CLINICAL VIGNETTE

A Case of Vitamin B12 Deficiency

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A sixty-year-old male with schizoaffective disorder and diabetes mellitus type II presented to the emergency room after collapsing. His past medical history also includes, nephrolithiasis, tardive dyskinesia and tobacco use disorder.

On the morning of admission, the patient reported profound lightheadedness and collapsed while standing in a parking lot. He stood up with the help of a bystander but was unable to maintain his balance and fell again, striking his head on the ground without loss of consciousness. He denied any preceding palpitations, diaphoresis, chest pain, dyspnea, or vertigo. There was no report of tonic-clonic movements, tongue biting or urinary incontinence. He ate breakfast that morning and denied any recent infectious symptoms. He did report chronic dizziness and smokes about one pack a day without significant alcohol use. His diet was balanced. Including meats and vegetables.

Upon arrival to the emergency room, vital signs were unremarkable, with BP 134/75 and pulse of 87 bpm. Labs included troponin < 0.04, hemoglobin 13.6, blood glucose 100. Electrocardiogram (EKG) demonstrated normal sinus rhythm 84 bpm, normal axis and intervals, T-wave flattening in lateral leads (V4-6). Head and cervical computed tomography (CT) demonstrated left parietal scalp hematoma. Computed tomography angiogram of chest demonstrated multiple pulmonary nodules and emphysema and he was admitted for observation.

On hospital day two, the patient stood up to use the commode with nursing supervision. He leaned to his left and was unable to maintain his balance. Nursing assessed him, unsafe to ambulate on his own. Magnetic resonance imaging with angiogram of brain and neck did not demonstrate any concerning pathology. His home medications included: citalopram 40mg daily, clonazepam 1mg tid, clozapine 400mg bid, ziprasidone 80mg bid, olanzapine 20mg daily, and metformin 1000mg bid. He had been taking this regimen for years. Additional labs included decreased hemoglobin from 13.6 to 10.7. MCV was 85. He had no evidence for overt bleeding and his vital signs remained stable including orthostatic vital signs. Additional labs for anemia and ataxia included undetectable vitamin B12 (<150) and normal levels of thyroid stimulating hormone, vitamin E, haptoglobin, bilirubin, lactate dehydrogenase, folate and ferritin.

Hematology was consulted for profound vitamin B12 deficiency and the patient was started on cyanocobalamin intramuscular injections 1000mcg daily for seven days, followed by weekly for one month, then monthly thereafter. Intrinsic factor antibody was negative. Homocysteine and methylmalonic acid levels were not checked given undetectable B12 level. Patient's hemoglobin remained stable throughout hospitalization. Anticipated improvement in neurologic symptoms secondary to vitamin B12 deficiency takes months and he was discharged to skilled nursing facility for physical therapy. Given concern for metformin-associated vitamin B12 deficiency, metformin dose was reduced to 500mg bid as A1C was 5.7.

Discussion

Vitamin B12, also known as cobalamin, is a water-soluble vitamin that is necessary for normal hematopoiesis and neurologic function. It is present in foods derived from animal products such as meats, dairy products and eggs. It is absorbed with intrinsic factor (IF), a product of the parietal cells lining the stomach mucosa, in the terminal ileum after being extracted by gastric acid.[1] Risk factors for vitamin B12 deficiency include pathology that impair ileal absorption (Crohn's disease), decreased intrinsic factor (atrophic gastritis, pernicious anemia, gastric bypass), transcobalamin II deficiency, inadequate intake (alcohol use, older age, vegan diet) and prolonged use of medications of greater than 12 months (histamine-2 blockers, proton pump inhibitors, metformin, and antiepileptics).[2]

There are currently no screening guidelines for B12 deficiency. It is important to recognize common and uncommon clinical features. Vitamin B12 deficiency affects approximately 6% of persons younger than 60 years and nearly 20% of those older than 60 years.[1,2] Presenting clinical manifestations of vitamin B12 deficiency may include hyperpigmentation, jaundice, vitiligo, glossitis and neuropsychiatric changes include areflexia, cognitive impairment, gait instability, parosmia, neuropathy.[2,3] Macrocytic or megaloblastic anemia, leukopenia, thrombocytopenia, thrombocytosis. Hepatic storage of vitamin B12 can delay clinical manifestations for up to ten years after the onset of deficiency.[3]

The initial evaluation of suspected vitamin B12 deficiency is a complete blood panel and a serum B12 level.[2] Low levels of serum cobalamin, less than 148 pmol/l, is highly sensitive for the diagnosis in the presence of signs and symptoms and/or hematological indices of vitamin B12 deficiency.[3] In liver disease, alcohol user disorder, and malignancy, vitamin B12 levels may be falsely elevated.[3] In addition, some patients may

have low to normal levels of vitamin B12. In such cases, it is important to check serum homocysteine and methyl-malonic acid levels if signs and symptoms of vitamin B12 deficiency exist.[3] In the right clinical setting, identification of a macrocytic anemia and blood smear findings of hyper-segmented neutrophils suggests vitamin B12 deficiency.[2]

Vitamin B12 deficiency can develop in various ways. In pernicious anemia, there is an autoimmune destruction of parietal cells and consequent impairment of intrinsic factor (IF) secretion. Deficiency can also occur from poor dietary intake in malnourished patients including the elderly and those with alcohol excess.[4] Vitamin B12 deficiency is characterized by hematological and neurological effects, ranging from mild manifestations such as fatigue and paresthesia to severe features like pancytopenia and degeneration of the spinal cord.[4]

The recognition and treatment of vitamin B12 deficiency is critical since it is a reversible cause of bone marrow failure and demyelinating nervous system disease.[5] Clinical recognition of vitamin B12 deficiency and confirmation of the diagnosis can be difficult when patients present with non-specific clinical features and missing this diagnosis can result in potentially severe complications. Following treatment of B12 deficiency, improvement of neurological symptoms often occurs in six weeks to three months, hemoglobin levels in 8 weeks and homocysteine and MMA in about 1 week.[5]

This 60-year-old man who was admitted for fall and collapse and found to have ataxia secondary to Vitamin B12 deficiency in the setting of chronic Metformin use. Long-term metformin use (5-10 years) is associated with vitamin B12 deficiency leading to anemia and neurologic symptoms. Routine measurement of B12 levels should be considered with chronic metformin.[6] Additional risk factors for vitamin B12 deficiency caused by metformin include use of prescribed acid suppressants and total years of metformin exposure.[6] Vitamin B12 deficiency associated with metformin is thought to be related to malabsorption. The most plausible explanation is interference by metformin on calcium-dependent membrane action responsible for vitamin B12-intrinsic factor absorption in the terminal ileum.[6] The Diabetes Prevention Program Outcomes study, a 13-year observational study identified clinical sequalae of vitamin B12 deficiency associated with long-term use of metformin[7] including peripheral neuropathy and anemia. Clinicians should be aware of this association and consider routine monitoring.

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