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Lina Begdache

Rani Marhaba

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Is it Time to Revisit Vitamin B12 for Mental Health and Cognitive Functions in Elderly?

Lina Begdache[1]* and Rani Marhaba[2]

[1]*Department of Health and Wellness Studies, Binghamton University, USA*

[2]*Department of Biological Sciences, Binghamton University, USA*

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***Corresponding author:** Lina Begdache, Department of Health and Wellness Studies, Binghamton University, New York, USA, Tel: 607-777-5299; Email: lina@binghamton.edu

Abstract

Decline in cognitive and motor functions and in mental health are commonly seen with aging. Although many reports attribute their etiology to aging, these conditions may have vitamin B12 deficiency as an underlying mechanism. Laboratory tests to assess vitamin B12 deficiency lack sensitivity and specificity largely due to absence of a gold standard for diagnosis. Additionally, patients with subclinical vitamin B12 deficiency have typically normal serum concentration levels and do not exhibit the classical symptoms of vitamin B12 deficiency. Furthermore, many comorbidities that exist with aging decrease vitamin B12 and bioavailaibility from the gut. If left untreated, vitamin B12 deficiency leads to irreversible nerve damage and brain atrophy which may result in mood alteration and cognitive decline. Microstructural changes in the myelin sheath have been described to alter the central nervous function. Additionally, elevated levels of serum homocysteine and epigenetic modifications have been documented with vitamin B12 deficiency. However, due to lack of vitamin B12 test sensitivity, many reports in the literature have failed to report a link between vitamin B12 deficiency and cognitive and mental health decline in elderly. The review suggests that there is a need to re-evaluate the role of vitamin B12 in these functions, especially in patients with comorbidities. Standardization of vitamin B12 testing across studies is needed to provide a better consensus of the actual role of vitamin B12 on cognitive function and mental health across populations.

Keywords: Vitamin B12; Cobalamin; Mood; Mental health; Cognitive functions; Elderly

Abbreviations: VB12D: Vitamin B12 Deficiency; CD: Cognitive Decline; IF: Intrinsic Factor; MMA: Methymalonic Acid; HCL: Hydrochloric Acid; PPI: Proton Pump Inhibitors; OCMP: One-Carbon Metabolism Pathway; HCY: Homocysteine

Introduction

Aging is often accompanied by a decline in cognitive and motor functions and in mental health. Although considered part of aging, these conditions may have vitamin B12 deficiency (vB12D) as an underlying mechanism. Research on the effect of vitamin B12 on brain health has dwindled down as many studies reported negative associations between vB12D and brain health. However, many patients exhibit broad or minor symptoms that leave vB12D undocumented. Additionally, laboratory tests to assess vB12D lack sensitivity and specificity largely due to absence of a gold standard for diagnosis [1]. In fact, many patients with subclinical vB12D exhibit normal serum concentration levels. Stereotypically, they are classified as asymptomatic based on the classical symptoms of vB12D. Additionally, the minimum concentrations of serum vitamin B12 for optimal neuronal health are not currently known, especially for those above the age of 50. If left untreated, vB12D leads to irreversible nerve damage and brain atrophy. Therefore, mood alteration and cognitive decline (CD) seen in the elderly population may be consequences of these changes. Increased risk of atrophic gastritis, higher prevalence of pernicious anemia and increased comorbidities with aging put elderly population at a higher risk for vB12D. Serum methylmalonicacid (MMA) and homocysteine levels are considered more sensitive biomarkers of vB12D than the actual serum levels of the vitamin. Classical clinical manifestations of vB12D include megaloblastic anemia and neurological dysfunctions. Typically, neurological and psychological symptoms of vB12D develop way before hematological changes [2]. In the Western world, vB12D is mostly linked to malabsorption since the Western diet is a rich source of animal food products. However, in the developing world vB12D is mostly due to low intake of meat.

Discussion

Vitamin B12

Vitamin B12, also known as cobalamin, is made-up of a corrin ring in which a cobalt atom is centrally positioned. Therefore, the structurally complex vitamin requires special carriers for transport and absorption from the ileum of the small intestine.

Salivary and gastric haptocorrins (R-proteins) bind vitamin B12 with high affinity to protect it from enzymatic degradation. The intrinsic factor (IF), which is secreted by the parietal cells of the gastric mucosa, aids with its distal absorption. Vitamin B12 is transferred to the IF in the intestinal lumen by means of a pH-dependent process and with the help of pancreatic proteases. Additionally, the cannalicular membrane of parietal cells host H+/K+ AT Pases or proton pumps that produce hydrochloric acid (HCL). Gastric acid assists with release of cobalamin from food by denaturing the tertiary and quaternary protein structures. Moreover, HCL converts pepsinogen into pepsin to further assist with vitamin B12 release from food.

Conditions that may lead to vitamin B12 deficiency

Cellular aging or senescence decreases organ function and ability to repair tissue damage. Consequently, the aging gastrointestinal tract experiences structural and functional changes that may impact bioavailability of a number of nutrients. Vitamin B12 is among those nutrients affected by these alterations. In atrophic gastritis, reduced acid production may have a pronounced impact on the bioavailability of cobalamin due to poor absorption [3]. Additionally, Proton Pump Inhibitors (PPIs) reduce the release of IF from parietal cells [3]; therefore, prolonged use of PPIs predisposes individuals to vB12D. The transfer of vitamin B12 from R-protein to IF requires pancreatic enzymatic degradation. Consequently, pancreatic insufficiency and chronic pancreatitis may contribute to vB12Das well [4]. Vegan and vegetarians are at risk since vitamin B12 is solely found in animal food [5]. Other population at risk include patients who have undergone vertical sleeve gastrectomy [6] or with compromised ileum (Celiac and Crohn's diseases) [7]. Those on metformin, on H2-receptor antagonists [8] or with end stage renal disease may also experience vB12D [9]. Alcohol drinking [10] and chronological aging [11] add to the etiology. Therefore, many conditions and comorbidities that are prevalent in elderly predispose to vB12D.

Although cobalamin deficiencies take years to develop, patients with compromised absorption are at a higher risk for developing the sub-clinical symptoms [12]. In fact, anxiety and depressive symptoms have been documented in patients with chronic pancreatic diseases [13], PPI use [14], inflammatory bowel diseases [15], veganism [16] and in old age. However, the majority of reports attribute mental distress to living with the disease, and cognitive decline in these patients is usually attributed to aging. Nevertheless, a review study described that vB12D is linked to anxiety and depressive symptoms [17]. Recent report describes that vB12D, as revealed by MMA test (nonetheless serum vitamin B12 levels were within a normal range), associates with poor cognitive functions after adjusting for age, sex, education, apolipoprotein E e4 status, and total homocysteine, folate, and creatinine [2]. Many reports describe a gradual microstructural integrity loss of the nervous system that may induce the sub-clinical symptoms. These tiny alterations are not detectable in imaging tests [2,18]. Mechanistically, vitamin B12 is a key co-factor for two essential enzymes involved in myelin biosynthesis, methionine synthase and L-methylmalonyl-coenzyme A mutase. However, individual components of the myelin sheath have differential turnover rates (ranging from 3 weeks to 3 months) which explain the microstructural abnormalities associated with vitamin B12 insufficiency. Therefore, nerve function may gradually decline as a result of loss of myelin integrity. Additionally, age is another factor that may alter the turnover rate of myelin biosynthesis [19].

One carbon metabolism and potential epigenetic modifications

Vitamin B12 plays a crucial role in the one-carbon metabolism pathway (OCMP), which is folate (vitamin B9), vitamin B12 and vitamin B6-dependent. OCMP is involved in genomic stability, antioxidant enzyme synthesis, DNA methylation, epigenetic modification, RNA editing, noncoding RNA, micro RNA. OCMP also contributes to metabolism of serotonin, dopamine and noradrenaline which are important neurotransmitters to support brain and mental health. Derangement of this pathway has been linked to abnormal metabolomic profile and increased risk for CD and mood alteration among other conditions. Epigenetic marks involve covalent modifications of DNA and post-translational modifications of histone proteins. Genomic DNA of eukaryotic cells (such as in human beings) is organized in the form of chromatin which exists on a wide continuum of euchromatin and heterochromatin structures. DNA is organized around core histone proteins (H2A, H2B, H3 and H4) forming the dynamic nucleosome. histone proteins are positively charged at their lysine and arginine residues which induces a favorable electrostatic interaction with the negative phosphate backbone of DNA. A set of histone and DNA-specific enzymes reprogram gene expression repertoire by orchestrating activation (acetylation) or repression (methylation) of a cluster of genes in response to environmental cues [20]. The OCMP is a source of methyl tags that methylate genes. These chemical alterationslead to chromatin remodeling which in turn alter the pattern of gene expression. Recent evidence suggests that aberrant gene expression in key brain regions like the hippocampus and prefrontal cortex reduces the ability of the brain to undergo neurogenesis and neuroplasticity, respectively. Reports in the literature describe that dysregulation of the OCMP associates with CD and mental distress; however, some conclusions state that the decline is independent of vB12D [21,22] while others associate it with CD. Interestingly, the studies that solely evaluated serum levels of vitamin B12 reported no link; while those that used the more sensitive biomarkers (such as MMA) reported an association [2,23]. Beside epigenetic modifications, disruption of the OCMP leads to hyperhomocysteinemia. Homocysteine is a thiol-containing non-protein amino acid that is synthetized by transmethylation of methionine in the OCMP. Accumulation of Hcy stimulates homocysteinylation of proteins where the free thiol group of Hcy forms a disulfide bond with another free thiol group derived from a cysteine (Cys) residue in a protein molecule. This structural modification alters the

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overall redox potential of proteins inducing oxidative stress and inflammation [24]. The latter have been reported to associate with hippocampal atrophy. Adult-induced neurogenesis in the hippocampus has been reported to produce robust synaptic plasticity which associates with improved cognitive functions and a positive mood [25]. Neuroinflammation negatively impacts neurogenesis and leads to hippocampal atrophy which has been associated with CD and mental distress [13,26]. In fact, consumption of dietary antioxidants in older adults associates with improved mental wellbeing, which may suggest a higher level of oxidative stress in this cohort [27]. Moreover, diets high in antioxidants (such as the Mediterranean diet) preserve hippocampal volume and reduce CD and mental distress [28].

Conclusion

Taken collectively, there is a need to re-evaluate the function of vitamin B12 in CD and mental health in elderly with comorbidities. Standardization of vitamin B12 testing across studies may provide a better consensus of the actual role of vitamin B12 on cognitive function and mental health across populations.

References

1. Berg, RL, Shaw GR (2013) Laboratory evaluation for vitamin B12 deficiency: The case for cascade testing. Clin Med Res 11(1): 7-15.
2. Köbe T, Witte AV, Schnelle A, Grittner U, Tesky VA, et al. (2016) Vitamin B12 concentration, memory performance, and hippocampal structure in patients with mild cognitive impairment. Am J Clin Nutr 103(4): 1045-1054.
3. Heidelbaugh JJ (2013) Proton pump inhibitors and risk of vitamin and mineral deficiency: Evidence and clinical implications. Ther Adv Drug Saf 4(3): 125-133.
4. Guéant JL, Champigneulle B, Gaucher P, Nicolas JP (1990) Malabsorption of vitamin B12 in pancreatic insufficiency of the adult and of the child. Pancreas 5(5): 559-567.
5. Asok AC (2003) Vegetarianism and vitamin B-12 (cobalamin) deficiency. Am J Clin Nutr 78(1): 3-6.
6. Pech N, Meyer F, Lippert H, Manger T, Stroh C (2012) Complications and nutrient deficiencies two years after sleeve gastrectomy. BMC Surgery 12(1): 12-13.
7. Dahele A, Ghosh S (2001) Vitamin B 12 deficiency in untreated celiac disease. Am J Gastroenterol 96(3): 745-750.
8. Reinstatler L, Qi YP, Williamson RS, Garn JV, Oakley J, et al. (2012) Association of biochemical B_{12} deficiency with metformin therapy and vitamin B_{12} supplements: The national health and nutrition examination survey, 1999-2006. Diabetes Care 35(2): 327-333.
9. Amini M, Khosravi M, Baradaran HR, Atlasi R (2015) Vitamin B12 supplementation in end stage renal diseases: A systematic review. Med J Islam Repub Iran 29: 167.
10. Laufer EM, Hartman TJ, Baer DJ, Gunter EW, Dorgan JF, et al (2004) Effects of moderate alcohol consumption on folate and vitamin B12 status in postmenopausal women. Eur J Clin Nutr 58(11): 1518-1524.
11. Hanna S, Lachover L, Rajarethinam RP (2009) Vitamin b_{12} deficiency and depression in the elderly: Review and case report. Prim Care Companion J Clin Psychiatry 11(5): 269-270.
12. Green R (2017) Vitamin B12 deficiency from the perspective of a practicing hematologist. Blood 129(19): 2603-2611.
13. Nordqvist C (2017) What's to know about chronic pancreatitis?
14. Kimura Y, Kamiya T, Senoo K, Tsuchida K, Hirano A, et al. (2016) Persistent reflux symptoms cause anxiety, depression, and mental health and sleep disorders in gastroesophageal reflux disease patients. J Clin Biochem Nutr 59(1): 71-77.
15. Bannaga AS, Selinger CP (2015) Inflammatory bowel disease and anxiety: Links, risks, and challenges faced. Clin Exp Gastroenterol 8: 111-117.
16. Hibbeln JR, Northstone K, Evan J, Golding J (2018) Vegetarian diets and depressive symptoms among men. J Affect Disord 225: 13-17.
17. Coppen A, Bolander-Gouaille C (2005) Treatment of depression: Time to consider folic acid and vitamin B12. J Psychopharmacol 19(1): 59-65.
18. Gupta K, Jain A, Rohatgi A (2018) An observational study of vitamin b12 levels and peripheral neuropathy profile in patients of diabetes mellitus on metformin therapy. Diabetes Metab Syndr 12(1): 51-58.
19. Ando S, Tanaka Y, Toyoda Y, Kon K (2003) Turnover of myelin lipids in aging brain. Neurochem Res 28(1): 5-13.
20. Nair N, Shoaib M, Storgaard-Sørensen C (2017) Chromatin dynamics in genome stability: Roles in suppressing endogenous DNA damage and facilitating DNA repair. Int J Mol Sci 18(7): E1486.
21. Mendonça N, Granic A, Mathers J, Martin-Ruiz C, Wesnes K, et al. (2017) One-carbon metabolism biomarkers and cognitive decline in the very old: The new castle 85+ study. J Am Med Dir Assoc 18(9): 806.e19-27.
22. Kim JM, Shin IS, Yang SJ, Kim SJ, Lee SY, et al. (2007) One-carbon metabolism and cognitive impairment in a Korean community population. Clinical Psychopharmacology and Neuroscience 5(2): 65-69.
23. Lehmann M, Gottfries CG, Regland B (1999) Identification of cognitive impairment in the elderly: Homocysteine is an early marker. Dement Geriatr Cogn Disord 10(1): 12-20.
24. Petras M, Tatarkova Z, Kovalska M, Mokra D, Dobrota D, et al. (2014) Hyperhomocysteinemia as a risk factor for the neuronal system disorders. J Physiol Pharmacol 65(1): 15-23.
25. Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, et al. (2011) Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature 472(7344): 466-470.
26. Valero J, Bernardino L, Cardoso FL, Silva AP, Fontes-Ribeiro, et al. (2017) Impact of neuro inflammation on hippocampal neurogenesis: Relevance to aging and Alzheimer's disease. J Alzheimers Dis 60(S1): S161-S168.
27. Begdache L, Chaar M, Sabounchi N, Kianmehr H (2017) Assessment of dietary factors, dietary practices and exercise on mental distress in young adults versus matured adults: A cross-sectional study. Nutr Neurosci 11: 1-11.
28. Gu Y, Brickman A, Stern Y, Habeck C, Razlighi Q,, et al. (2015) Mediterranean diet and brain structure in a multiethnic elderly cohort. Neurology 85(20): 1744-1751.

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