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CLINICAL VIGNETTE

A Case of Severe Pernicious Anemia and Subacute Combined Degeneration Associated with Recreational Nitrous Oxide Use

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Case

A 44-year-old male with history of polysubstance use with nitrous oxide, tobacco, marijuana, and cocaine presented to the emergency department with diffuse paresthesias, abdominal bloating, and dyspnea.

Four weeks prior, the patient reported onset of progressive numbness and paresthesias of all four extremities and trunk along with diffuse weakness that limited ambulation and activities of daily living. His family reported confusion with poor concentration and problem-solving skills. The patient also reported constipation with abdominal bloating and dyspnea also over the past month. He denied headaches, fevers, nausea, vomiting, diarrhea, or urinary or bowel incontinence. He did not follow a restrictive diet and had no recent travel or sick contacts. Family history was notable for pernicious anemia on the paternal side. Social history included polysubstance use with recreational nitrous oxide for the last two years, using up to 24 canisters a day for the past two months prior to admission. He also used tobacco daily, and intermittent cocaine, marijuana, and alcohol.

On admission, the patient was afebrile and hemodynamically stable. Physical exam was notable for diminished motor strength (3/5) globally, decreased fine touch and vibratory sensation, decreased proprioception, ataxic gait, and moderate abdominal distension with tympany. Labs included normal Hgb, WBC and platelets on admission but developed mild normocytic anemia on hospital day 3 with hemoglobin of 12.3 g/dL and hematocrit of 37.1%. Vitamin B12 level was decreased at 146 pg/mL (reference of 213 to 816) with elevated homocysteine of 171.9 umol/L (reference <11.4), elevated methylmalonic acid of 44620 nmol/L (reference of 87-318), and positive intrinsic factor antibody. Parietal cell antibody was negative. Metabolic panel, iron studies, folate, vitamin B1, vitamin B6, and TSH. HIV and RPR were also normal. Peripheral blood smear was notable for occasional hypersegmented neutrophils.

MRI brain was unremarkable, however, MRI spine demonstrated degenerative disc disease of the cervical spine from C5-7 and thickening of the ligamentum flavum, moderate spinal canal narrowing with effacement of the CSF surrounding the cord and minimal ventral cord flattening. CT of the abdomen and pelvis was negative.

The patient had severe vitamin B12 deficiency complicated by subacute combined degeneration of the spinal cord. His genetic predisposition with the positive intrinsic factor antibody suggested autoimmune gastritis, which along with extensive nitrous oxide use contributed to his Vitamin B12 deficiency, which led to his acute clinical and functional decline.

The patient was started on daily intramuscular (IM) vitamin B12 1000mcg supplementation while in the hospital with planned taper to weekly followed by monthly IM supplementation after discharge. He received inpatient physical and occupational therapy to improve mobility and strength. On day 7 of hospitalization, patient's vitamin B12 level normalized, and he was discharged to an acute rehabilitation center. Neuropathic pain persisted at the rehabilitation center despite different medical therapies. Transcutaneous electric nerve stimulation provided significant benefits. He will schedule outpatient endoscopies given increased risk/ incidence of GI cancers among patients with pernicious anemia.

Discussion

Vitamin B12, also referred to as cobalamin, is a critical cofactor necessary for cell maturation and neuronal development. Deficiencies can result in a myriad of hematologic and neurodegenerative complications. Fortunately, the clinical manifestations of vitamin B12 deficiency can be reversible, making early diagnosis and treatment important.[1]

Cobalamin is derived primarily from animal food sources such as meats, eggs, fish, shellfish, and dairy products.[2,3] Once con-

sumed, Vitamin B12 is freed as a micronutrient by stomach acid and binds with salivary R-binder in the gastric lumen.[3] In the duodenum, pancreatic protease dissociates vitamin B12, which then binds with intrinsic factor (produced by gastric parietal cells) and is absorbed in the terminal ileum, with the assistance of specialized "cubam" receptors.[3,4] Disruption anywhere along this pathway can result in low serum B12 levels and associated clinical manifestations. Those following a strict vegan or strict vegetarian diets are at increased risk of developing vitamin B12 deficiency due to decreased dietary intake of vitamin B12.[5] Reduced absorption due to H. Pylori infection, use of medications such as metformin or proton-pump inhibitors, pancreatic insufficiency, small bowel pathology, and surgical changes to the gastrointestinal tract have all been implicated in B12 deficiency.[1,5–7] However, autoimmune atrophic gastritis, also known as pernicious anemia, remains the most common cause of B12 deficiency with reported prevalence ranging from 50 to 4000 cases per 100,000 persons.[1,8] Pernicious anemia results from antibodies that target H+/K+ ATPase in the gastric parietal cells and/or intrinsic factor, leading to atrophic gastritis and poor B12 absorption.[9] Theories have also explored the possible role of H. pylori in the development of autoimmune gastritis through molecular mimicry, although evidence remains equivocal.[10–12]

At the cellular level, nitrous oxide, a colorless gas colloquially known as "whippets" or "laughing gas", is a potent inhibitor of vitamin B12 and can precipitate deficiencies and associated neurologic disease.[13–16] In clinical medicine, nitrous oxide is commonly used as an anesthetic, especially in obstetrics and dentistry, and has received increased recognition in treating refractory depression.[17,18] However, with its ability to produce instantaneous physiologic and psychedelic effects (e.g., euphoria, analgesia, depersonalization/ derealization), recreational nitrous oxide is gaining popularity, with reported lifetime prevalence as high as 29% in the United States in 2014.[19,20] Nitrous oxide exhibits deleterious effects by oxidizing vitamin B12, changing its valency, and rendering it inactive.[19] Deficiencies and associated clinical manifestations can be seen after prolonged or even single use, especially among those with underlying susceptibility for vitamin B12 deficiencies.[14,15,21]

Vitamin B12 is used as a cofactor for two major biochemical reactions involving methionine synthase and L-methyl malonyl-coenzyme A mutase.[1] In the former reaction, B12 acts as the integral cofactor in the recycling of methyl-tetrahydrofolate to tetrahydrofolate (THF), while simultaneously coupling it to generation of methionine from homocysteine.[1] Generation of THF is necessary for purine and pyrimidine synthesis, and disruption to this process leads to improper DNA and RNA synthesis. The subsequent nuclear-cytoplasmic dyssynchrony most notably affects rapidly dividing cells such as the hematopoietic cell lines. This classically results in isolated anemia with macrocytosis and/or megaloblastic on peripheral blood smears.[6]

High levels of homocysteine are seen in B12 deficiency and are often used as a marker to diagnose deficiency, although elevated levels are not specific to Vitamin B12 deficiency. Elevated levels of methylmalonic acid (used as a proxy for L-methylmalonyl CoA) have a higher specificity for diagnosing cobalamin deficiency. However, isolated elevations of methylmalonic acid have been described in the context of renal insufficiency.[1,3,6]

Subacute combined degeneration (SACD) of the spinal cord is a potentially devastating complication of vitamin B12 deficiency. While the exact mechanism is unclear, evidence suggests that elevated levels of methylmalonyl CoA and associated byproducts like propionyl CoA leads to improper myelin synthesis and aberrant fatty acid accumulation.[22] Lack of methionine, a critical precursor for neuronal sheath stability, is also thought to play a role in the demyelinating manifestations of cobalamin deficiency. Demyelination classically affects the dorsal column, lateral corticospinal tract, and spinocerebellar tract leading to decrease proprioception and vibratory sensation, symmetric paresthesias, muscle weakness, hyperreflexia, spasticity, and sensory ataxia, which were seen in our patient.[1,22] Diagnosis can include MRI of the spine, which classically appears as the "inverted V" sign, alluding to the symmetric linear T2-hyperintensity of the dorsal column seen in the cervical and thoracic spine on imaging.[23] However, the absence of MRI findings, as was the case in our patient, does not completely rule out SACD of the spine.[24] Some studies report lower sensitivity of MRI findings in diagnosing SACD, underscoring the importance of considering SACD in the right clinical context even in the absence of classic MRI findings.[24,25] Notably, MRI in our patient did show moderate disc disease and the effacement of CSF adjacent to the cord and ventral cord flattening, which could also indicate underlying spondylotic myelopathy, in part contributing to some of his neurologic findings.

Although described as pernicious "anemia", frank anemia is often a later manifestation of disease.[6] Many patients, like ours, present first with neuropsychiatric manifestations of B12 deficiency, which can make diagnosis challenging.[26,27] Such presentations may develop with normal serum B12 level,[28–30] as serum levels may not be reflective of cellular level deficiencies. Diagnosis should therefore be made in the context of metabolite levels (e.g., homocysteine and methylmalonic acid) and correlated to the patient's clinical presentation.[6] Recreational nitrous oxide is a risk factor for B12 deficiencies and should be screened for in the right clinical context.

Treatment for pernicious anemia involves lifelong supplementation, usually given intramuscularly,[9] although recent data suggest that high dose oral supplementation might be equally effective.[31–33] Gastroenterology should also be consulted for thorough evaluation. Patients may need to undergo an upper endoscopy, which is the gold standard in diagnosing autoimmune gastritis but can also evaluate for GI malignancies given increased risk among this population.[34]

Conclusion

Pernicious anemia is a common cause of vitamin B12 deficiency.[1] However, frank anemia is usually a later manifestation of this disease process, and patients are often asymptomatic or present first with neuropsychiatric manifestations, as was the case with our patient.[6] The patient's family history of pernicious anemia along with the presence of intrinsic factor antibodies suggested a genetic susceptibility for an underlying autoimmune process. His daily nitrous oxide use likely contributed to his B12 deficiency and rapid functional decline.

Paresthesias and muscle weakness can have significant impact on a patient's functional status. A multidisciplinary approach involving vitamin supplementation along with intensive physical and occupational therapy should be offered to improve a patient's overall functional status. Screening for inhalant drug use is often missed and with it, potential opportunities for adequate counseling for patients. Meetings with a substance use counselor may be beneficial to address any underlying substance use (e.g., nitrous oxide use) contributing to B12 deficiency.

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