach responsible for secreting intrinsic factor are destroyed (these cells are also responsible for secreting acid in the stomach). Because intrinsic factor is crucial for the normal absorption of B12, its lack in pernicious anemia causes a deficiency. Many other subtler kinds of vitamin B12 deficiency and their biochemical effects have since been elucidated.

Keywords: *Pernicious anemia, neurological, RBC, methylcobalamin, intrinsic factor*

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.

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 cobalamine 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 achlorohydria.

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 methylymalonyl-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 parasities 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
2.
     1.   motor-sensory polyneuropathy (parasthesias, numbness and weakness)
     2.   mononeuropathy (optic or olfactory)
     3.   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. Macrocystic 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 through 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 patients 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.

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