CLINICAL VIGNETTE

Vitamin B_{12} Deficiency Presenting with Neurologic Dysfunction in a 20-Year-Old Male Without Anemia

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Case

A 20 year-old-male with no past medical history presented to the emergency department complaining of bilateral upper and lower extremity paresthesias for two weeks, in addition to weakness in all his extremities. His symptoms rapidly progressed two weeks prior to admission, advancing from paresthesias to extremity weakness, difficulty ambulating, trouble gripping objects and falls. Six months prior, he also presented to the emergency department with upper extremity paresthesias. Antecedent to both his presentations, he had no history of trauma, gastrointestinal symptoms, recent vaccinations, fevers, upper respiratory symptoms, or localizing neurological signs.

On physical exam, muscle bulk and tone were normal and he appeared well-nourished. His exam was notable for 3+/5 lower extremity strength bilaterally, 4/5 upper extremity strength bilaterally and ataxic gait. He required assistance with ambulation, becoming dyspneic with simple ambulation. The remainder of his physical exam was unremarkable.

Labs on admission demonstrated a mild leukocytosis which resolved without intervention. He did not have anemia or macrocytosis. Red blood cells and lymphocytes were near the lower limit of normal and the remainder of his complete blood count was unremarkable. His comprehensive metabolic panel demonstrated no abnormalities. ESR and CRP were within normal limits. Urine drug screen was positive for opiates and THC. Lumbar puncture demonstrated the sole abnormality of elevated protein. CSF culture had no growth and studies for oligoclonal bands were negative.

CT head and MRI brain were unremarkable. MRI of the cervical and thoracic spine demonstrated diffuse, abnormal T2 hyperintensity throughout the posterior spinal cord centered in the dorsal column. The patient was initiated on IV solumedrol given the concern for a possible demyelinating process and neurology was consulted.

The following day, HIV and syphilis studies resulted and were non-reactive. Serum B_{12} level was low at 174 pg/mL (ref. 239 - 931 pg/mL) and the patient was diagnosed with B_{12} deficiency. The patient declined to stay inpatient for further workup, treatment initiation and monitoring after his diagnosis. He was discharged with intramuscular B_{12} with follow-up for treatment response and to complete studies to determine the underlying cause of his deficiency.

Discussion

Vitamin B_{12} is a water-soluble vitamin occurring both naturally and through fortification. Additionally, it is found in animal products such as fish, eggs, dairy, shellfish and meat.[1] The primary site of vitamin B_{12} absorption is in the terminal ileum after binding with intrinsic factor, a protein synthesized and secreted by parietal cells of the stomach.[2,3] Common causes of vitamin B_{12} deficiency are related to pathologic states leading to the inability to absorb B_{12}. Examples are pernicious anemia (lack of intrinsic factor), inflammatory bowel disease, surgeries or congenital abnormalities of the GI tract, insufficient dietary intake (i.e vegan diet), and prolonged use of common medications such as H_2 blockers, proton pump inhibitors (> 12 months of use) and metformin (>4 months of use).[2,4]

Physiologically, vitamin B_{12} has the crucial role of central nervous system development and myelination. In general, vitamin B_{12} is necessary for DNA synthesis, amino acid production and red blood cell production by functioning as a cofactor for enzymes methionine synthase and L-methylmalonyl-CoA mutase. L-methylmalonyl-CoA mutase is a mitochondrial enzyme which assists in the catabolism of ketogenic amino acids and oxidizes odd-chain fatty acids. Methionine synthase is a cytosolic enzyme and methylates homocysteine (a vascular toxin and neurotoxin), which is vital for the synthesis of methionine used in DNA synthesis.[2,3] During the metabolism of vitamin B_{12}, intermediates accumulate when the vitamin is absent, such as methylmalonic acid (MMA). Serum MMA levels become elevated only in vitamin B_{12} deficiency,[5] with the sensitivity for detecting B_{12} deficiency being greater than 95%.[4] It is important to note that homocysteine may also accumulate if B_{12} is deficient, but serum homocysteine will also be elevated in folate deficiency as well.[5] Additionally, B_{12} deficiency may present in individuals where its ability to act as a cofactor is impaired, such as in nitrous oxide (N_2O) abuse (which are also known as "whippets"). Oxidation of B_{12} due to nitrous oxide leads to downstream effects resulting in reduced DNA and myelin synthesis, which may precipitate B12 deficiency and its clinical sequelae.[6]

In clinical practice, vitamin B_{12} is most often measured by serum concentration; however, when measuring B_{12} in the serum, intracellular vitamin B_{12} may not be reflected accurately. Due to this, it is useful to send MMA and homocysteine levels to confirm the diagnosis of B_{12} deficiency.[2,5] Measuring serum MMA and homocysteine is recommended to confirm defici-

ency in patients with low-normal levels of vitamin B_{12} who are otherwise asymptomatic; or, in patients with low-normal levels who have neurologic deficits or lab findings such as macrocytic anemia.[4,5]

The effects of B_{12} deficiency may manifest as megaloblastic anemia, low white blood cells, low red blood cells and low platelets due to insufficient DNA and protein synthesis. Furthermore, patients may exhibit glossitis such as in pernicious anemia, and a myriad of neurologic deficits including dementia.[2] Myelopathy due to B_{12} deficiency, known as subacute combined degeneration, results in degeneration of dorsal and lateral white matter of the spinal cord. This can cause paresthesias of the extremities, progressive weakness, ataxia, paraplegia and incontinence.[7,8]

While the classic laboratory finding of B_{12} deficiency is anemia with macrocytosis, not all patients with B_{12} deficiency will have anemia and/or macrocytosis. Some patients may even present with neurologic abnormalities such as paresthesia, sensory loss, ataxia and dementia in the absence of anemia and/or macrocytosis.[2,9] Aforementioned, in such instances, serum MMA and homocysteine levels would have diagnostic utility.

Treatment of B_{12} deficiency often produces successful clinical results for patients. B_{12} supplementation usually halts the progression of symptoms, producing neurologic improvement in most patients.[5] However, complete resolution of symptoms and complete return to previous baseline is less frequent. MRI imaging following appropriate supplementation may also show resolution of imaging changes.[8] Intramuscular therapy, compared to oral therapy, demonstrates more rapid results in improving neurologic symptoms and lab abnormalities such as anemia. Given the rapid improvement seen with intramuscular vitamin B12, it should be considered as initial therapy in patients with neurologic dysfunction and severe states of deficiency.[4]

Conclusion

Vitamin B_{12} deficiency can be present in asymptomatic patients, or may present with progressive development of neurologic symptoms. Serum studies do not always demonstrate anemia and/or macrocytosis even if the patient has already developed neurologic symptoms, as was the case in this young patient with paresthesia and weakness. Symptomatic, or asymptomatic patients with low-normal serum B_{12} levels should undergo testing of serum MMA and homocysteine levels to diagnose B_{12} deficiency, as serum B_{12} levels do not always correlate to intracellular concentrations. Common causes of deficiency are insufficient dietary intake, malabsorption, nitrous oxide abuse and common medications such as metformin, H_2 blockers and proton pump inhibitors. Treatment of B_{12} deficiency is often successful and may halt symptom progression, in addition to neurologic improvement in most patients. Unfortunately, the patient did not return for his scheduled outpatient follow up visits and did not respond to telephone messages. Review of electronic medical records did not show ambulatory or ED visits in the six months since discharge.

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