

Vitamin B₁₂ Levels and Psychiatric Symptomatology: A Case Series

Naveen Jayaram, M.B.B.S., M.D.
Mukund G. Rao, M.B.B.S., M.D.
Aniruddh Narasimha, M.B.B.S.
Dhanya Raveendranathan, M.B.B.S., M.D.
Shivarama Varambally, M.B.B.S., M.D.
Ganesan Venkatasubramanian, M.B.B.S., M.D.
B. N. Gangadhar, M.B.B.S., M.D.

Cobalamin (Vitamin B₁₂) has been implicated in the pathogenesis of various neuropsychiatric disorders. A review of 19 patients (14 vegetarians) with demonstrable vitamin B₁₂ deficiency showed varied psychiatric symptomatology, with the majority not having significant hematological or neurological manifestations.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2013; 25:150–152)

Cobalamin (Vitamin B₁₂), a water-soluble essential vitamin, has a vital role in DNA synthesis during cell division.¹ It is also linked with synthesis of neurotransmitters such as dopamine and serotonin, and thus has been implicated in the pathogenesis of various neuropsychiatric disorders.² In earlier times, a one-carbon hypothesis of schizophrenia was hypothesized, citing impaired transmethylation leading to an accumulation of toxic metabolites.³

Although varied psychiatric manifestations caused by vitamin B₁₂ deficiency have been described, the possibility of psychiatric disorders being caused by B₁₂ deficiency is often overlooked. Psychiatric manifestations of vitamin B₁₂ deficiency can include depression, apathy, irritability, dementia, catatonia, delirium, and hallucinations.^{4,5} Higher vitamin B₁₂ levels are thought to be associated with a more favorable outcome in depression.⁶ A study in general psychiatric inpatients reported the incidence of vitamin B₁₂ deficiency to be

4%–6%.⁷ Neuropsychiatric abnormalities are reported to be present in up to 28% of patients in the absence of any change in the hematocrit values or increase in red cell mean corpuscular volume (MCV); these indices are usually the most commonly investigated for B₁₂ deficiency. Hence, a vitamin B₁₂ level estimation is warranted in such conditions.

Poor intake or absorption causes vitamin B₁₂ deficiency. It is synthesized by bacteria and is found only in animal-derived products such as meat, egg, and dairy products, but not in plant-derived products. With improved nutrition, vitamin B₁₂ deficiency is relatively rare in developed countries, but is still prevalent in the developing world. In particular, it is prevalent in the Indian population, as a pure vegetarian diet is followed by various sections of society.⁸ In this case series, we report on 19 patients where vitamin B₁₂ deficiency and psychiatric symptomatology were coexistent.

CASE SERIES

A large number of our cases were diagnosed with psychosis. The systemic examinations were within normal limits for all, except in the case of three patients, one of whom had sensory deficits in both lower limbs; the other two had pallor. Table 1 shows the clinical characteristics of patients who had serum B₁₂ levels in the lower range of normal.

Of the patients who had psychosis, the majority of them had prominent Schneiderian first-rank symptoms, most commonly, thought alienation phenomena, commenting and 3rd-person auditory hallucinations, delusions of persecution and reference, and passivity phenomena. Those with depression had characteristic features of depression—prominently depressive cognitions, anhedonia, easy fatigability, and somatic symptoms. The patient with episodic psychosis had prominent psychotic symptoms, but no classic first-rank

Received June 8, 2012; accepted October 16, 2012. From the Dept. of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore, India. Send correspondence to Dr. Shivarama Varambally, Dept. of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore, India; e-mail: drvarambally@gmail.com

Copyright © 2013 American Psychiatric Association

symptoms. The patient with bipolar disorder had classic manic symptoms.

DISCUSSION

This report highlights the importance of assessment of Vitamin B₁₂ in patients with psychiatric illness. All patients presented with psychiatric symptoms alone, and were diagnosed to have coexistent vitamin B₁₂ deficiency only on subsequent evaluation. B₁₂ deficiency was suspected in these patients in view of their vegetarian diet; of 19 patients, 14 had followed a strict vegetarian diet. A functional B₁₂ deficiency is known to be common in vegetarians, as Vitamin B₁₂ is not present in plant products.¹ However, because of the cross-sectional design of our study, cause–effect relationship cannot be inferred, and the association could be primary or secondary to the psychiatric disorder, or incidental. However, there has been a report of psychotic symptoms deemed to be resistant to psychotropic treatments that dramatically improved after administration of Vitamin B₁₂.^{4,9,10}

Although reports of dementia-like syndrome have also been documented in the existing literature, this is less likely in our cohort because these patients were predominantly middle-aged. Most of the elderly population in our hospital would be attending a separate clinic dealing with Geriatric Psychiatry.

The majority of the patients did not have significant hematological and neurological manifestations, and Vitamin B₁₂ deficiency was diagnosed on laboratory assessments. Pallor was also absent on physical examination in all but two of the cases. Also, in a few of the patients, B₁₂ levels were in the lower limit of the normal range, lending credence to earlier reports suggesting that psychiatric manifestations often predate the neurological symptoms, at times by as much as a few years.¹¹ Also, psychiatric manifestations can occur before the levels of vitamin B₁₂ are below 175 pg/L, and it has been proposed that the threshold needs to be increased to 660 pg/L.¹¹ Studies also mention a “window period” within which treatment may reverse changes, after which axonal demyelination and other pathological changes may be irreversible.¹⁰

Recently, obtaining vitamin B₁₂ levels in all psychiatric patients has also been recommended, as mild vitamin B₁₂ deficiency could have been present and undetected for long periods of time.⁸ In particular,

TABLE 1. Summary of Clinical Case Characteristics

Diagnostic Characteristics	Number (%)
Paranoid schizophrenia	11 (58)
Undifferentiated schizophrenia	3 (15.8)
Episodic psychosis	1 (5.3)
Bipolar affective disorder	1 (5.3)
Depressive disorders	3 (15.8)
B ₁₂ level <225 pg/ml	15 (78.9)
Vegetarian	14 (73.6)
Age >45	8 (42.1)
Female sex	13 (68.4)

screening patients with psychiatric illness in high-risk groups, such as elderly persons, those on a vegetarian diet, and having gastrointestinal disorders was recommended.¹⁰ Serum B₁₂ estimation is a simple and sensitive laboratory investigation, and a level above 600 pg/ml is advisable.¹² Also, the possibility of testing B₁₂ levels in those patients not on a vegetarian diet but not responding to conventional treatments might be indicated.

A major limitation of our study was a lack of corresponding folic acid level measurement, which was not possible in our set-up for logistic reasons; however, there were sufficient clinical grounds to consider a primary B₁₂ deficiency in isolation.

CONCLUSIONS

Most of the patients in our series had no major physical comorbidity that is known to be associated with cobalamin deficiency, and they were predominantly vegetarians. Hence, a high index of suspicion must be exercised in psychiatric patients who are vegetarians and who present with symptoms that are refractory to conventional psychotropics or antidepressants. Also, based on our observations, a syndromal psychotic illness in patients who are vegetarians may merit Vitamin B₁₂ assessment.

In summary, this report emphasizes the importance of investigation for vitamin B₁₂ deficiency in psychiatrically ill patients, especially those in high-risk groups. The downstream changes due to impaired DNA synthesis leading to the development of psychopathology are, as yet, unknown. Future studies are needed to further evaluate the role of vitamin B₁₂ in the pathogenesis of psychiatric disorders.

Conflict of interest: None declared.

References

1. Herrmann W, Lorenzl S, Obeid R: [Review of the role of hyperhomocysteinemia and B-vitamin deficiency in neurological and psychiatric disorders: current evidence and preliminary recommendations]. *Fortschr Neurol Psychiatr* 2007; 75:515–527
2. Catalano G, Catalano MC, O'Dell KJ, et al: The utility of laboratory screening in medically ill patients with psychiatric symptoms. *Ann Clin Psychiatry* 2001; 13:135–140
3. Regland B: Schizophrenia and single-carbon metabolism. *Prog Neuropsychopharmacol Biol Psychiatry* 2005; 29:1124–1132
4. Catalano G, Catalano MC, Rosenberg EI, et al: Catatonia: another neuropsychiatric presentation of vitamin B₁₂ deficiency? *Psychosomatics* 1998; 39:456–460
5. Holmes JM: Cerebral manifestations of vitamin B₁₂ deficiency. *BMJ* 1956; 2:1394–1398
6. Hintikka J, Tolmunen T, Tanskanen A, et al: High vitamin B₁₂ level and good treatment outcome may be associated in major depressive disorder. *BMC Psychiatry* 2003; 3:17
7. Brett AS, Roberts MS: Screening for vitamin B₁₂ deficiency in psychiatric patients. *J Gen Intern Med* 1994; 9:522–524
8. Marks PW, Zukerberg LR: Case records of the Massachusetts General Hospital. Weekly Clinicopathological Exercises: Case 30-2004: a 37-year-old woman with paresthesias of the arms and legs. *N Engl J Med* 2004; 351:1333–1341
9. Masalha R, Chudakov B, Muhamad M, et al: Cobalamin-responsive psychosis as the sole manifestation of vitamin B₁₂ deficiency. *Isr Med Assoc J* 2001; 3:701–703
10. Raveendranathan D, Shiva L, Venkatasubramanian G, et al: Vitamin B12 deficiency masquerading as clozapine-resistant psychotic symptoms in schizophrenia. *J Neuropsychiatry Clin Neurosci* 2013; 25:e34–e35
11. Berry N, Sagar R, Tripathi BM: Catatonia and other psychiatric symptoms with vitamin B₁₂ deficiency. *Acta Psychiatr Scand* 2003; 108:156–159
12. Dommissie J: Subtle vitamin B₁₂ deficiency and psychiatry: a largely unnoticed but devastating relationship? *Med Hypotheses* 1991; 34:131–140