

Vitamin B12 Deficiency: An Important Reversible Co-Morbidity in Neuropsychiatric Manifestations

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ABSTRACT

Background: Vitamin B12 deficiency is a common condition causing neurologic, cognitive, psychiatric, and mood symptoms. With varied religious, ethnic, and socioeconomic heterogeneity among the people in India greatly influencing their dietary habits and with the high prevalence of *Helicobacter pylori* infection, Vitamin B12 deficiency is not uncommon, but is often under recognized due to the lack of classical symptomatic presentation. **Materials and Methods:** Retrospective study on Vitamin B12 deficiency with neuropsychiatric symptoms in patients who attended neurology, psychiatry, and geriatric OPDs for a period of 1 year in a specialized neuropsychiatric institute in South India. **Results:** Out of 259 patients who had Vitamin B12 deficiency (<220 pmol/L), 60 had neuropsychiatric symptoms. Among them the Vitamin B12 levels were <150 (severe), 150-200 (moderate), and 201-220 pmol/L (mild) in 19, 24, 17 patients, respectively. Twenty one were diagnosed with Posterior dementias, 20 with frontotemporal dementia, 7 with Schizophrenia, 4 each with Parkinson's disease and alcohol-dependent syndromes (ADS), 3 with bipolar affective disorder, and 1 with Creutzfeldt-Jakob disease. Eight patients also had hypothyroidism. First symptom of presentation was behavioral disturbances in 30 (50%), memory loss in 20 (33.9%), and sensorimotor and movement disorders in 9 (15.3%), and 56.7% were vegetarians while 43.3% were nonvegetarians. In our study, Vitamin B12 deficiency was more prevalent in elderly males (56.67%) and was associated with increased severity of behavioral disturbances ($P = 0.043$) which was the most common presentation. Memory loss was present in 16 (84.2%) patients of severe Vitamin B12 deficiency. Hindi mental status examination (HMSE) score was graded as <20, 20-24, 24-31 in 37 (61.7%), 10 (16.7%), and 13 (21.7%) patients, respectively. Cognitive decline in Vitamin B12 deficiency was significantly associated with increased serum cholesterol ($P = 0.019$) and was significantly prevalent in neurological disorders when compared with primary psychiatric illnesses ($P = 0.001$). Mean folate and mean homocysteine in our study was 11.7 ± 6.44 ng/ml and 17.77 ± 5.45 μ mol/L, respectively. Eighty percent of the population had normal folate levels whereas mean homocysteine values were much higher than that of the western population (10-12 μ mol/L). **Conclusion:** Vitamin B12 deficiency though common in India is often overlooked. It increases the load of cognitive decline and accentuates vascular risk factors in neuropsychiatric illnesses. Vitamin B12 deficiency also increases homocysteine levels contributing to the vascular comorbidity in cerebro and cardiovascular illnesses. So prevention, early detection, and management of this reversible Vitamin B12 deficiency state is of profound importance.

Key words: Cognitive decline, co-morbidity, elderly, folate, homocysteine, neuropsychiatric illness, neuropsychiatry, Vitamin B12, Vitamin B12 deficiency

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INTRODUCTION

Vitamin B12 (cobalamin) is a complex water soluble micronutrient, chiefly available in animal protein. It serves as a cofactor for methionine synthesis by transfer of methyl group to homocysteine which is

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an atherogenic and potential endothelial toxin. This conversion of homocysteine to methionine forms demethylated tetrahydrofolate (THF) which is required for DNA synthesis. Further metabolism of methionine to S-Adenosyl methionine (SAM) is essential for myelin synthesis and maintenance of neuronal integrity as well as neurotransmitter regulation.^[1,2]

Vitamin B12 deficiency is a common but often under recognized condition causing neurologic, cognitive, psychiatric, and mood symptoms. Diverse religions, ethnic, and socioeconomic heterogeneity of the people of Asian countries particularly in India greatly influencing their dietary habits and with the high prevalence of *Helicobacter pylori* infections,^[3] use of oral contraceptive pills,^[4] diabetic medications like metformin,^[5] presence of intestinal parasites especially *Diphyllobothrium latum* (fish tapeworm),^[6] and chronic alcoholism,^[7] Vitamin B12 deficiency in India is not uncommon. But it is often under recognized due to the lack of classical symptomatic presentation.

According to Refsum *et al.*, In India Vitamin B12 deficiency is seen in about 3.8% of the population.^[8] About 75% of the subjects had metabolic signs of cobalamin deficiency, which was only partly explained by the vegetarian diet.^[8]

In the developed countries, 6% of those aged 60 years and above are Vitamin B-12 deficient (plasma Vitamin B-12, 148 pmol/L).^[9] The prevalence of subnormal Vitamin B12 concentration in elderly varies from 3-40.5% depending on the cut-off used for defining deficiency of the cobalamin level in serum.^[10] In developing countries, deficiency is much more common, starting in early life and persisting across the life span and the prevalence of deficiency increasing with age.^[9]

According to previous studies there is no much information on the extent of Vitamin B12 deficiency in elderly Indians as determined by plasma Vitamin B12 levels.^[10] Therefore, studying the co-morbid Vitamin B12 deficiency status in neuropsychiatric symptoms in the elderly thus becomes important as it is a potentially reversible burden.

MATERIALS AND METHODS

We did a retrospective study analyzing the hospital records for a period of 1 year from 31st May 2011 to 1st June 2012. Data were collected from the patients of geriatric age group (>60 years)^[11] who had Vitamin B12 deficiency (220 pmol/lit)^[9,12] and presented with neuropsychiatric symptoms in neurology and geriatric clinic services of our institute. Study was approved under the institutional ethical committee. Patients with

chronic infections, malignancies, and intracranial space occupying lesions were excluded.

Vitamin B12 levels were assayed by Siemens IMMULITE 1000 Immunoassay System and results obtained in pmol/L.

Data were analyzed using SPSS version 16 software and results obtained.

RESULTS

Among 259 patients of geriatric age group (>60 years) who had neuropsychiatric manifestations, 16% ($n = 60$) had Vitamin B12 deficiency (<220 pmol/L). Among 60 patients, the Vitamin B12 levels were <150 pmol/L (severe), 150-200 pmol/L (moderate), and 201-220 pmol/L (mild) in 19, 24, 17 patients, respectively [Figure 1].

Twenty-one patients were diagnosed with posterior dementias (Alzheimers disease and diffuse lewy body dementia), 20 (33.33%) had features of Frontotemporal dementia, 7 with Schizophrenia, 4 each with Parkinson's disease and alcohol-dependent syndromes (ADS), 3 with bipolar affective disorder, and 1 with Creutzfeldt-Jakob disease. 8 patients also had hypothyroidism. First symptom of presentation was behavioral disturbances in 30 (50%), memory loss in 20 (33.9%), and motor/movement disorders in 9 (15.3%) [Figure 2].

In our study, Vitamin B12 deficiency was more prevalent in elderly males (56.67%) and was associated with increased severity of behavioral disturbances ($P = 0.043$) which was the commonest presentation [Figure 3].

Hindi mental status examination (HMSE) score was graded as <20, 20-24, 24-31 in 37 (61.7%), 10 (16.7%) and 13 (21.7%) patients, respectively. Cognitive decline

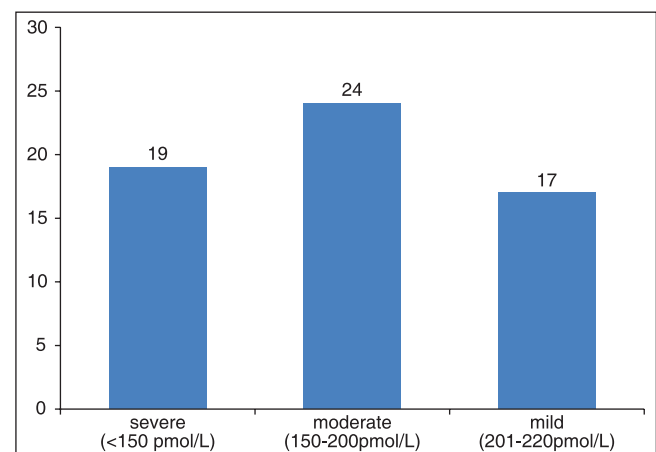


Figure 1: Patients with Vitamin B12 deficiency

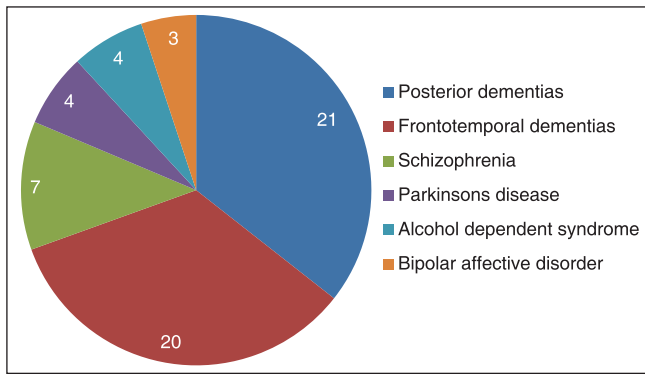


Figure 2: Disease distribution among Vitamin B12 deficient patients

in Vitamin B12 deficiency was significantly ($P = 0.019$) associated with increased serum cholesterol and was significantly prevalent in neurological disorders when compared with psychiatric illnesses ($P = 0.001$). Mean folate and mean homocysteine in our study was 11.7 ± 6.44 ng/ml and 17.77 ± 5.45 μ mol/L, respectively. Eighty percent of the population had normal folate levels whereas mean homocysteine values were much higher than that of the western population (10-12 μ mol/L).

DISCUSSION

More than one fifth (23.16%) of the patients we studied had concomitant Vitamin B12 deficiency (<220 pmol/L). This illustrates the high magnitude of co-morbid Vitamin B12 deficiency burden in this geriatric age group (>60 years) who presented with neuropsychiatric manifestations.

Vitamin B12 levels were divided into mild (201-220 pmol/Lit), moderate(150-200 pmol/Lit) and severe deficiency (<150 pmol/Lit) states based on previous studies.^[9,12]

Thirty four (56.7%) were vegetarians among the 60 patients, and interestingly there was an increased prevalence of Vitamin B12 deficiency in nonvegetarians who constituted 26 patients (43.3%). This shows that even nonvegetarians are also vulnerable unlike the previous studies.^[13] Further studies are required for looking into the dietary patterns in Vitamin B12 deficiency in strict vegetarians comparing with nonvegetarians.

Seventeen (28.33%), 24 (40%), 19 (31.67%) patients had mild, moderate, and severe Vitamin B12 deficiency states, respectively. When moderate and severe deficiency values were put together there were 43 patients (71.67%) who had considerably lower levels of Vitamin B12. This implicates the severity of this deficiency as well as the need for early parenteral

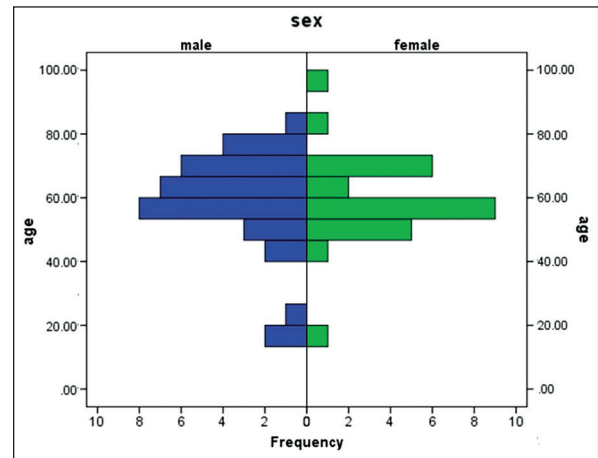


Figure 3: Gender distribution of Vitamin B12 deficient patients

intervention in patients with neuropsychiatric manifestations.

Twenty-one patients were diagnosed clinically and radiologically with Posterior dementias (Alzheimers disease and diffuse Lewy body dementia), 20 (33.33%) had features of frontotemporal dementia, 7 with Schizophrenia, 4 each with Parkinson’s disease, and alcohol-dependent syndromes (ADS), 3 with bipolar affective disorder, and 1 with Creutzfeldt-Jakob disease. This shows Vitamin B12 deficiency burden is more among patients who had neurodegenerative dementias.

Eight patients also had hypothyroidism. Because of the synergistic occurrence of Vitamin B12 deficiency and hypothyroidism,^[14] screening for hypothyroidism becomes important in neuropsychiatric patients presenting with Vitamin B12 deficiency. Thus, Vitamin B12 deficiency can be one of the important causes of reversible cognitive decline, acting as a second hit in hypothyroid patients.

In our study, Vitamin B12 deficiency was more prevalent in elderly males (56.67%) and was associated with increased severity of behavioral disturbances ($P = 0.043$) which was the commonest presentation. First symptom of presentation was behavioral disturbances in 30 (50%), memory loss in 20 (33.9%), and sensorimotor/movement disorders in 9 (15.3%). This shows that behavioral disturbances and cognitive decline can be exaggerated in these neuropsychiatric patients due to the comorbid Vitamin B12 deficiency. Thus, when evaluating geriatric patients with behavioral disturbances and memory loss, Vitamin B12 deficiency should also be borne in mind in addition to neurodegeneration and primary psychiatric illnesses.

Mean folate in this population was 11.7 ± 6.44 ng/ml and 80% of the population had normal folate levels. Folate

and Vitamin B12 have a significant interrelationship in myelination as well as maturation of RBCs. In our study majority of the patients had normal range of folate levels paving a way to study the exclusive role of Vitamin B12 deficiency in increasing cognitive burden.

Mean homocysteine values were $17.77 \pm 5.45 \mu\text{mol/L}$ which was much higher than that of the western population ($10\text{-}12 \mu\text{mol/L}$) as described in several previous Indian studies.^[8] This higher homocysteine level in Indian population could be indicative of the susceptibility to cerebrovascular and cardiovascular illnesses which can be potentially prevented by administering Vitamin B12 and folic acid.

Hindi mental status examination (HMSE) was scored and graded as severe (<20), moderate ($20\text{-}24$) and mild ($24\text{-}31$) cognitive decline in 37 (61.7%), 10 (16.7%), and 13 (21.7%) patients, respectively. Majority of the patients were observed to have severe cognitive decline which could be also due to the Vitamin B12 deficiency which is potentially reversible. Cognitive decline in Vitamin B12 deficiency was significantly ($P = 0.019$) associated with increased serum cholesterol and was significantly prevalent in neurological disorders when compared with psychiatric illnesses ($P = 0.001$). Our study shows that dyslipidemia in conjunction with Vitamin B12 deficiency significantly affects cognitive function ($P = 0.019$).

Further studies are required to ascertain the dietary patterns, clinical presentations, as well as the treatment outcomes after Vitamin B12 administration.

CONCLUSION

Vitamin B12 deficiency is found to be more prevalent and severe in geriatric age group with neuropsychiatric manifestations irrespective of the dietary status. From our study Vitamin B12 deficiency is found to increase the cognitive decline and aggravate the behavioral symptoms especially in the neurodegenerative dementias particularly among elderly males. Mean folate was found to be in the normal range in the majority, whereas serum homocysteine levels were elevated contrary to the previous studies from western countries indicating the higher risk of endothelial injury among Indian population. Interestingly, we also found the cognitive decline to be higher in patients who had dyslipidemia in addition to Vitamin B12 deficiency. As per our knowledge this study is the first of its kind addressing the need for identifying, evaluating, and managing the reversible comorbid neuropsychological

burden due to Vitamin B12 deficiency among elderly patients presenting with neuropsychiatric disorders. Early detection and management of Vitamin B12 deficiency can thus lessen the cognitive burden in elderly patients.

REFERENCES

- Nielsen MJ, Rasmussen MR, Andersen CB, Nexø E, Moestrup SK. Vitamin B12 transport from food to the body's cells — a sophisticated, multistep pathway. *Nat Rev Gastroenterol Hepatol* 2012;9:345-54.
- Nachum-Biala Y, Troen AM. B-vitamins for neuroprotection: Narrowing the evidence gap. *Biofactors* 2012;38:145-50.
- Bhatia P, Kulkarni JD, Pai SA. Vitamin B12 deficiency in India: Mean corpuscular volume is an unreliable screening parameter. *Natl Med J India* 2012;25:336-8.
- Berenson AB, Rahman M. Effect of hormonal contraceptives on Vitamin B12 level and the association of the latter with bone mineral density. *Contraception* 2012;86:481-7.
- Tung ML, Tan LK. Long term use of metformin leading to Vitamin B12 deficiency. *Diabetes Res Clin Pract* 2014.pii: S0168-8227(14)00015-1.[Epub ahead of print].
- Goodman KI, Salt WB 2nd. Vitamin B12 deficiency. Important new concepts in recognition. *Postgrad Med* 1990;88:147-50, 153-8.
- Fragasso A, Mannarella C, Ciancio A, Sacco A. Functional Vitamin B12 deficiency in alcoholics: An intriguing finding in a retrospective study of megaloblastic anemic patients. *Eur J Intern Med* 2010;21:97-100.
- Refsum H, Yajnik CS, Gadkari M, Schneede J, Vollset SE, Orning L, *et al.* Hyperhomocysteinemia and elevated methylmalonic acid indicate a high prevalence of cobalamin deficiency in Asian Indians. *Am J Clin Nutr* 2001;74:233-41.
- Allen LH. How common is Vitamin B-12 deficiency? *Am J Clin Nutr* 2009;89:693S-6S.
- Shobha V, Tarey SD, Singh RG, Shetty P, Unni US, Srinivasan K, *et al.* Vitamin B12 deficiency & levels of metabolites in an apparently normal urban south Indian elderly population. *Indian J Med Res* 2011;134:432-9.
- Alzheimer's & Related Disorders Society of India (2010). The Dementia India Report: prevalence, impact, costs and services for Dementia. (Eds) Shaji KS, Jotheeswaran AT, Girish N, Srikala Bharath, Amit Dias, Meera Pattabiraman and Mathew Varghese. ARDSI, New Delhi. [Last accessed on March 28, 2014].
- Fine EJ, Soria E, Paroski MW, Petryk D, Thomasula L. The neurophysiological profile of Vitamin B12 deficiency. *Muscle Nerve* 1990;13:158-64.
- Gammon CS, von Hurst PR, Coad J, Kruger R, Stonehouse W. Vegetarianism, Vitamin B12 status, and insulin resistance in a group of predominantly overweight/obese South Asian women. *Nutrition* 2012;28:20-4.
- Jabbar A, Yawar A, Waseem S, Islam N, Ul Haque N, Zuberi L, *et al.* Vitamin B12 deficiency common in primary hypothyroidism. *J Pak Med Assoc* 2008;58:258-61.

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