

## Case Reports

# Life threatening vitamin B<sub>12</sub> deficiency: will timely screening make a difference?

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## INTRODUCTION

While Vit.B12 deficiency is common, with a prevalence of about 15% in the elderly<sup>[1-3]</sup>, and recommendations for treatment available, detection of deficiency at the pre-clinical stage by appropriate screening does not always take place. Our report is an example of life threatening Vit.B12 deficiency diagnosed at age 56, with the onset of Vit.B12 depletion likely to have begun in the previous decade. Further, the patient had sickle cell trait along with Vit.B12 deficiency, a combination only sporadically reported.

## CASE REPORT

A 56 year old caucasian male with no significant past medical illness presented to our University hospital with a history of lethargy, weakness, anorexia, pallor and icteric sclera for a few months. He denied use of medications inclusive of acid lowering agents (H<sub>2</sub> blockers or proton pump inhibitors) and vitamins of any kind. Dietary habits were omnivorous. Physical examination confirmed marked pallor and jaundice. Vital signs were stable; rest of the examination including nervous system was unremarkable.

Hemoglobin: 24g • L<sup>-1</sup>, Hematocrit: 6.9%, MCV: 75fl, Platelet: 64 × 10<sup>9</sup> • L<sup>-1</sup>, Corrected reticulocyte count: 0.004, Blood smear: anisocytosis, poikilocytosis and macroovalocytosis with hypersegmented neutrophils, Folate: 12.1 µg • L<sup>-1</sup>, Iron: 1.57 µg • L<sup>-1</sup>, TIBC: 59, Ferritin: 764 µg L<sup>-1</sup>, LDH: 15500U/L, and Haptoglobin: 31 mg • L<sup>-1</sup>. Hemoglobin electrophoresis: HbA 0.67, HbS 0.30. Direct

Coomb's test: negative. Vitamin B12: 57ng L<sup>-1</sup> (Normal 200-900ng L<sup>-1</sup>), Intrinsic factor antibodies: positive. Bone marrow aspirate and biopsy: erythroid hyperplasia with megaloblastic features. Upper endoscopy and gastric biopsy revealed chronic gastritis with mucosal atrophy. Colonoscopy was normal except for hemorrhoids.

Therapy included a total of 6 units of packed red blood cells. Vitamin B12 therapy was initiated as daily intramuscular injections, 1 000 µg daily for 3 days. Clinical improvement was dramatic and the patient was discharged shortly.

## DISCUSSION

Our patient presented with pancytopenia and a life-threatening drop in Hb to 24 g • L<sup>-1</sup>. Though the hematologic manifestations were severe, interestingly, there was no evidence of peripheral neuropathy, myelopathy, dementia or any neuropsychiatric manifestations. In view of omnivorous dietary habits, a dietary deficiency from inadequate consumption of Vit. B12 was unlikely. Neither was the patient on any antacids or other acid lowering agents. Proton pump inhibitors and H<sub>2</sub> blockers, widely used as prescription and over the counter agents for upper gastrointestinal symptoms have been associated with Vit. B12 deficiency. Acid peptic activity is important in the initial step where Vit. B12 is separated from food protein; lack of acid may cause food-cobalamin malabsorption, a common cause of Vit.B12 deficiency<sup>[4,5]</sup>.

An average omnivorous American diet provides 5 µg-15µg of Vit.B12 per day. Animal products such as meat, poultry, fish, eggs and dairy products are rich sources of Vit.B12. Plant sources contain Vit.B12 only if they are contaminated with microorganisms<sup>[6,7]</sup>. As a result, vegans are at a higher risk of becoming Vit. B12 deficient over a period of time. When consumed, Vit.B12 attaches to an 'R' binder (haptocorrin) present in saliva, after it is separated from food protein by acid in the stomach. The pancreas secretes proteases, which at an alkaline pH beyond the stomach digests the 'R' binder facilitating the attachment of intrinsic factor (IF) to B12. IF-B12 complex is absorbed via receptors in the distal ileum. An efficient enterohepatic circulation of Vit.B12, wherein most of the Vit.B12 secreted in the bile is reabsorbed, is the reason why it takes anywhere upto 20 years to become Vit.B12 deficient if one stops consuming

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Vit.B12<sup>[6,8]</sup>.

PA was the most likely cause of Vit.B12 deficiency in our patient. The age of onset with advanced disease by mid fifties and absence of any other basis like gastric or small intestinal surgery, chronic pancreatitis, *Crohn's* disease and other causes of malabsorption makes PA the probable diagnosis. The presence of IF antibodies, which is more specific for PA than parietal cell antibodies and seen in about 40% of patients with PA, lends credence to our assumption<sup>[9]</sup>. The additional finding of Vit.B12 deficiency with sickle cell trait in this patient is not common. Patients with severe sickle cell disease may have unrecognized Vit. B12 deficiency<sup>[10]</sup>. Furthermore, routine folate supplementation in sickle cell anemia prior to determining Vit.B12 status has been considered risky, as it can mask the findings of Vit.B12 deficiency<sup>[11]</sup>.

The spectrum of Vit.B12 deficiency has been elaborately described in 4 stages<sup>[8,12]</sup>. Stages 1 and 2 represent Vit.B12 depletion and stages 3 & 4 represent Vit.B12 deficiency with lab abnormalities and clinical manifestations. Our patient presented with full-blown stage 4 disease, suggesting that he would have been in the pre-clinical stage for many years prior to presentation. Screening for Vit.B12 deficiency would avert the morbidity associated with deficiency states. While in the past there have been no precise guidelines for screening, more recently several approaches have been described. Screening is aimed at reaching a diagnosis at the onset of depletion, i.e. at the pre-clinical stage. The literature suggests several options-from doing nothing until one is symptomatic, to screening all individuals, or an individualized approach<sup>[4,13,14]</sup>.

Our approach to screening and treatment of Vit. B12 deficiency has been described previously<sup>[13]</sup>. Here initial screening is recommended for a select group of individuals at first contact. Included are patients with unexplained anemia, gastritis, acid lowering states from use of certain drugs, autoimmune diseases, HIV disease, *Crohn's* disease, multiple sclerosis, thyroid disease, malabsorption syndromes and vegans. In all other patients the initial screening is recommended at age 50, and thereafter every 5 years until age 65. Annual screening is suggested after age 65. Although normal Vit.B12 levels range from 200 to 900ng • L<sup>-1</sup>, values between 200 and 400ng • L<sup>-1</sup> may need further evaluation including serum (or urine) homocysteine and methyl malonic acid to assess for presence of true deficiency<sup>[13,14]</sup>.

Treatment for Vit.B12 deficiency is generally initiated with intramuscular injections of Vit.B12, the usual dose being 1 000 µg daily for 3-5 days. Doses vary from 100 to 1 000 µg • d<sup>-1</sup> larger doses are accompanied by greater losses in the urine<sup>[6]</sup>. Maintenance therapy may be by any of 3 routes intramuscular (IM), oral or intranasal. IM

injections are given every 1 to 3 months. Oral administration necessitates larger doses; 500 to 1 000 µg • d<sup>-1</sup> are needed to ensure absorption in PA where 1% maybe absorbed even in the absence of IF<sup>[15]</sup>. However compliance with oral administration will always remain in question. Intranasal administration of Vit.B12 has been approved in 1998; this form of Vit.B12 is administered weekly (500 µg • wk<sup>-1</sup>) and attains levels comparable to maintenance with IM route<sup>[13,15]</sup>.

## CONCLUSION

The case illustrates the importance and need for timely screening for Vit.B12 deficiency. Delay in diagnosis and treatment resulted in a near fatal presentation of a common disease. The primary care physician should be aware that there is a window of opportunity for diagnosis and treatment; several complications of Vit.B12 deficiency are irreversible if early treatment is not provided. The treatment modalities are several and inexpensive, with no side effects. Selection of screening tests and choice of maintenance therapy may be individualized based on patient and physician preferences. Timely screening and treatment of Vit. B12 deficiency will make a difference.

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