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Deficiency of vitamin B_{12} and its relation with neurological disorders: a critical review

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Abstract

B_{12} is an essential vitamin for human body which reduces the chances of neurological diseases, birth defects, and chronic disorders. It is a vital micro-nutrient for maintaining the brain health. This review sorts out some causes of vitamin B_{12} (B_{12}) deficiency and develops its link with neurological disorders. The portals include PubMed, Google Scholar, Directory of Open Access Journals (DOAJ), Pak MediNet, and Science Direct were search for literature retrieval. Study of literature revealed that deficiency of this vitamin occurs primarily due to insufficient dietary intake which results in a group of neurological symptoms in adults as well as infants. These neurological disorders include apathy, anorexia, irritability, growth retardation, and developmental regression. It may also involve in delayed myelination or demyelination of neurons. It was concluded that B_{12} is vital micro-nutrient for healthy brain in children, younger, and elders. Various conditions are responsible for deficiency of B_{12}. A timely and proper supplementation is necessary if it is dietary deficiency.

Keywords: Deficiency, B_{12}, Disorders, Neurological, Review

Introduction

B_{12} is a water-soluble complex organic compound. It is required for normal development of animals, human beings, and even several microorganisms (Allen, 2004). Body is unable to synthesize in sufficient amount and must be taken in diet. It has a complex structure and contains a metallic ion along with cobalt. Several of its forms exist. However, cobalamin and cyan cobalamin are the most common forms (Andersen et al., 2010). It is synthesized by microorganisms in cows and sheep. In cows, it is transferred to muscle from rumen and other tissues. Human beings get this vitamin from diet consisting of cows flesh (Selhub, 2002). Other nutritional sources are eggs and dairy products. Strict vegetarians develop deficiency of B_{12} and must take fortified supplements (Black, 2008). Being water-soluble, B_{12} can flush out from organisms. Further, fat cells or fatty acid unable to stored it. Therefore, daily consumption level or upper intake level (UL) yet to establish (Kanazawa et al., 1983).

Several strong evidences prove that severe B_{12} deficiency leads to neuropathy or pernicious anemia, ileal resections, and gastrectomy (Dagnelie et al., 1989; Kozyraki et al., 1999). The pernicious anemia is rarely recorded in dietary B_{12} deficient people except young infants with solely breast feeders or strict vegetarians (Dagnelie et al., 1989).

Forms of B_{12}

If B_{12} has mineral cobalt, then it is cobalamin (Fyfe et al., 2004). Other forms include methyl cobalamin, deoxyadenosylcobalamin, hydroxocobalamin, and cyanocobalamin. Methyl cobalamin is the most active circulating form in humans and present in nutrition supplements. The body needs to convert this form into either methyl cobalamin or 5-deoxyandenosylcobalamin for its absorption (Briani et al., 2013) (Fig. 1).

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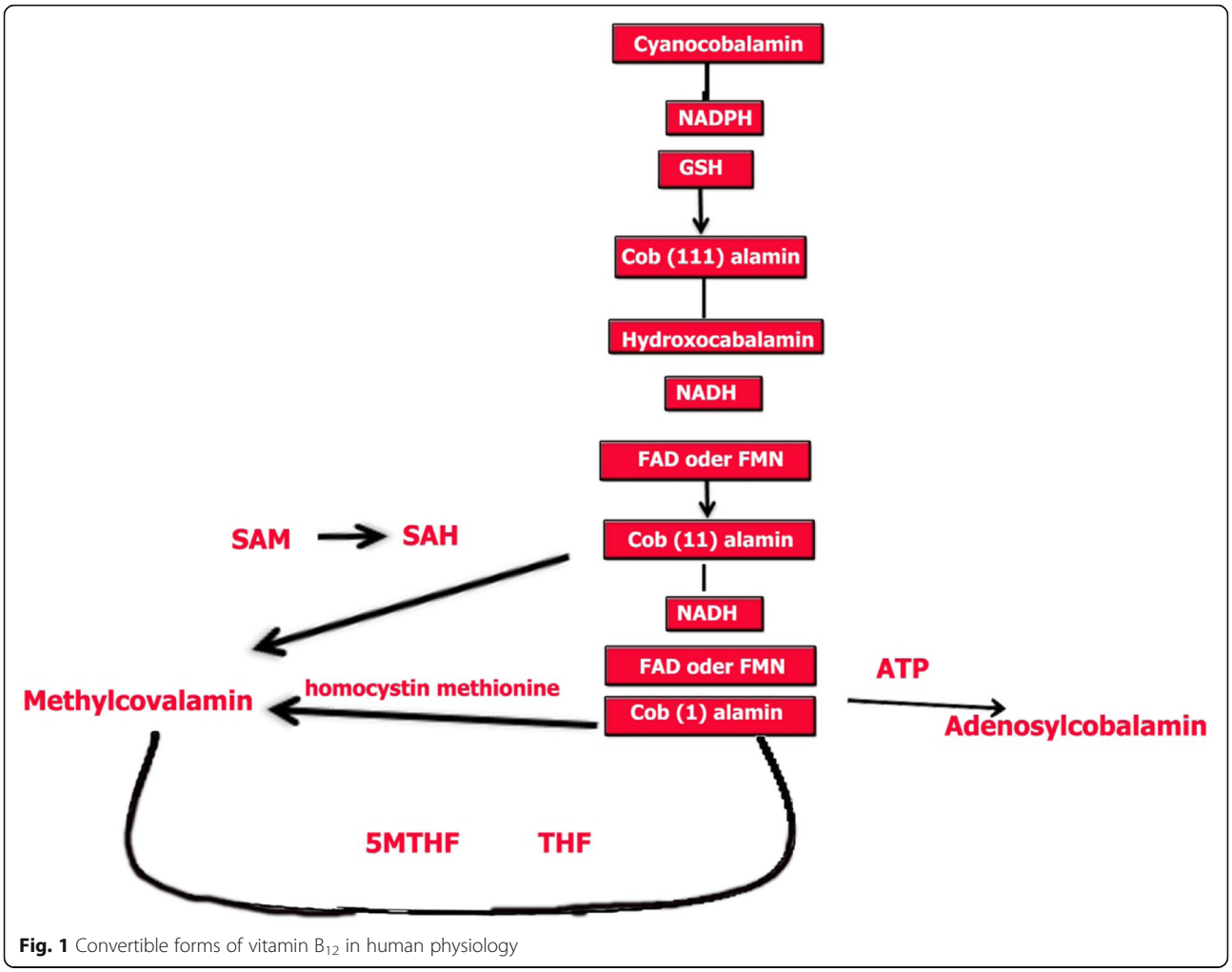

Fig. 1 Convertible forms of vitamin B_{12} in human physiology

Absorption and metabolism

Digestive system absorbs the cobalamin in three steps:

1. Food protein bounded with B_{12} is released by the action of gastric acid and pepsin and then taken by transcobalamin I (TCI) and then transported to the duodenum (Moestrup & Verroust, 2001).
2. An alkalizing action performed by pancreatic juices with its enzymes (tripsin, chymotrypsin and elastase) breakdown TCI and liberates cobalamin which joins an intrinsic factor (IF). The synthesis of this factor is carried out in parietal cells in the fundus and cardia of the stomach (Christensen & Birn, 2002; Nexo, 1998). It protects cobalamin and carries cubilin in the ileum.
3. Finally, IF-cobalamin complex shows tendency of binding towards cubilin and then taken up the enterocyte by a calcium-dependent passive transport mechanism system (Chanarin et al., 1978).

The chemical structure of cobalamin shows 1 cobalt atom with 4 pyrrole rings in corrin ring as a central part (Eschenmoser, 1988). Cobalamin has different names due to attached radical. For example, it is cyanocobalamin when attach atom is cyano radical, a highly stable compound. When attaches with adenosyland methyl radical, it is called adenosylcobalamin and methylcobalamin.

Cobalamin absorbed in ileum through cubilin receptor. It is a complex structure of cubilin, proteins—megalin and amnion associated transmembrane protein (AMN) (Nykjaer et al., 2001). Its molecular weight is 460 kDa and exists in proximal tubule. Absorption is carried out at acidic pH at 5.4. Three cobalamin-binding proteins (ascobalophilins), one carrier haptocorrin, or R protein are associated with absorption and recorded in mature granulocytes and monocytes of precursor cells. It is also observed in the saliva, bile, gastric acid, and breast milk secreted by exocrine epithelial cells (Nykjaer et al., 2001) (Fig. 2).

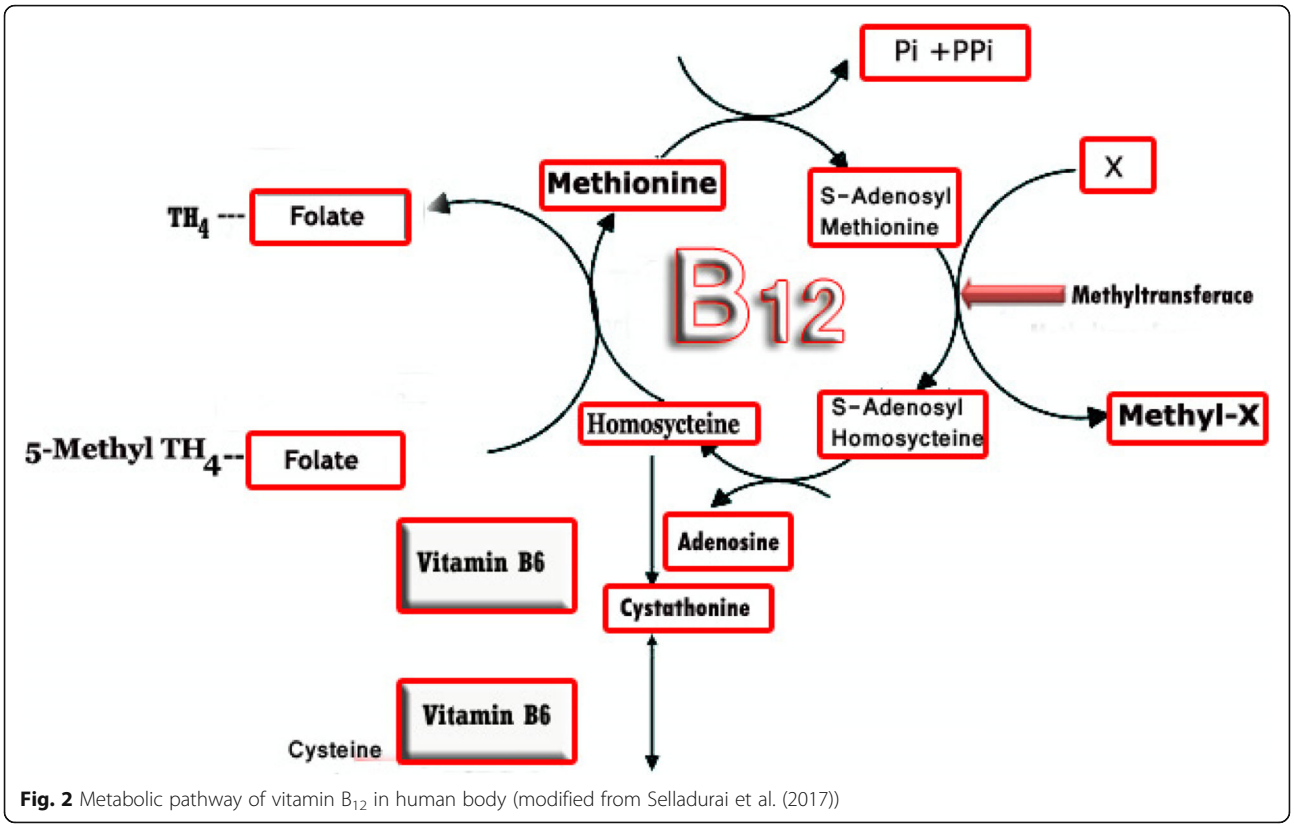

Fig. 2 Metabolic pathway of vitamin B_{12} in human body (modified from Selladurai et al. (2017))

Importance of B_{12}

Being micronutrient, B_{12} is essential for production and maintenance of RBCs and myelination of nerve cells. It also aids in neurotransmitter, DNA, and RNA production. Many people supplement the B_{12} via injections on a regular basis to a boost in energy level (de Benoist, 2008) (Fig. 3).

Pathophysiology

As origin of B_{12} is the bacterial synthesis in rumen of ruminant animals therefore, meat is a good source. After entry in the stomach, B_{12} is bounded to R-binders (protein) secreted by the salivary glands and stomach. While passing through the small intestine, pancreatic enzymes cleave B_{12} form R-binder and bound with intrinsic factor (IF). This IF is secreted by the parietal cells and glycoprotein in nature. B_{12} is then transported to plasma and bind with transcobalamin intracellularly. The absorption is very efficient in the distal ileum (enterohepatic recirculation). It takes many years a vegan person to deplete as long as his intestinal and hepatobiliary systems are intact. The liver is the largest storage site, and total body pool is about 2500 μg in normal adult.

Strict vegetarians are at high risk of deficiency. However, bacterial and insect contamination in food stuffs protects them to some extant against deficiency. Contamination of ruminant feces in vegetables and drinking water could also serve as a source of dietary B_{12} for vegetarians or economically poor areas of the world. Specific symptoms of deficiency are presented in Fig. 4.

Causes of deficiencies

Deficiency exists among all age, economic classes, races, and sexes. It is the most common nutritional deficiency in the USA (Allen, 2004). Diagnosis at early stage and its remedy is extremely necessary to prevent neurologic disorders, poor outcomes, or premature death (de Benoist, 2008). Some causes of deficiencies are as follows.

Pernicious anemia

Pernicious anemia is the most common cause of B_{12} deficiency. It is an auto-immune condition which affects 1 in 10,000 population. In this disease, an intrinsic factor required for absorption of B_{12} from food into the gastrointestinal tract is absent. However, the condition is common among people of over 60, in women, with family history and some autoimmune conditions including Addison's disease and vitiligo (Reid, 2010).

Autoimmune AG develops in condition when body produces antibodies against healthy stomach cells normally produced against viruses and bacteria. People with autoimmune AG target acidic juices producing healthy stomach cells. Intrinsic factor is also under influence of these antibodies and causes pernicious anemia. Deficiency of

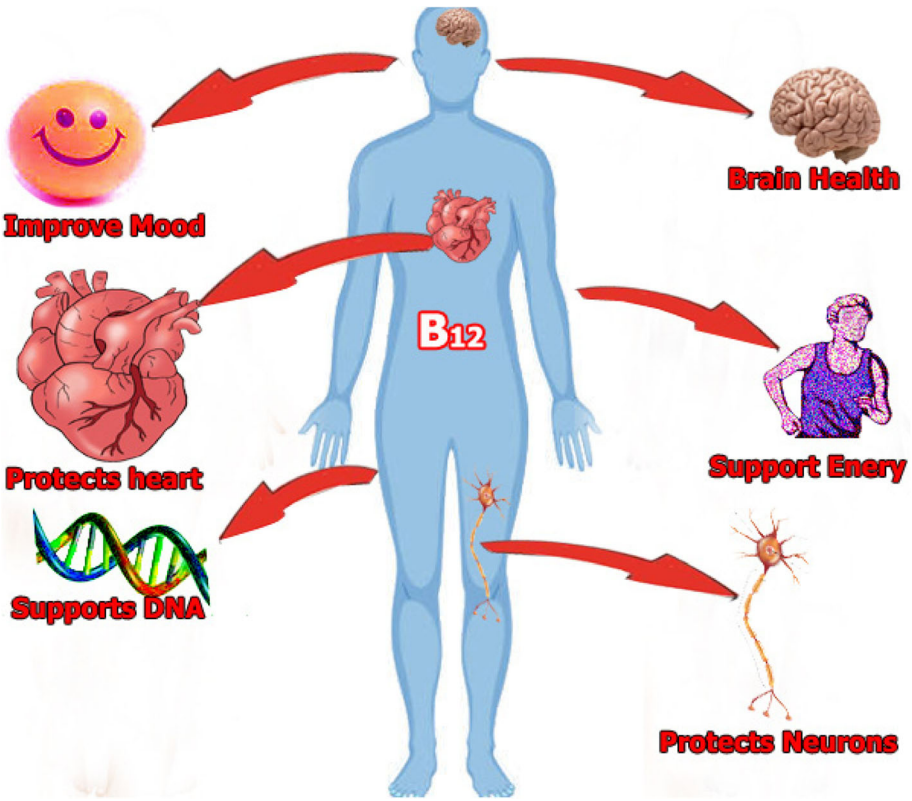

Fig. 3 Some key functions of vitamin B_{12} in human physiology

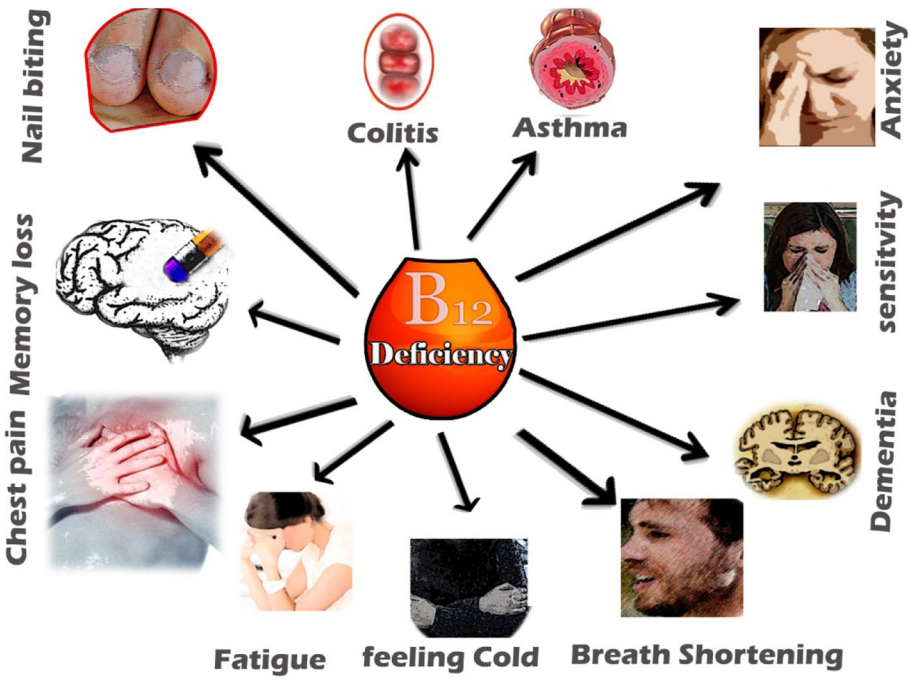

Fig. 4 Signs and symptoms in B_{12} Deficiency

B_{12} make impossible to produce enough healthy RBCs (Reynolds et al., 1993). B_{12} deficiency also occurs in abdominal tuberculosis when there is involvement of the terminal ileum.

Malabsorption

Absence or deficiency of HCl, pepsin, and haptocorrin (HC), *R-protein* or factor makes it difficult to B_{12} to extract from food in the stomach and transport intact in the small intestine (Wrong et al., 1981). Further, disorder in the stomach lining, and insufficient saliva and gastric juice also arise these circumstances (Katz et al., 1974). Absorption in the intestine requires intrinsic factor, pancreatic juice, and calcium. Deficiency or absence of any of these factors causes malabsorption (Veeger et al., 1962).

Rare genetic disorder can result in absence of transcobalamin. This leads to inadequacy of B_{12} for cells. Sometimes, transcobalaminis sufficiently available; however, large amount of biologically inactive B_{12} analogs binds with it and prevents actual vitamin B_{12} from binding to transcobalamin. Therefore, a deficiency can develop in spite of good absorption (Booth & Heath, 1962). Genetic disorder can also alter the structure and production of specific enzymes which changes B_{12} in coenzyme. In this step, genetic disorder prevents necessary metabolic processes from taking place in cells (Hakami et al., 1971) (Fig. 5).

Vegan diet

Some religious belief can also cause the deficiency. For example, the vegetarian people who do not eat the meat due to religious reasons have risk of B_{12} deficiency. Vegans usually have low B_{12} but higher folate concentrations. Half of the vegans having B_{12} deficiencies have a higher risk of developing clinical symptoms (Herrmann & Geisel, 2002).

Diagnosis

Diagnosis can be performed in a number of ways. A typical method is screening the patients for serum B_{12} level. However, the level of methylmalonic acid in serum is measured if the suspicion is strong and B12 level is low normal (Budson & Solomon, 2015).

Treatment of deficiency

Supplementation with B_{12} is conducted to treat deficiency either orally (if vegan diet) or parenterally (if atrophy gastritis). Monitoring is necessary with treatment, and cognition should return to normal (Budson & Solomon, 2015).

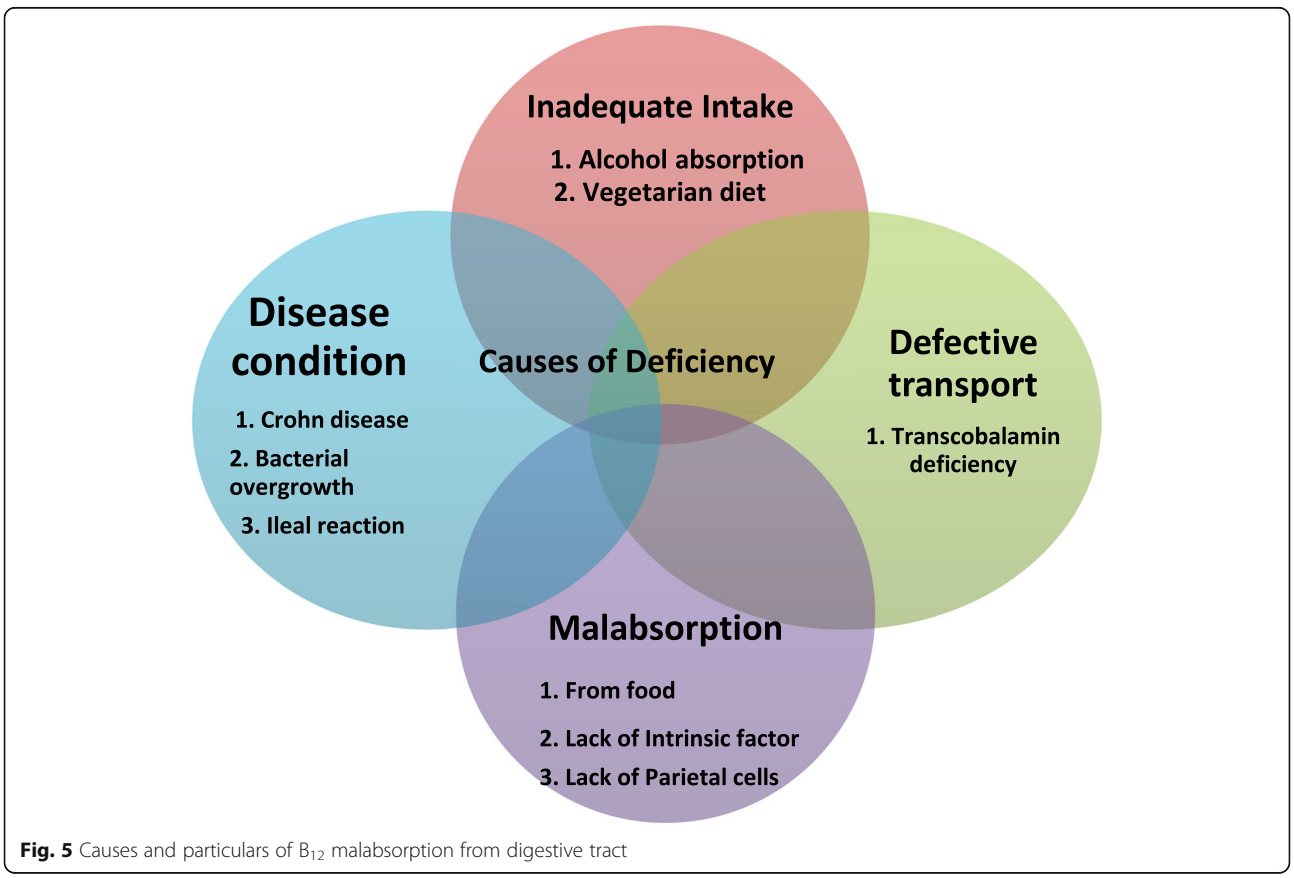

Fig. 5 Causes and particulars of B_{12} malabsorption from digestive tract

Neurological disorders

People from all age groups are suffered with depression, severe anxiety, and psychiatric disorders. These patients are prescribed costly psychotropic drugs, narcotics, or benzodiazepines; however, actually the problem is B_{12} deficiency (Selhub et al., 2008). Some diseases caused by B_{12} deficiency are as follows.

Myeloneuropathy

Myelopathy caused by lower concentration of B_{12} is *subacute combined degeneration* because symptoms develop slowly. It is also "combined" because multiple neurological symptoms develop in this degeneration (Aaron et al., 2005). The posterior column of spinal card is major part to damage. This part is the most important which controls and carries sensory information regarding vibrations, light touch, and position to brain. As a consequence of B_{12} deficiency, DNA is also damaged and leads to neurological damage; therefore, people feel numbness tingling (Román et al., 2002). The autonomic nerves can also be target of damage as these nerve fibers run through the spinal cord. In addition, it may also diminish vision and sense of smell. People may develop dementia in the final stage (Selhub et al., 2008).

Demyelination

B_{12} has important immune modulatory and neurotrophic effects in addition to role as cofactor in myelination (Miller et al., 2005). B_{12} deficiency and multiple sclerosis (MS) both have pathophysiological condition like inflammatory and neurodegenerative disorder. Resemblances in clinical findings and MRI presentation, it is very difficult to diagnose between B_{12} deficiency and MS. Further, decrease in levels of B_{12} demonstrated in patient with multiple sclerosis (Miller et al., 2005).

Alzheimer's disease

If a person feels behavior changes and agitation, it could be symptoms of Alzheimer disease. However, it can also be related to low levels of vitamin B_{12}. Deficiency produces large amount of mononuclear IL-6 in the peripheral blood. It is associated with slowly onset of Alzheimer disease which worse over time (Burns et al., 2009). In 60 to 70% cases, it causes dementia. The early symptom is short-term memory loss (Politis et al., 2010). The transcobalamin or holo TC level is associated with cognitive function and Alzheimer's disease (Renvall et al., 1989). However, this association with Alzheimer's disease was only present in patients with high homocysteine level. Further, low level of cobalamin in tissue or an interaction between homocysteine and cobalamin could also be the reason (Refsum, 2001). In Alzheimer's disease, dementia is caused by low level of B_{12} in serum of elderly persons (Osimani et al., 2005).

Atrophy or Brain shrinkage

The term atrophy means loss or shrinkage of cells. In brain atrophy, neurons and their connections waste away and cause the brain shrinkage than normal size. Infants with atrophy were diagnosed with vitamin B_{12} deficiency (de Jager, 2014). Other risk factor is homocysteine (Hcy) accumulation in plasma (Hogervorst et al., 2002; McCaddon et al., 2001). Conversion of Hcy to its metabolites, i.e., *S*-adenosyl methionine and glutathione depends on three vitamins as cofactors. These vitamins include B_9 (methyl folate), B_{12} (cobalamin), and B_6 (pyridoxine) (Morris et al., 2005; Refsum, 2001; Refsum et al., 2006). Suboptimal supply of B-vitamin in diet, remethylation of Hcy through methionine synthase is lowered and Hcy in plasma rise (Birch et al., 2009).

Sub-acute combined degeneration

Sub-acute combined degeneration (SCD) is progressive degenerative disorder which targets the spinal cord. It may also affect the nerves of the eyes and peripheral nervous system (Reynolds et al., 1993). B_{12} deficiency is the cause of SCD. In this disorder, damage to myelin sheath is occurred and followed by degeneration in axons (Victor & Lear, 1956). Initial symptoms are numbness, clumsy movements, and tingling sensation. Other symptoms are visual problems, weakness, cognitive disturbances, erectile dysfunctions, and abnormal reflexes in the bladder (Morris et al., 2005). Early B_{12} supplementation gives better results. However, delay can reduce the chance of recovery and lost the functionality (Werder, 2010).

Vascular complications

Elevated level of homocysteine in blood could be the risk factor for stroke along with other vascular complications (Tomkin et al., 1971). Quinlivan et al. (2002) demonstrated folic acid, and B_{12} fortified food could lower homocysteine levels and reduced the risk of vascular disease.

Neuropsychiatric abnormalities

Psychiatric problems are associated with B_{12} deficiency in adults between the ages of 40–90 years and rarely affect people of younger age (Stanger et al., 2003). The psychiatric manifestations include cognitive changes (like memory decline), depression, delusions, hallucinations, and dementia (Engelborghs et al., 2004). The mechanisms behind are instable production of neurotransmitters and elevated homocysteine and methylmalonic acid (MMA) level in B_{12} deficient people. Screening and supplementation of

B_{12} should be considered if there is no other obvious cause of a psychiatric disorder (Zengin et al., 2009).

Infantile seizures

During infancy, epileptic seizures have varied clinical presentations. It may have different outcomes according to etiology. B_{12} is also a rear cause of infantile seizures. Infants have the most common symptoms of B_{12} deficiency like feeding difficulties, seizures, growth retardation, megaloblastic anemia, developmental delay, hypotonia, microcephaly, lethargy, involuntary movements, irritability, and cerebral atrophy. Rarely, involuntary movements and seizures are the initial symptoms of deficiency. Involuntary movements are also reported after start of B_{12} supplementation in few cases. However, no information is present in literature regarding seizures (Benbir et al., 2007).

Poor fetal brain and cognitive development

Vitamin B_{12} and folate play a key role in fetus brain development. Both are also crucial for myelination in new born baby in first 2 years and till puberty (Hellegers et al., 1957). As B_{12} deficiency constrained in myelination, child develops varied cognitive and intellectual problems depending upon the area of the nervous system affected (Graber et al., 1971). Deficiency of both in pregnant women needs supplements in order to prevent neurological disorders in fetus (Wilson et al., 1999). Elderly people face problem to absorb this vitamin from food sources so its deficiency can be fulfilled with supplements (Rosenberg, 2005). Vegans also face deficiency which may be restored by supplements. Minimum per take uptake to prevent the deficiency provided in Table 1 (IOM, 1998).

Table 1 Age-wise requirement of vitamin B_{12} (microgram) in human (IOM 1998)

Age	Requirement per day (μg)
0–6 months	0.4
7–12 months	0.5
1–3 years	0.9
4–8 years	1.2
9–13	1.8
14 years and older man	2.4
14 years and older women	2.4
Pregnant women	2.6
Breast feeding women	2.8

Conclusion

It was concluded that B_{12} is vital micro-nutrient for maintaining healthy brain in children, youngers, and elders. Various conditions are responsible for B_{12} deficiency. A timely and proper supplementation is necessary if it is dietary deficiency. This supplementation can prevent the damage to nervous system. Deficiency may leads to cognitive decline and vascular risk factors in neuropsychiatric disorders. Therefore, recognition and early management reverse deficiency state. Some behavioral or psychological disorders are related to dementia and depression which can be improved with B_{12} supplementation.

Abbreviations

B12: Vitamin B12; DOAJ: Directory of Open Access Journals; HC: Haptocorrin; Hcy: Homocysteine; IF: Intrinsic factor; IOM: Institute of Medicine; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; SCD: Sub-acute combined degeneration; TCI: Transcobalamin I; UL: Upper intake level

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Authors' contributions

AN and NNK search the different data base for literature retrieval. MSK arrange, compile the format, and handle the correspondence. HN and SS selected the literature and finalize the manuscript. The authors read and approved the final manuscript.

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Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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