

Vitamin B₁₂ Deficiency and Depression in the Elderly: Review and Case Report

To the Editor: Vitamin B₁₂ is a water-soluble essential vitamin. A member of vitamin B complex, vitamin B₁₂ is also called *cobalamin* because it contains the metal cobalt. Vitamin B₁₂ is synthesized by bacteria and is found mainly in meat, egg, and dairy products but lacks a reliable plant source.¹ It is essential for the formation of red blood cells and maintenance of a healthy nervous system as well as for the rapid synthesis of DNA during cell division. It is believed that B₁₂ along with folic acid may help prevent disorders of central nervous system development, mood disorders, and dementias. Megaloblastic anemia is the common and serious illness associated with B₁₂ deficiency, but it is believed that a mild decrease in the B₁₂ level is associated with neurologic and psychiatric problems such as ataxia or mood disturbances.¹

A common cause of vitamin B₁₂ deficiency is poor intake or absorption.² The protein-bound vitamin B₁₂ is released by hydrochloric acid in the stomach during digestion. Once released, B₁₂ combines with the gastric intrinsic factor, and this complex is absorbed in the intestinal tract. Although vitamin deficiencies are relatively uncommon in the Western world, it is estimated that 10% to 15% of individuals over the age of 60 years may suffer from B₁₂ deficiency and it is believed that atrophic gastritis type B, which may afflict 20% to 50% of the elderly, may lead to poor absorption of B₁₂ and folate.²⁻⁴ As the population ages, nutrition and its impact on the health of the elderly become increasingly important in health maintenance of the elderly. In this report, we describe an elderly woman who suffered from severe psychotic depression who did not improve with conventional treatment but recovered significantly following administration of vitamin B₁₂, illustrating the possibility that vitamin B₁₂ deficiency may play a role in the development of mood disorder.

Case report. Ms A, a 66-year-old married, African American retired teacher, was living with her daughter and granddaughter. She was seen in 2004 by one of the authors (S.H.) in the outpatient clinic following a psychiatric hospitalization for *DSM-IV* major depressive disorder with psychosis. The patient and the family reported a 6-month history of sad mood and lack of energy, interest, and motivation along with sleep disturbances following the loss of Ms A's foster children. She had no family history or past history of mental illness or substance abuse.

During those 6 months, she stayed in her bed most of the time, was sad and withdrawn, and cried often. She neglected self-care and hygiene and lost about 30 pounds of body weight. In August 2004, she was hospitalized (as noted in the previous paragraph) following worsening of her condition that included agitation, sleeplessness, and a fear that something bad was going to happen to her. She reported no hallucinations or suicidal ideas. She was treated with sertraline 150 mg/d and risperidone 2 mg/d and stayed in the hospital for 10 days.

At the time she was seen in the clinic for follow-up (less than a month after discharge from the hospital), she had a noticeable stiffness in her gait but otherwise was healthy physically. She was well dressed and groomed but exhibited slow psychomotor activity. She appeared withdrawn and was slow in her speech. She denied feeling sad but was

tearful and depressed during the interview. She did not exhibit any overt psychotic symptoms but continued to have a vague fear that something bad might happen to her. She had no suicidal thoughts but was generally hopeless about herself and her future. She did not exhibit any evidence for intellectual decline (score of 25 out of 30 on the Mini-Mental State Examination⁵) or neurologic deficits.

The patient was maintained on treatment with sertraline and risperidone and had a working diagnosis of major depressive disorder with psychotic features, in partial remission. As part of the initial workup, blood tests were ordered, including thyroid-stimulating hormone, vitamin B₁₂, and folate levels. All laboratory results were within normal limits except vitamin B₁₂, which was extremely low: the patient had a serum level of < 100 pg/mL (normal range: 200 to 900 pg/mL).

At this point, the patient was referred to her primary care physician to follow up on her low vitamin B₁₂ level. She was treated with a series of vitamin B₁₂ injections, after which the serum B₁₂ level increased to within normal limits (500 pg/mL). Following this, she showed significant improvement with her mood. Along with her mood, other symptoms and activities such as sleep, hygiene, self-care, and activity level improved. The treating psychiatrist (S.H.) discontinued the risperidone and reduced the dose of sertraline to 100 mg/d, and the patient recovered to her baseline levels of mood and functioning soon thereafter. She continues to take sertraline.

A serum vitamin B₁₂ level between 200 pg/mL and 900 pg/mL is considered normal, but a threshold of 300 to 350 pg/mL is recognized as a marker for a desirable status in the elderly. The laboratory diagnosis is usually based on low serum vitamin B₁₂ levels or elevated serum methylmalonic acid and homocysteine levels. Elevated homocysteine is an important marker for vitamin B₁₂ and/or folate deficiency. Classic deficiency symptoms such as megaloblastic anemia often fail to appear with subtle deficiencies, as they are usually late clinical signs of severe deficiency.^{3,4} Symptoms of vitamin B₁₂ deficiency include anemia, neuropathy, and neuropsychiatric disorders.⁶

Depression, dementia, and mental impairment are often associated with vitamin B₁₂ and folate deficiency, especially in the elderly.¹ Vitamin B₁₂ and folic acid are crucial for the transmethylation of neuroactive substances such as myelin and neurotransmitters (hypomethylation hypothesis). There are several theories concerning potential associations between depression and levels of vitamin B₁₂ and folate. Vitamin B₁₂ and folate are connected with the synthesis of monoamines such as dopamine and serotonin and are involved in single carbon transfer methylation reactions connected with the production of these monoamine neurotransmitters that are implicated in the pathophysiology of neuropsychiatric disorders such as depression and psychosis.⁷

Vitamin B₁₂ is also required for the synthesis of S-adenosylmethionine (SAM), which is needed as a methyl donor in many methylation reactions in the brain. Since SAM has antidepressant properties, it is conceivable that an inhibited synthesis may cause a reduction in SAM and may result in depression. This view is supported by a study⁸ which found that depressed subjects had significantly higher methylmalonic acid levels than nondepressed subjects. Detrimental effects on mood due to actions in the

methylmalonic acid metabolism pathway have not been extensively studied and need further investigation. Psychiatric manifestations can occur in the presence of low serum B₁₂ levels but in the absence of the other well-recognized neurologic and hematologic abnormalities of pernicious anemia.¹ Such symptoms may precede hematologic symptoms by months or years and may present as the only symptoms related to deficiency.

Durand and colleagues⁹ reported a similar case in 2003, in which a 64-year-old woman with no prior history of mental illness was hospitalized for confusion and a 2-month history of severe depression with delusions and Capgras' syndrome. She also had delusions with lability of mood and hypomania prior to the hospitalization. She was found to have severe vitamin B₁₂ deficiency, with a serum vitamin B₁₂ level of 52 pmol/L and a folate level within normal limits. Antibodies to parietal cells were positive in the serum and antibodies to intrinsic factor were negative. Her mental state improved dramatically within a few days following vitamin B₁₂ replacement therapy (hydroxycobalamin 1000 ng/d IM for 10 days) and iron replacement therapy, and all her symptoms disappeared within 9 days of treatment. Evidence for neuropsychiatric symptoms related to vitamin deficiency is sparse, but when there is such a causal relationship the treatment response is dramatic and at times life saving.

In view of the high prevalence of mild, preclinical B₁₂ deficiency, routine cobalamin supplementation in the general population, especially the elderly, may be advisable.¹⁰ Supplementation with high doses of oral cobalamin is as effective as cobalamin administered by intramuscular injection to correct plasma markers of vitamin B₁₂ deficiency, but the effects of lower oral doses of cobalamin on such markers are uncertain. However, a routine intake of 100 to 250 µg/d in the absence of malabsorption may be adequate to prevent deficiencies. Such an intervention may prevent major suffering in many elderly individuals.

In conclusion, our patient illustrates the importance of considering the possibility of B₁₂ deficiency and serum B₁₂ determinations in patients for whom nutritional deficiency is suspected, especially among the elderly. It may also be prudent to consider this possibility in all patients with organic mental disorders, atypical psychiatric symptoms, poor response to conventional treatment, and fluctuating symptomatology. Assessment of B₁₂ levels should be included as a standard evaluation with treatment-resistant depressive disorders, dementia, psychosis, or risk factors for malnutrition or among individuals with history

of poor nourishment as well as patients who are above age 50. It is, however, encouraging to know that replacement of vitamin B₁₂ in the presence of a deficiency is beneficial therapeutically. Large-scale controlled studies and surveys of vitamin status among the elderly and mentally ill may shed more light on this topic and may help improve the care of the mentally ill.

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Financial disclosure: None reported. **Funding/support:** None reported.

doi:10.4088/PCC.08100707

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