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CLINICAL VIGNETTE

A Classic Case of Autoimmune Atrophic Gastritis

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A 55-year-old male presented with three-weeks of lower extremity numbness, lower extremity weakness, and ataxia with concurrent memory difficulties. He denied headache, vision changes, upper extremity numbness or weakness, dysarthria, or dysphagia. He also denied following a vegetarian diet or prior gastric or intestinal surgeries. His past medical history was significant for essential hypertension, remote history of heavy alcohol use, and recent diagnosis of hypothyroidism.

Physical exam revealed a temperature of 36.5 degrees Celsius, 115/88mmHg, pulse 79/min, respiratory rate 18/min, and oxygen saturation of 96% on room air. Neurologic exam was significant for normal muscle bulk and tone, normal strength in the bilateral lower extremities, decreased proprioception in the bilateral lower extremities (left greater than right), decrease in light touch sensation distal to the knees bilaterally, intact vibratory sensation, positive Romberg, and ataxic gait. The remainder of the exam was unremarkable.

Labs were significant for hemoglobin 13.7g/dL, mean corpuscular volume 130 fL, vitamin B12 less than 146 pg/mL. Folate and iron studies were within normal. Homocysteine and methylmalonic acid were both elevated, 114 mcmol/L and 94100 nmol/L, respectively. MRI of the brain without contrast revealed a non-specific foci of white matter signal surrounding the frontal horn of the right ventricle and right frontal lobe, but was otherwise unremarkable. MRI of the cervical and thoracic spine with and without contrast were unremarkable. Intrinsic factor antibody returned positive. Patient was diagnosed with subacute combined degeneration secondary to cobalamin deficiency in the setting of autoimmune atrophic gastritis. He was started on vitamin B12 1000mcg intra-muscular every other day with improvement in his symptoms.

Discussion

Autoimmune atrophic gastritis, also referred to as pernicious anemia, is relatively rare in the United States, affecting approximately 150 per 100,000 people.[1] However, it is one of the most common causes of vitamin B12 (cobalamin) deficiency world-wide.[2] It affects all ages, with median between 70 to 80 years old.[3] Pernicious anemia was first described in 1849 by Addison.[2] It is an autoimmune condition which results in impaired absorption of vitamin B12 from the ileum due to the autoimmune destruction of gastric parietal cells and/or intrinsic factor glycoprotein.[3,4] Patients often have coexisting autoimmune conditions such as autoimmune thyroiditis and diabetes type 1.[1,3]

Parietal cells and intrinsic factor protein play an essential role in the absorption of vitamin B12. Intrinsic factor is a glycoprotein produced by the parietal cells within the gastric mucosa. The intrinsic factor protein binds to vitamin B12 within the intestinal lumen forming an intrinsic-factor-vitamin B12 complex (IF-B12). The IF-B12 complex then binds to receptors on the microvilli of terminal ileal cells transporting vitamin B12 across the epithelium.[5]

Autoimmune atrophic gastritis may result in chronic atrophic gastritis[6] via the destruction of parietal cells by activation of pathologic Th1 CD4 T cells.[7] These pathologic T cells target the gastric H/K ATPase that is normally found on gastric mucosal secretory membranes. Parietal cell antibodies present in autoimmune atrophic gastritis also target H/K ATPase. Parietal cells produce hydrochloric acid as well as intrinsic factor protein. This results in a loss of intrinsic factor protein as well as decreased gastric acidity, or achlorhydria.[7]

The clinical manifestations of pernicious anemia often involve the blood and nervous systems. This is best understood by elucidating the role of vitamin B12 as an essential cofactor in many metabolic pathways, including fatty acid metabolism and cell replication. Myelin sheaths of neurons are highly dependent on fatty acid metabolism, thus vitamin B12 deficiency often results in nerve transmission dysfunction. DNA synthesis is highly dependent on vitamin B12, hence processes that require intense replication, such as hematopoiesis are often affected.[8]

Vitamin B12 deficiency may be difficult to diagnose as patients may present with a myriad of symptoms of differing severity[2] including non-specific symptoms such as fatigue, dry skin, hair loss, or common gastrointestinal symptoms.[1] Additionally, low cobalamin affects both the white and gray brain matter as well as peripheral nerves leading to a plethora of neurologic presentations including subacute combined degeneration of the spinal cord, large fiber neuropathy, cognitive disorders, and ataxia.[9] Patients may also present with symptoms secondary to anemia. Less common manifestations of cobalamin deficiency include skin hyperpigmentation, vitiligo,[4] glossitis, infertility, and thrombosis.[3] There appears to be increased risk of thrombosis thought to be secondary to hyperhomocysteinemia.[3] This may lead to a higher risk of myocardial infarction or stroke.[10]

Of note, clinical manifestations are often delayed by up to 10 years, due to significant hepatic storage.[4]

Vitamin B12 deficiency may be difficult to diagnose in the absence of macrocytic anemia or decreased serum cobalamin levels.[1] About one third of patients may have normocytic anemia and normal B12 levels.[1] Achlorhydria often leads to iron deficiency anemia which may predate the onset of pernicious anemia by many years[7] and occurs in about one fifth of patients with vitamin B12 deficiency.[1] While all cell lines may be affected, megaloblastic anemia is the most common finding.[4] Interestingly, the severity of megaloblastic anemia is inversely correlated with the degree of neurologic dysfunction for unknown reasons.[3]

Initial testing for vitamin B12 deficiency includes a complete blood count and serum vitamin B12 level. If the serum vitamin B12 level is low, vitamin B12 deficiency is confirmed. If the level is low-normal or normal, but a high index of suspicion remains, serum methylmalonic acid should be obtained. High serum methylmalonic acid confirms a diagnosis of vitamin b12 deficiency.[4] Elevated serum homocysteine level also supports the diagnosis, but is less specific.[3] Patients who have no obvious etiology to explain their hypovitaminosis, or who have concomitant autoimmune disease, should be tested for intrinsic factor and/or parietal cell antibodies. If present, a diagnosis of autoimmune atrophic gastritis is made. If negative, but a high index of suspicion remains, a serum gastrin level should be obtained. An elevated gastrin level would confirm the diagnosis of autoimmune atrophic gastritis. The Schilling test, previously the gold standard diagnostic study for PA, is no longer available in the United States.[4]

The treatment of vitamin B12 deficiency includes supplementation typically administered via intramuscular or deep subcutaneous injection. There are several different treatment schedules, but all emphasize more frequent vitamin B12 dosing in patients with severe symptoms. If symptomatic anemia or neurologic symptoms are not present, or there is no concern for malabsorption or medication adherence, then treatment with either vitamin B12 1000mcg IM weekly for 4 weeks followed by vitamin B12 1000mcg IM monthly or vitamin B12 1000mcg-2000mcg oral daily until anemia or symptoms resolve is suggested.[11,12] If the cause of Vitamin B12 deficiency is reversible, treatment can be discontinued when vitamin B12 stores are replete.[11,12] If symptomatic anemia or neurologic symptoms are present, or there is concern for malabsorption or medication adherence, intramuscular injections should be given every other day for up to 3 weeks or until no further improvement is noted, then weekly for 4 weeks followed by every month. If the cause of Vitamin B12 deficiency is irreversible such as pernicious anemia, then lifelong therapy is recommended.[11,12] If folate deficiency is also present, vitamin B12 replacement should be initiated first to prevent subacute combined degeneration of the spinal cord.[4]

Methylmalonic acid and total homocysteine serum levels decrease immediately after treatment, and may be useful in monitoring for adequate vitamin B12 repletion, particularly in the acute setting. With adequate vitamin B12 replacement, megaloblastic anemia should correct within eight weeks. Neurologic symptoms may require weeks to months to resolve. Patients with more chronic and severe neurologic symptoms may not exhibit complete recovery despite adequate supplementation. Thus, it is important to identify and treat cobalamin deficiency promptly.[3]

Chronic atrophic gastritis is associated with an increased risk of gastric cancer as well as gastric carcinoids.[6] Gastric mucosal atrophy may lead to intestinal metaplasia, which increases the risk for gastric cancer. Given the decrease in gastric acidity, gastrin is released by antral G cells without negative feedback inhibition, which leads to hyperplasia of enterochromaffin-like cells and gastric carcinoids.[7] Serum biomarkers, including pepsinogen 1, pepsinogen 2, pepsinogen 1/2 ratio, and gastrin levels, are often referred to as the "serologic gastric biopsy," and have been used to aid in diagnosing chronic atrophic gastritis; hence signifying those at higher risk for developing malignancy.[7] Some experts recommend upper endoscopy at time of diagnosis to confirm gastritis and rule out malignancy.[3] Nevertheless, all patients with autoimmune atrophic gastritis should be monitored closely for development of gastrointestinal symptoms.

Our patient presented with classic neurologic symptoms seen in vitamin B12 deficiency, including lower extremity weakness, numbness, ataxia, and impaired memory. He had recently been diagnosed with hypothyroidism, thus raising our suspicion for an autoimmune etiology. He denied any other risk factors for cobalamin deficiency including dietary restrictions, malabsorption etiologies, the use of antacids, or the use of metformin. Labs revealed a low serum vitamin B12 level and elevated methylmalonic and homocysteine levels. Intrinsic factor was ordered and returned positive clinching the diagnosis of autoimmune atrophic gastritis. Patient was treated with vitamin B12 intra-muscularly every other day for a minimum of 3 weeks given his significant neurologic symptoms. He was informed that he would require life-long vitamin B12 supplementation and close outpatient follow-up.

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