VITAMIN B12 DEFICIENCY PRESENTING WITH MYELONEUROPATHY: A CASE REPORT AND REVIEW OF THE LITERATURE.

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Summary

The neurologic manifestations of vitamin B_{12} deficiency, although uncommon, are the result of its effects on the brain, optic nerves, peripheral nerves, and spinal cord. Myeloneuropathy, resulting in sensory disturbances, weakness, and spasticity, is known as subacute combined degeneration and primarily involves the dorsal, and lateral spinal columns as well as the peripheral nerves. Subacute combined degeneration is treatable and the symptoms are potentially reversible if detected at an early stage. We present the clinical as well as the laboratory findings in a patient with subacute combined degeneration who had resolution of the clinical neurological manifestations with B_{12} therapy.

Key words: Vitamin B12 deficiency, myeloneuropathy.

Introduction

Historical background

The association between anemia, gastrointestinal and neurologic abnormalities has been recognized in several clinical and postmortem case reports and series by Combe, Addison, and Fenwick since the early 19th century.[1]

In 1877, Gardner and Osler coined the term pernicious anemia (PA) to describe a patient with progressive arm numbness and difficulty with buttoning and using tools.[1] Liechtenstein in 1884 reported the association of PA and spinal cord disease but attributed both to tabes dorsalis.[2] Lichtheim in 1887[3] and Minnich in 1892[4] recognized the histologic differences in the spinal cord between PA and tabes dorsalis.

In 1900, Russell et al coined the term subacute combined degeneration of the spinal cord.[5] The existence of vitamin B-12 deficiency neuropathy was also recognized in 1958.[6]

Vitamin B12 myelopathy although uncommon is usually seen in middle life, the average age of onset being about 50 years. It can begin in the 20s or as late as 70. Both sexes are affected equally.[7] Familial occurrence is uncommon, but is nevertheless described.

In Europe, the prevalence of vitamin B-12 deficiency is 1.6-10%.[7] A hospital population-based study in India found a prevalence of 0.88% with borderline values of 3.8%.[8] There is no known relationship between neurologic symptoms and race.[9] Studies in Africa and the United States have shown higher vitamin B-12 and transcobalamin II levels in black than in white individuals. Additionally, blacks have lower hydroxycobalamin (HC) levels and metabolize it more efficiently than whites.[10]

Case Report

A 56 year-old female trader presented with 2 years history of numbness and peppery sensation of both hands with the latter progressing to involve her feet bilaterally. There was also progressive weakness of both lower and upper limbs which culminated into inability to walk 2 weeks prior to presentation. There was no sphincteric dysfunction.

Two weeks prior to presentation, she developed band-like gripping painful sensation on the abdominal region of her trunk. She also had back ache. She did not have visual or hearing impairment and she did not consume cassava/cassava products heavily neither did she drink alcohol. She equally had progressively worsening darkening of her hands and feet. However her

urine did not darken or turn red on standing. She does not drink alcohol and was not a vegetarian. Examination revealed an ill-looking lady with angular stomatitis bilaterally as well as depapillated tongue. She had darkening of hands and feet with dystrophic nail changes. Nervous system examination revealed normal mentation and cerebration. Fundoscopy revealed normal disc. She had spastic quadriparesis, with Medical Research Council (MRC) power grade 4 in the upper limbs and grade 3 in the lower limbs. She had wasting of the small muscles of the hands, plantar reflexes were extensor bilaterally with glove and stocking hypoaesthesia and impaired joint position and vibration sensations bilaterally. Rombergs test could not be elicited and the gait could not be assessed due to the degree of limb weakness.

A complete blood count showed a hemoglobin concentration of 8.0 g/dl (normal range, 13.5-17.5 g/dl) with an elevated mean corpuscular volume of 142 fl (normal range, 80-100 fl). Blood film appearance showed macrocytosis with hypersegmented neutrophils and atypical mononuclear cells. Bone marrow smear revealed megaloblasts. These results were consistent with Vitamin B12 deficiency.

HIV I & II screening as well as stool microscopy for ova and parasite were negative. Serum B_{12} assay, Schilling test, cervical magnetic resonance imaging (MRI), and nerve conduction study (NCS) and electromyogram (EMG) were not done due to non availability of the facilities in the hospital.

An assessment of myeloneuropathy, due to subacute combined degeneration (SCD) of the spinal cord was made. She was immediately commenced on intramuscular hydroxycobalamin, 1mg alternate day for 5 doses, thereafter weekly for 6 weeks and then monthly. She equally had carbamazepine and amitriptiline for her neuropathic pain.

By about the 12th day of the commencement of treatment, the band-like pain had subsided and the power increased to MRC grade 5- and 4 in the upper limbs and lower limbs respectively. At the end of the second week she started ambulating with support and by the third month she was ambulating without support with disappearance of sensory symptoms.

Discussion

Vitamin B_{12} is contained in essentially all meat and dairy products. Total body stores are 2 to 5 mg, of which half is stored in the liver.[11] The recommended daily intake is 2 mcg/d in adults.[11] Because vitamin B-12 is highly conserved through the enterohepatic circulation, cobalamin

deficiency from malabsorption develops after 2-5 years and deficiency from dietary inadequacy in vegetarians develops after 10-20 years. Its causes are mainly nutritional and malabsorptive, pernicious anaemia being most common.

Physiology of absorption

After ingestion, the low stomach pH cleaves cobalamin from other dietary protein. The free cobalamin binds to gastric R binder, a glycoprotein in saliva, and the complex travels to the duodenum and jejunum, where pancreatic peptidases digest the complex and release cobalamin. Free cobalamin can then bind with gastric intrinsic factor (IF), a 50-KD glycoprotein produced by the gastric parietal cells, the secretion of which parallels that of hydrochloric acid. Hence, in states of achlorhydria, IF secretion is reduced, leading to cobalamin deficiency. Importantly, only 99% of ingested cobalamin requires IF for absorption. Up to 1% of free cobalamin is absorbed passively in the terminal ileum. This is why oral replacement with large vitamin B-12 doses is appropriate for PA.

Once bound with IF, vitamin B-12 is resistant to further digestion. The complex travels to the distal ileum and binds to a specific mucosal brush border receptor, cublin, which facilitates the internalization of cobalamin-IF complex in an energy-dependent process. Once internalized, IF is removed and cobalamin is transferred to other transport proteins, transcobalamin I, II, and III (TCI, TCII, TCIII). Eighty percent of cobalamin is bound to TCI/III, whose role in cobalamin metabolism is unknown. The other 20% binds with TCII, the physiologic transport protein produced by endothelial cells. Its half-life is 6-9 min, thus delivery to target tissues is rapid.

The cobalamin-TCII complex is secreted into the portal blood where it is taken up mainly in the liver and bone marrow as well as other tissues. Once in the cytoplasm, cobalamin is liberated from the complex by lysosomal degradation. An enzyme-mediated reduction of the cobalt occurs by cytoplasmic methylation to form methylcobalamin or by mitochondrial adenosylation to form adenosylcobalamin, the 2 metabolically active forms of cobalamin.

Vitamin B-12 role in the peripheral and central nervous systems

The neurologic manifestation of cobalamin deficiency is less well understood. Central nervous system (CNS) demyelination may play a role, but how cobalamin deficiency leads to demyelination remains unclear. Reduced S-adenosylmethionine (SAM) or elevated methylmalonic acid (MMA) may be involved.[12]

SAM is required as the methyl donor in polyamine synthesis and transmethylation reactions. Methylation reactions are needed for myelin maintenance and synthesis. SAM deficiency results in abnormal methylated phospholipids such as phosphatidylcholine, and it is linked to central myelin defects and abnormal neuronal conduction, which may account for the encephalopathy and myelopathy.[12] In addition, SAM influences serotonin, norepinephrine, and dopamine synthesis. This suggests that, in addition to structural consequences of vitamin B-12 deficiency, functional effects on neurotransmitter synthesis that may be relevant to mental status changes may occur.[12] Parenthetically, SAM is being studied as a potential antidepressant.

Another possible cause of neurologic manifestations involves the other metabolically active form of cobalamin, adenosylcobalamin, a mitochondrial cofactor in the conversion of L-methylmalonyl CoA to succinyl CoA. Vitamin B-12 deficiency leads to an increase in L-methylmalonyl-CoA, which is converted to D-methylmalonyl CoA and hydrolyzed to MMA. Elevated MMA results in abnormal odd chain and branched chain fatty acids with subsequent abnormal myelination, possibly leading to defective nerve transmission.[12]

More recent studies propose a very different paradigm: B-12 and its deficiency impact a network of cytokines and growth factors, ie, brain, spinal cord, and cerebrospinal fluid (CSF) tumor necrosis factor (TNF)-alpha; nerve growth factor (NGF), interleukin (IL)-6 and epidermal growth factor (EGF),[13] some of which are neurotrophic, and others neurotoxic. Vitamin B-12 regulates IL-6 levels in rodent CSF. In rodent models of B-12 deficiency parenteral EGF or anti-NGF antibody injection prevents, like B-12 itself, the SCD-like lesions.[13]

In human and rodent serum and CSF, concomitantly with a vitamin B-12 decrease, EGF levels are decreased, while at the same time, TNF-alpha increases in step with homocysteine levels. These observations provide evidence that the clinical and histological changes of vitamin B-12 deficiency may result from up-regulation of neurotoxic cytokines and down-regulation of neurotrophic factors.[13]

Nitrous oxide (N_2O) pathomechanisms in vitamin B-12 deficiency

N_2O can oxidize the cobalt core of vitamin B-12 from a 1^+ to 3^+ valance state, rendering methylcobalamin inactive, inhibiting hydroxycobalamin (HC) conversion to methionine and depleting the supply of SAM. Patients with sufficient vitamin B-12 body stores can maintain cellular functions after N_2O exposure, but in patients with borderline or low vitamin B-12 stores, this oxidation may be sufficient to precipitate clinical manifestations.[14]

Etiology

Inadequate vitamin B-12 absorption is the major pathophysiologic mechanism and may result from several factors, namely;

- **Intrinsic factor deficiency**: leading to pernicious anemia, an autoimmune disorder. Pernicious anemia accounts for 75% of the causes of vitamin B12 deficiency. Destruction of gastric mucosa from gastrectomy and H-pylori infection may also lead to intrinsic factor deficiency and consequent vitamin B12 deficiency.
- **Deficient vitamin B-12 intake**: Intake may be inadequate because of strict vegetarianism (rare), breastfeeding of infants by vegan mothers, alcoholism, or following dietary fads.
- **Disorders of terminal ileum**: Tropical sprue, celiac disease, enteritis, exudative enteropathy, intestinal resection, Whipple disease, ileal tuberculosis, and cublin gene mutation on chromosome arm 10p12.1 in the region designated MGA 1, which affects binding of the cobalamin-IF complex to intestinal mucosa (Imerslünd-Grasbeck syndrome), are disorders that affect the terminal ileum.
- **Competition for cobalamin**: Competition for cobalamin may occur in blind loop syndrome or with fish tapeworm (Diphyllobothrium latum).
- **Abnormalities related to protein digestion related to achlorhydria**: Abnormalities include atrophic gastritis, pancreatic deficiency, proton pump inhibitor use, and Zollinger-Ellison syndrome, in which the acidic pH of the distal small intestine does not allow the cobalamin-IF complex to bind with cublin.
- **Medications**: include colchicine, neomycin, and *p*-aminosalicylic acid.
- **Transport protein abnormality**: Abnormalities include transcobalamin II deficiency (autosomal recessive inheritance of an abnormal *TCN2* gene on chromosome arm

22q11.2-qter resulting in failure to absorb and transport cobalamin) and deficiency of R-binder cobalamin enzyme.

- **Disorders of intracellular cobalamin metabolism:** These disorders result in methylmalonic aciduria and homocystinuria in infants.
- **Increased vitamin B-12 requirement:** Requirement is increased in hyperthyroidism and alpha thalassemia.
- **Other causes** such as acquired immune deficiency syndrome (AIDS), vitamin B-12 deficiency is not infrequent. Although the exact etiology remains obscure, it is likely a multimodal process involving poor nutrition, chronic diarrhea, ileal dysfunction, and exudative enteropathy. Low vitamin B-12 levels may be more common in late than in early HIV disease.[15]
- **N_2O exposure** can occur iatrogenically (ie, anesthesia) or through abuse ("whippets").

Clinical Course

Although the clinical features of vitamin B-12 deficiency may consist of a classic triad of weakness, sore tongue, and paraesthesias, these are not usually the chief symptoms.

The neurologic features are attributable to pathology in the peripheral and optic nerves, posterior and lateral columns of the spinal cord (subacute combined degeneration), and in the brain. Interestingly, hematologic and neurologic manifestations are occasionally dissociated. An inverse correlation in the severity of both manifestations has been suggested. In patients with neuropsychiatric abnormalities, 28% lack anemia or macrocytosis.

Clinical manifestations due to vitamin B-12 deficiency are unrelated to etiology. In a prospective comparative study between antiparietal cell antibody positive and negative patients, no significant difference was shown in clinical, electrodiagnostic, and radiological features.[16]

Onset is subacute or gradual, although more acute courses have been described, in particular after N_2O exposure. In 1986, Schilling described 2 patients with unrecognized vitamin B-12 deficiency that developed paraesthesias and poor manual dexterity 1-3 months after brief N_2O exposure.[17] In 1995, Kinsella and Green described a 70-year-old man with paraesthesias and hand clumsiness after 2 exposures to N_2O over 3 months.[18]

Also in 1991, Healton summarized his experience with a large group of patients as follows:[19]

- Isolated neuropathy was reported in 25% of patients.
- Myelopathy occurred in 12% of cases.
- A combination of neuropathy and myelopathy was noted in 41%.
- Neuropsychiatric manifestations, such as recent memory loss with reduced attention span and otherwise normal cognition, depression, hypomania, paranoid psychosis with auditory or visual hallucinations (megaloblastic madness), violent behavior, personality changes, blunted affect, and emotional liability, were reported in 8% of patients.
- Ocular findings included a cecocentral scotoma and occurred in 0.5% of cases.
- Others have described optic atrophy, nystagmus, small reactive pupils, and chiasmatic lesion causing bitemporal hemianopia.
- Normal findings were noted on neurologic examination in 14% of patients despite paresthetic symptoms.

Both the above revealed that myeloneuropathy is the most predominant mode of presentation. This is the mode our patient presented with.

Nonneurologic manifestations include the following:

- General - Lemon-yellow waxy pallor, premature whitening of hair, flabby bulky frame, mild icterus, and blotchy skin pigmentation in dark-skinned patients
- Cardiovascular - Tachycardia, congestive heart failure
- Gastrointestinal - Beefy, red, smooth, and sore tongue with loss of papillae that is more pronounced along edges

Laboratory Diagnosis

Routine hematologic and chemistry tests

- Hematologic abnormalities may be absent at the time of neurologic presentation. Vitamin B-12 deficiency produces the classic picture of macrocytic anemia, with a mean corpuscular value (MCV) greater than 100 fL. The MCV correlates with estimated vitamin B-12 level
- MCV of 80-100 fL (normal) indicates less than 25% probability of vitamin B-12 deficiency. MCV of 115-129 fL indicates a 50% probability. MCV greater than 130 fL indicates a 100% probability[10]. We relied on MCV value of 142 fL as facility for serum B12 assay was not available in our center.

- Peripheral blood smear shows macro-ovalocytosis, anisocytosis, and poikilocytosis, as well as basophilic stippling of the erythrocytes and Howell-Jolly bodies. Reticulocyte count can be within the reference range or low.
- Hypersegmentation (>5% of neutrophils with > 5 lobes or 1% with > 6 lobes) of polymorphonuclear cells may occur without anemia. Thrombocytopenia is observed in approximately 50% of patients, and platelets often have bizarre size and shape.
- Bone marrow smear revealing megaloblastic changes is often diagnostic of Vitamin B12 deficiency and is definitive[16]: (i) some patients may have received B12 supplements prior to their referral to us which can influence the serum B12 levels; (ii) in a vitamin B12-deficient state, the levels first fall in the neuronal tissues and only much later is it reflected in the serum vitamin B12 levels. Therefore, a diagnosis of B12 deficiency might be missed if we solely rely on the serum levels; (iii) the presence of megaloblasts in the bone marrow is virtually diagnostic of vitamin B12 or folate deficiency. However, a serum vitamin B12 assay is mandatory in all cases of suspected B12 deficiency.
- Serum indirect bilirubin and lactate dehydrogenase (LDH) may be elevated because PA can have a hemolytic component.
- Achlorhydria is present in many patients with PA.
- Schilling test: The Schilling test is used to determine the etiology of vitamin B-12 deficiency in patients with normal IF antibodies.

A diagnosis of Vitamin B12 deficiency with subacute combined degeneration of the spinal cord was established in our patient based on the clinical presentation in conjunction with the megaloblastic bone marrow smear.

Imaging Studies

- In patients with myelopathy, MRI may reveal regional T2 and fluid-attenuated inversion recovery (FLAIR) hyperintensities mainly in the thoracic posterior columns with possible extension into the brain stem. In patients with chronic disease, atrophy of the spinal cord is observed.[20]
- Brain MRI may show T2 and FLAIR hyperintensities in the cerebral white matter and around the fourth ventricle.[20]

Nerve conduction study (NCS)/EMG

- Sensory nerves are usually more affected than motor nerves and are more severely affected distally than proximally.[21]
- Mixed demyelinating-axonal picture are seen, with axonal sensory polyneuropathy being the most predominant.[21]

These modes of investigations (MRI and NCS) were not carried out on our patient because of non-availability.

Treatment

- Establish the diagnosis and etiology of vitamin B-12 deficiency and treat with adequate doses.
- The consequences of vitamin B-12 deficiency, encephalopathy, myelopathy, and peripheral and optic neuropathy require adequate medical care.
- Physical therapy and occupational therapy are needed to improve gait, balance, and arm function. Patients may require canes or a walker for ambulation and safety.
- In patients with encephalopathy, neuropsychological interventions may improve cognition, social functioning, and interpersonal relationships.
- Patients with PA are at increased risk for gastric carcinoma, colorectal adenocarcinoma, and carcinoid tumors and must be monitored.
- Combined team management involving a neurologist, a hematologist, and a gastroenterologist is required.
- Vitamin B-12 deficiency due to low intake, will benefit from eating food that contains vitamin B-12 such as meat, eggs, cheese, and yogurt. Supplementation is also required when religious or cultural restrictions render dietary changes impossible.
- Standard drug treatment is parenteral vitamin B-12: oral treatment requires very large doses and even when intrinsic factor is given, the results are inconsistent.
- Numerous treatment regimens have been proposed, including cobalamin 1000mcg intramuscular/subcutaneous given every 2 or 3 days for five doses to restore tissue stores. Followed by 100-1000mcg per week for 6 months, then 100-1000 mcg/month for life. Folic acid is not only ineffective in treating Vitamin B12 deficiency, but may be

deleterious as the administration of folate load can produce a secondary B12 deficiency with exacerbation of neurological symptoms.

- In addition to cobalamin replacement, oral IF supplementation is being evaluated. Supplementation with SAM or methionine-rich diets are being studied for N_2O-induced myeloneuropathies.
- Diagnosis and treatment of tapeworm infection and celiac and Crohn diseases can improve intestinal vitamin B-12 absorption. With blind loop syndrome, tetracycline can normalize the intestinal flora and vitamin B-12 absorption.

Prognosis

- Therapy with vitamin B-12 in subacute combined degeneration stops progression and improves neurologic deficit in most patients.[22]
- Younger patients with less severe disease and short duration of illness do better.[22]
- In a large retrospective review of 57 patients with subacute combined degeneration, absence of sensory level, absent Rhomberg sign, and flexor planter reflex were associated with good prognosis.[22]
- On spinal MRI, involvement of less than 7 spinal segments, cord swelling, and enhancement, but not cord atrophy, were associated with better prognosis.[22]
- Clinical improvement is most pronounced in the first 2 months but continues up to 6 months.[22]

In conclusion, though a fairly uncommon condition, Vitamin B12 deficiency should be considered in every patient that presents with myeloneuropathy. Early recognition and prompt treatment is very essential as it is reversible. Early treatment also minimizes the extent of permanent neurological deficit.

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