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# LONG TERM VITAMIN B12 DEFICIENCY, COMPLICATION AND ITS MANAGEMENT IN VEGANISM NEWBORN

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**Abstract:**

*B-12 (cobalamin) is a complex molecule in which a cobalt atom is contained in a corrin ring, an important organic cofactor essential for the neurological and hematological integrity, strictly found in non-vegetarian diets and milk products, long run abstinence of these ingredients in diet results into its deficiency exhibiting neurological clinical manifestation which is, in general not seen but with strict long term deficiency such as in strict vegetarian leads to the clinical manifestation such as weakness, paraesthesia and numbness.*

*Management of this manifestation can be done with vitamin B12 supplements or encouraging consuming the synthetic form of the vitamin, meat and egg that is rich source of Vit.B12, therefore this short review will focus to disclose the mechanism and management that correlates the effect of long term deficiency of Vitamin B12.*

**Key words:** *vitamin, non-vegetarian diets, par-aesthesia, neurology.*

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## INTRODUCTION:

The newborn's vitamin B12 storage exclusively comes from placenta transfer; later from animal food. Severe vitamin B 12 deficiency produces a cluster of neurological symptoms in infants, including irritability, failure to thrive, apathy, anorexia, and developmental regression, which respond remarkably and rapidly to vit.B12 supplementation. The underlying mechanisms may involve delayed myelination or demyelination of nerves; alteration in the S-adenosylmethionine:S-adenosylhomocysteine ratio; imbalance of neurotrophic and neurotoxic cytokines; and/or accumulation of lactate in brain cells[1,2].

**Patho-physiology of Neurological Manifestations**

Vitamin B12 deficiency is known to be associated with signs of demyelination, usually in the spinal cord. Lack of vitamin B12 in the maternal diet during pregnancy has been shown to cause severe retardation of myelination in the nervous system of child of strictly vegetarian parents presented with severe psychomotor retardation and vit.B12 associated megaloblastic anemia, brain atrophy with signs of retarded myelination, the frontal and temporal lobes being most severely affected. It was concluded that this myelination retardation was due to insufficient intake of vitamin B12 and vitamin B12 therapy was instituted. The patient responded well with improvement of clinical and imaging abnormalities.

Cobalmin operates in two important enzymatic reactions in humans, in which first is the conversion of methylmalonyl-coenzyme A to succinyl-coenzyme A and the second is the conversion of homocysteine to methionine. Deficiency of this viamin leads to accumulation of methylymalonyl-CoA and homocysteine in the serum, and these can be used as surrogate markers of vitamin B-12 deficiency. Mechanism of neurological damage in vit B12 deficiency is still not fully elucidated, however hypothesized that impaired methionine synthesis may lead to depletion of S-adenosylmethionine which is required for the synthesis of myelin phospholipids and secondly considered 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 B12 deficiency [2, 3, 4, 5].

I.

II.

**Pharmacokinetics of vit. B12:**

There are 4 compounds such as cynocobalamin, hydroxycobalamin, methylcobalamin & adenosylcobalamin possessing vit. B12 activity. Their basic structures are same with cobalt within a central corrin ring. It is synthesized in nature by microorganisms & humans obtain it by ingesting foods of animal origin. The liver, kidney, sea fish, egg yolk, meat, milk & cheese are rich dietary sources of vit.B12.The vit. B12 is also synthesized by colonic microflora but this not absorbed. The commercial source is Streptomyces Griseus, as a byproduct of streptomycin industry [4].

Daily requirement: Adult-- 1 to 3 mcg, pregnancy & lactation—3 to 5 mcg The liver stores about 2-8 mg of vit.B12 which takes about 3-5 years to be completely depleted after cessation of vit.B12 absorption from the gut. It is not metabolized in liver & it is excreted mainly in bile about 3-7 mcg/ day out of which about 0.5- 1 mcg is reabsorbed by enterohepatic circulation but when dose exceeds > 100 mcg, a large part is excreted through urine due to saturation of plasma protein binding sites of vit. B 12 [5, 6].

Usually, a normal daily diet contains 5-30 mcg of vit.B12 out of which only 1-3 mcg is absorbed. This ingested vit. B12 binds to the Intrinsic Factor [ a glycoprotein, MW 60,000 ] synthesized by gastric parietal cells. The cobalamin- intrinsic factor [ IF ] complex passes to the terminal ileum where it binds to the specific receptors present on intestinal mucosal cells & gets absorbed by active carrier mediated transport. Then, this newly absorbed vit. B12 binds to transcobalamin to form holotranscobalamin [ 20-30 % of plasma vit.B12 ] which is biologically active form to be delivered to the cells. About 70% of of vit.B12 present in the blood is bound to haptocorrin [ holohaptocorrin] which is taken up & stored in the liver[6,7.8].

## CLINICAL MANIFESTATION OF VIT B12:

Vitamin B12 deficiency frequently causes hematological abnormalities, glossitis, peripheral neuropathy, weakness, hyperreflexia, ataxia, loss of proprioception, poor coordination, and affective behavioral changes. These manifestations may occur in any combination; many patients have the neurological defects without macrocytic anemia [6].

## HAEMOPOIETIC SYSTEM :

1. Megaloblastic macrocytic anaemia, may be often associated with mild leukopenia or thrombocytopenia or both, [ earliest manifestation].
2. Abnormalities of epithelial structures , particularly of alimentary tract leading to glossitis, atophy of tongue, malabsorption & even atophy of vagina.

**Neurological Complications:**

In about 40% of Cbl-deficient exhibits neuropsychiatric syndromes characterized by progressive and variable deterioration of the spinal

cord, peripheral nerves and cerebrum. Sensory impairment is the initial abnormalities, most often presenting as distal and symmetrical paraesthesiae of the lower limbs and frequently associated with ataxia. Almost all patients demonstrate loss of vibratory sensation, often in association with diminished proprioception and cutaneous sensation and a Romberg sign, with advancement corticospinal tract involvement is common along with abnormal reflexes, motor impairment and, ultimately, spastic paraparesis, minor exhibits mental or psychiatric disturbances or autonomic signs, but these rarely if ever occur in the absence of other neurological changes [9-12].

**Metabolic Mechanism of Neurological Manifestation:**

Metabolic mechanisms comprise as a result of a secondary disturbance in folate metabolism (8) neurologic defects had higher mean levels of folate (due to folate trap) (27.9 versus 15.4 nM), AdoMet (117.2 versus 78.6 nM), cysteine (462 versus 325 microM), and cys-gly (85.0 versus 54.7 microM) than neurologically unaffected patients that restored all metabolic changes with cobalmin therapy to normal. (Fig1) [9]

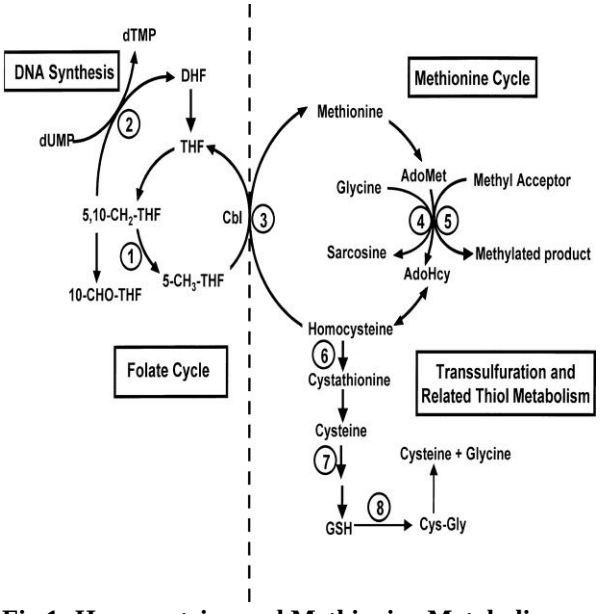


**Fig 1: Homocysteine and Methionine Metabolism (right) and Folate Metabolism (left).**

AdoHcy indicates *S*-adenosylhomocysteine; AdoMet,*S*-adenosylmethionine; Cbl, cobalamin; 5,10-$CH_2$-THF, 5,10-methylenetetrahydrofolate; 5-$CH_3$-THF, 5-methyltetrahydrofolate; 10-CHO-THF, 10-formyltetrahydrofolate; Cys-Gly, cysteinylglycine; DHF, dihydrofolate; dTMP, deoxythymidine monophosphate; dUMP, deoxyuridine monophosphate; GSH, glutathione; THF, tetrahydrofolate. Mediating enzymes for reactions are as follows: (1) 5,10-methylenetetrahydrofolate reductase; (2) thymidylate synthase; (3) methionine synthase (requires cobalamin and 5-methyltetrahydrofolate); (4) glycine *N*-methyltransferase; (5) a variety of cellular methyltransferases; (6) cystathionine β-synthase; (7) γ-glutamylcysteine synthetase, followed by a reaction mediated by glutathione synthetase; (8) γ-glutamyl transpeptidase (occurs extracellularly).

**Management of Neurological Manifestation in Vegetarianism:**

Vegetarianism can be subdivided into lacto-vegetarianism (a diet without meat and fish) and veganism (a diet without any animal foods that includes dairy products and eggs). A vegan diet has more risk of having deficiencies of vitamin B12, and several minerals, such as calcium, iron and zinc. However, modestly even a lacto-vegetarian diet has risk of deficiencies of vitamin B12 and possibly certain minerals, such as iron. In medical practice, the possibility of vitamin B12 deficiency in subjects consuming meat or fish < or = once a week deserves serious consideration, evaluation is measured using sensitive and specific deficiency markers such as the levels of methyl-malonic acid in plasma or urine. Alternative dietary sources of vitamin B12 instead of meat are fish (especially fatty fish is a good source of vitamin B12), or a vitamin-B12-supplementation recommended[13] to a strictly vegetarian diet can be treated with vitamin B12 supplementation for strict vegetarians, who eat no meat, fish, eggs, or dairy products.

**Deficiency Vitamin B 12 Causes:**

**Dietary Intake and Absorption** — Animal products (meat and dairy products) provide the only dietary source of Cbl for humans. The usual Western diet contains 5 to 7 mcg of cobalamin per day, while the minimum daily requirement is listed as 6 to 9 mcg per day Total body stores of Cbl are 2 to 5 milligrams (2000 to 5000 mcg), approximately one-half of which are in the liver. As a result, it takes years to develop vitamin B12 deficiency after absorption of dietary B12 ceases.

1. Inadequate intake in veganism & breast-fed infants of vegan mothers.
2. Increased demand : pregnancy, lactation & infancy.
3. Pernicious Anaemia : Dietary Vit. B12 is not absorbed due to the absence of Intrinsic Factor [ IF

] because of the autoimmune destruction of gastric parietal cells.
4. Reduced absorption of vit. B 12 in cases such as Achlorhydria, gastrectomy, gastric carcinoma, chronic gastritis, malabsorption syndrome ,tropical sprue & old age .
5. Absorption of vit. B 12 is decreased by drugs such as phenytoin, zidovudine, aminosalicylic acid, antacids, nicotine, large doses of vitamin C & Nitrous oxide [ prolonged exposure] [11].
6. Intestinal infestation of Fish Tape worm which consumes vit. B 12.
7. Congenital abnormality: Defects in enzymes & deficiency of transcobolamin.
Clinical manifestations of vit. B 12 deficiency:

**II.NEUROLOGY SYNDROME**:
Subacute combined degeneration of both posterior [ ataxia ] & lateral [ spastic paralysis ] columns of spinal cord, peripheral neuropathy, parasthesia in peripheral nerves, numbness, weakness, depressed stretch reflexes spasticity, ataxia, mental confusion, poor memory, hallucination & psychosis [ in late stage ].

**Diagnosis of vitamin B 12 Deficiency**:
This is very important because blood picture of Megaloblastic Anaemia occurring due to deficiency of either folic acid or vit. B 12 is indistinguishable. Hence, it needs utmost care to confirm the diagnosis of such anaemia whether it is due to deficiency of folic acid or vit. B 12 before institution of therapy. No doubt, administration of folic acid alone in vit. B12 deficiency will certainly improve the abnormalities of haemopoietic system but it will aggravate or precipitate the neurological abnormalities by diverting the small amount of vit. B 12 already present in the body to haemopoiesis [12-16].
Similarly, Vit.B 12 also should not be administered for undiagnosed megaloblastic anaemia. Proper haematological & biochemical workup is essential in determining the cause prior to the commencement of therapy. Even administration of a single dose of vit. B12 can interfere with the haematological picture for weeks leading to delay in diagnosis & starting the correct treatment [7].
The total plasma vit. B 12 is estimated which includes both holotranscobolamin & holoheptocorrin [Normal: 150 to 450 p mol/ L] & estimation of plasma holotranscobolamin alone is more sensitive & specific for vit. B 12 deficiency [Normal: 33 to 91 ng/ L].

**Management & Treatment of vit. B12 Deficiency & Prophylaxis**:
Preparation: Cyanocobalamin,, hydroxycobalamin & methylcobolamin are available both for oral & parenteral therapy. The choice of route depends on the cause of deficiency & severity of clinical states. It is rather wise, initially to add 2-5 mg folic acid & iron preparations orally to vit. B12 therapy.
1. Pernicious Anemia: Patient needs lifelong parenteral vit. B.12 therapy due to absence of Intrinsic Factor in stomach. Cyonocobolamin is the preparation of choice. Dosage schedules: It is administered intramuscularly in a dose of 1 mg [ 1000 mcg] once a week for eight weeks followed by 1 mg i.m. every month lifelong. It can also be administered by deep subcutaneous route but never by i.v. route(17)
2. Prophylaxis for VEGANS: Either cyanocobalamin or hydroxycobalamin is administered 1000 mcg i.m. thrice a week for two weeks to replenish body store of vit. B12 followed by 1 mg i.m. every three months as maintenance dose.
3. Tobacco & Alcohol Amblyopia: Hydroxyccbalamin is administered 1 mg i.m. once a week for 10 weeks.
4. Trigeminal neuralgia, multiple sclerosis & other neuropathies: Methylcobalamin is given orally [17-19].

## CONCLUSSION:
Vit. B12 acts as a coenzyme in certain important metabolic pathways. It is necessary for the conversion of homocysteine to methionine. It is required by all cells for synthesis of DNA, normal haemopoiesis & for maintenance of myelim, furthermore, in therapeutic armamentarium, there is no substitute of vit. B12 therapy in Pernicious Anaemia. It is indispensable for the treatment of pernicious anaemia, there is no second alternative. It is also absolutely needed for Vegans & breast-fed infants of vegan- mother whose diets do not contain it at all. & for other neuropathies.

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