CLINICAL VIGNETTE

Metformin and Vitamin B12 Deficiency

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Case Report

The patient is a 53-year old male with type-2 diabetes who reports fatigue, lethargy, and paresethesias in his feet over the past year. He also reports recent heartburn without any other GI symptoms. He's been on metformin and glipizide for the last two years and his sugars have been well-controlled. He's denies chest pain, shortness of breath, dizziness, or headaches.

Past medical history includes hemorrhoids. He takes a daily multivitamin and reports no drug allergies. He rarely drinks alcohol but drinks 3-4 cups of black coffee per day. He smokes 5-10 cigarettes per day and is contemplating stopping smoking. He has a family history of type-2 diabetes, CAD, and hyperlipidemia.

His blood pressure is 124/80, pulse 72, weight 225 pounds, BMI 35, and temperature was normal. His complete examination is normal except for slight loss of pinprick and light sensation in the feet.

Labs include a normal CBC, chemistries, ESR, and TSH. His A1C was 6.2%. Vitamin B12 level is low at 175 pg/ml.

General Discussion and Epidemiology

Metformin is a first line treatment for type-2 diabetes which has been available in the United Kingdom since 1958 and in the United States since 1995[1]. It is generally well-tolerated by most patients[2]. The most common side effects gastrointestinal such as abdomen pain and a change in bowel habits[2]. Its most serious side effect is lactic acidosis, which is rarely seen if metformin is avoided in high-risk patients[2]. Metformin has been linked to risk of vitamin B12 deficiency reported to occur in 10-30% of patients[3,4]. Metformin reduces vitamin B12 levels by 14%.(5,6) This side effect was not well recognized until a 2006 study of Chinese patients showed that the risk of vitamin B12 deficiency increases with the dose and duration of treatment with metformin[7,8].

Etiology and Pathophysiology

Metformin reduces vitamin B12 levels by several mechanisms including effects on calcium absorption in the distal ileum and direct toxicity in the ileum[9]. Calcium supplementation partially reverses metformin-induced vitamin B12 malabsorption[9]. Metformin also causes changes in gut bacteria which can affect vitamin B12 metabolism[10]. Vitamin B12 deficiency is more common in the elderly who take metformin[11]. Other risk factors include the use of proton pump inhibitors, vegetarian diet, excessive use of alcohol, and Celiac disease[12]. Simultaneous use of metformin and a proton pump inhibitor increases the risk of neuropathy, cognitive decline, and megaloblastic anemia[13]. Metformin also affects vitamin B12 levels through alterations in the metabolism of methionine, homocysteine, methylmalonic acid, and succinyl-CoA[1].

Clinical Features

Diabetic patients have an increased risk of peripheral neuropathy.1 In addition, metformin increases the risk of vitamin B12 deficiency, neuropathy, and other diabetic complications[8]. Internal stores of B12 are initially sufficient to sustain levels[14]. Vitamin B12 levels can diminish over time resulting in significant laboratory abnormalities and clinical morbidity[15]. B12 deficiency usually presents with distal bilateral loss of pinprick and vibratory sense to just above the ankles with intact reflexes and motor strength[4]. The neuropathy precedes the hematologic abnormalities of microcytosis and megaloblastic anemia[2]. The anemia is generally reversible but the neurologic progression is irreversible once demyelination and nerve degeneration has occurred[10]. Both the central and peripheral nervous system are affected with numbness and paresethesias of the lower extremities followed by ataxia and diminished cognition[10].

Diagnosis and Testing

There is no consensus on how best to screen patients on metformin for vitamin B12 deficiency[10]. As vitamin B12 deficiency is more common in diabetics, some advocate annual screening of all diabetics with a focus on the elderly[10]. Screening for vitamin B12 deficiency is most important in patients who have

been on metformin for more than one year[14]. Levels of methylmalonic acid and vitamin B12 are checked if vitamin B12 deficiency is suspected[10].

Treatment

Vitamin B12 deficiency is usually treated with intramuscular injections or oral tablets depending on the severity of the deficiency and the circumstances of the patient[10]. The best treatment is a combination of vitamin B12 and calcium as well as adjustment in the metformin regimen[10]. Some guidelines recommend that patients on metformin receive nutritional counseling to ensure that the diet is rich in vitamin B12[7]. Some patients have preexisting diabetes-related neuropathy and may not recognize the problem[14]. Neuropathy is usually slow to improve with some complications being irreversible[4]. These patients are tested for other causes of malabsorption, Celiac disease, Crohn's disease and Helicobacter pylori infection[13].

Prognosis

The prognosis for recovery is excellent so long as the vitamin B12 deficiency is diagnosed early in the course of the illness[1]. Permanent nerve damage can occur if the deficiency persists[10].

Our patient was started on intramuscular B12 injections and noted gradual improvement in neurologic symptoms over the next three months.

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