CLINICAL VIGNETTE

Proton Pump Inhibitor Use Contributing to Vitamin B12 Deficiency

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Clinical Presentation

A 65-year-old man presented for a routine follow up. His chronic problems include impaired glucose tolerance, hypogonadotropic hypogonadism, essential hypertension, gastroesophageal reflux disease and benign prostatic hyperplasia. His labs included a low hemoglobin of 11.1 g/dL with elevated mean corpuscular volume (MCV) of 102 fL. His vitamin B12 level was low at 138 pg per milliliter with normal folate level. Other labs included a ferritin of 24 ng/mL, iron of 50 mcg/dL and TIBC 420 mcg/dL. The patient had a history of iron deficiency anemia evaluated with negative upper endoscopy, colonoscopy and capsule endoscopy. He was treated with iron supplementation with intermittent adherence. Celiac sprue evaluation was negative. Daily medications included amlodipine 5 mg, tamsulosin 0.4 mg, and pantoprazole 40 mg. When the patient was evaluated, he had no neurologic complaints. His physical exam was normal without impaired position or vibration sense. He reported a "poor diet" but denied following a vegetarian diet and did not use alcohol. Serum methylmalonic acid level was >700 nmol per liter, and the patient was started on oral cyanocobalamin 1000 ug. Long term proton pump inhibitor use may have contributed to his vitamin B12 deficiency.

Discussion

Macrocytic anemia occurs in 2-4% of adults, and 6% of older adults.[1] Macrocytic anemias are divided into either megaloblastic or non-megaloblastic anemia. Megaloblastic anemias originate due to abnormal cell division of RBC precursors in the bone marrow from vitamin B12 or folate deficiency. Non-megaloblastic anemias may be due to hypothyroidism, alcohol abuse, myelodysplastic syndrome (MDS), and liver dysfunction. Chronic use of 80 grams of alcohol per day impacts the hematologic system and can contribute to a macrocytic anemia.[1] Alcohol abuse will cause macrocytosis even before the development of anemia. Macrocytic anemia can also result from antiretroviral medications. Many other medications impair the use of vitamin B12 or folate including hydroxyurea, valproic acid, phenytoin, and methotrexate. Other common medications decrease the absorption of vitamin B12 including, metformin, H2 blockers and proton-pump inhibitors.[2]

B12 deficiency may be caused by pernicious anemia, total or partial gastrectomy, gastric bypass, and inflammatory bowel disease.[3] These conditions interfere with absorption of vitamin B12. Pernicious anemia is an autoimmune cause of vitamin B12 deficiency due to autoantibodies against intrinsic factor which is needed to bind ingested vitamin B12. In gastrectomy and bariatric surgery, lack of gastric acid decreases the absorption of vitamin B12 from ingested food. Crohn's disease can cause vitamin B12 deficiency with ileum or ileal/ileocolonic resections of the site of the vitamin B12-intrinsic factor complex absorption. B12 deficiency can also occur those with a strict vegetarian diet or limited intake of meat and dairy.

Signs and symptoms of B12 deficiency include fatigue, headache, numbness and problems with gait.[3] Physical exam can include pallor, edema, impaired vibration sensation, impaired position sense and ataxia.[3] Laboratory findings in vitamin B12 deficiency include macrocytic anemia, low vitamin B12 levels and an elevated methylmalonic acid level. A peripheral smear in B12 deficiency will show macrocytic anemia and hypersegmented neutrophils.

In pure vitamin B12 deficiency, vitamin B12 levels will be low and folate levels will be normal. Vitamin B12 levels less than 200 pg/ml are suggestive of B12 deficiency while levels greater than 350 pg/ml make the diagnosis unlikely. Values between 200-350 pg/ml may indicate either low-normal vitamin B12 level or deficiency. Methylmalonic acid (MMA) testing should be performed if vitamin B12 deficiency is suspected. In patients with vitamin B12 levels between 200-350 pg/ml, MMA testing can clarify if B12 deficiency exists. Total homocysteine can also be checked. MMA and homocysteine will be elevated in most cases of B12 deficiency while only homocysteine levels in patients with folate deficiency. Mild elevations of MMA in the range of 300-700 can occur with renal failure.[3] Most cases of vitamin B12 deficiency will have MMA>1000 nmol per liter. Further testing for the etiology of B12 deficiency is important and includes ruling out pernicious anemia by checking for anti-intrinsic factor or anti-parietal cell antibodies. Patients with pernicious anemia should have endoscopic evaluation to rule out gastric carcinoid and other cancers.[3]

Treatment of B12 deficiency with oral or injected vitamin B12. With vitamin B12 injections, 10% of the dose stays in the body.[3] Severe vitamin B12 deficiency can be treated initially with several daily injections of 1000 ug followed by monthly injections.[3] High dose daily oral treatment with 1000-2000 ug is an effective alternative.[3] One study compared parenteral versus high-dose oral vitamin B12 repletion in pernicious anemia, atrophic gastritis and ileal resection, found similar

correction of hematologic abnormalities. Blood counts start to improve within 2 months of initiation of vitamin B12. Neurologic manifestations resolve within 6 months of treatment of the vitamin B12 deficiency. Pernicious anemia requires lifelong treatment with vitamin B12.[3]

REFERENCES

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