CLINICAL VIGNETTE

Excessive Nitrous Oxide Use Leading to Severe Vitamin B12 Deficiency, Manifesting with Neuropathy that may be Confounded with Possible New Diagnosis of Multiple Sclerosis

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Case Presentation

A 35-year-old woman with a past medical history of depression, anxiety, attention-deficit hyperactive disorder, chronic low back pain, obesity, and chronic insomnia presented to the emergency room for worsening generalized weakness as well as numbness and tingling in her bilateral upper and lower extremities, which had been present for 3-4 weeks. She reported increased anxiety and stress from graduate school and had increased Fluoxetine, from 10 mg to 20 mg around the time her symptoms began. The patient had attributed her symptoms to the increased dose of Fluoxetine. She reduced the dose back to 10 mg, and eventually discontinued it completely over the following 2 weeks at the advice of her primary care provider. However, her symptoms continued. Prior to her admission, she was having mechanical falls and inability to ambulate or stand because of her weakness. The numbness and tingling also progressed proximally and exacerbated her chronic low back pain, which prompted her emergent evaluation. Upon further interview, she acknowledged recently using recreational nitrous oxide up to fifty times daily for the last 1-2 months, in addition to occasional edible marijuana, to help cope with her stress and anxiety. Her most recent use was a few days prior to admission. There were no other changes in her diet and no recent travel. She had not been using any tobacco products or excess alcohol.

Her home medications included Dextroamphetamine/Amphetamine 15 mg daily, and as needed Melatonin 10 mg nightly or Diphenhydramine 25 mg nightly. She used over-the-counter pain medications including Acetaminophen and Ibuprofen as needed for her chronic low back pain.

Her vital signs were normal, afebrile with a temperature of 98.4 F, blood pressure of 120/86, pulse of 79, and O2 saturation of 98% on room air. Significant physical exam findings included paraspinal tenderness to palpation around the L2-3 area, decreased sensation to light touch in bilateral hands and feet, and mild tenderness to palpation at bilateral feet.

Labs included a CBC with macrocytosis without anemia with an MCV of 103. Chemistry panel was unremarkable. Given her macrocytosis, B12 was ordered and was returned undetectable. TSH was suggestive of subclinical hypothyroidism. Lumbar puncture revealed an initial cell count not suggestive of infection, while specific studies including West Nile, myelin basic protein, and oligoclonal bands were submitted. MR imaging with contrast was performed on the cervical, thoracic, and lumbar spine, for which her cervical imaging suggested abnormal intramedullary spinal cord signaling between C2-C5, thoracic imaging was negative, and lumbar imaging was only suggestive of L4-5 and L5-S1 degenerative disc disease with disc bulging without stenosis. Radiology reported the signal on cervical imaging as consistent with myelitis or demyelination.

Neurology was consulted and treatment was initiated with subcutaneous B12 repletion as well as IV (Methylprednisolone) for a 5-days for myelopathy. Concern for a new diagnosis of multiple sclerosis remained. After her B12 level was normalized, she was transitioned to oral B12 supplementation. Her symptoms improved mildly over the following nine days, however because she still needed significant rehabilitation, she was transferred to the acute rehabilitation unit for continued physical therapy. Her CSF studies later returned positive for oligoclonal bands and presence of myelin basic protein.

Discussion

Our patient with new-onset generalized weakness, numbness and tingling had multiple factors and potential diagnoses to explain her symptoms, including significant B12 deficiency due to excessive nitrous oxide use, cervical myelitis/myelopathy, and the presence of oligoclonal bands in the CSF suggestive of a new diagnosis of multiple sclerosis. Given its acute onset, it was difficult to discern if there was a predominant characteristic driving the patient's symptoms in light of these different findings. As practitioners in the community we tend to investigate the more common etiologies, however this case presents a unique scenario which may have been missed had the details not been thoroughly scrutinized.

Vitamin B12 deficiency is known to cause neurologic changes affecting peripheral nerves and the posterior and lateral columns of the spinal cord, and can cause paresthesias, numbness, decrease in vibration and proprioception, and ataxia. Nitrous oxide, which has traditionally been used in clinical practice as an anesthetic, has more recently been associated with widespread recreational use through over-the-counter availability.[1] Various case reports have cited the incidence of

Vitamin B12 deficiency due to nitrous oxide toxicity as a cause of subacute combined spinal cord degeneration.[2,3] A young sickle-cell disease patient had multiple episodes of vaso-occlusive crises which were treated with nitrous oxide.[2] He presented with ascending sensorimotor symptoms and bladder dysfunction and was initially thought to have Guillain-Barre syndrome. However, despite treatment his neurologic symptoms persisted and ultimately his symptoms were attributed to abnormal Vitamin B12 metabolism caused by repeated nitrous oxide administration.

Nitrous oxide is thought to impair metabolism of Vitamin B12 by binding to and oxidizing its cobalt ion, preventing it from binding to methionine synthase and rendering it inactive.[1,2] This enzyme is present in the pathway of myelin sheath production. While nitrous oxide toxicity is often associated with a sensory predominant myeloneuropathy, it has been postulated that nitrous-oxide associated motor neuropathy or neuronopathy may develop independently from Vitamin B12 deficiency.[4] Early identification of this underlying condition followed by a treatment plan that includes both Vitamin B12 supplementation and concurrent abstinence from nitrous oxide use has been shown to help improve or resolve symptoms. In cases where patients continued to use nitrous oxide while taking Vitamin B12 supplements, a delay in symptom progression was noted, but Vitamin B12 supplementation alone is thought not sufficient to protecting against the adverse effects.[5]

Conclusion

In conclusion, our 35-year-old female patient who presented with generalized weakness and paresthesias in her bilateral upper and lower extremities most likely had cervical myelitis/ myelopathy in the setting of Vitamin B12 deficiency caused by excessive nitrous oxide use, with a possible new diagnosis of multiple sclerosis also contributing. Her symptoms improved somewhat after Vitamin B12 administration, however she continued to require physical therapy and rehabilitation. In the evaluation of peripheral neuropathy and other neurologic symptoms, physicians should consider Vitamin B12 deficiency as a potential cause and if present, screen for possible nitrous oxide use, whether iatrogenic or recreational, as these are potentially reversible causes of neuropathy. In addition to providing Vitamin B12 repletion, it is also important to discontinue use of nitrous oxide if it is suspected to be a contributing cause.

REFERENCES

1. **Keddie S, Adams A, Kelso ARC, Turner B, Schmierer K, Gnanapavan S, Malaspina A, Giovannoni G, Basnett I, Noyce AJ**. No laughing matter: subacute degeneration of the spinal cord due to nitrous oxide inhalation. *J Neurol*. 2018 May;265(5):1089-1095. doi: 10.1007/s00415-018-8801-3. Epub 2018 Mar 3. PubMed PMID: 29502317; PubMed Central PMCID: PMC5937900.
2. **Chaugny C, Simon J, Collin-Masson H, De Beauchêne M, Cabral D, Fagniez O, Veyssier-Belot C**. [Vitamin B12 deficiency due to nitrous oxide use: unrecognized cause of combined spinal cord degeneration]. *Rev Med Interne*. 2014 May;35(5):328-32. doi: 10.1016/j.revmed.2013.04.018. Epub 2013 Jun 14. French. PubMed PMID: 23773901.
3. **Stockton L, Simonsen C, Seago S**. Nitrous oxide-induced vitamin B12 deficiency. *Proc (Bayl Univ Med Cent)*. 2017 Apr;30(2):171-172. PubMed PMID: 28405070; PubMed Central PMCID: PMC5349816.
4. **Morris N, Lynch K, Greenberg SA**. Severe motor neuropathy or neuronopathy due to nitrous oxide toxicity after correction of vitamin B12 deficiency. *Muscle Nerve*. 2015 Apr;51(4):614-6. doi: 10.1002/mus.24482. Epub 2015 Feb 24. PubMed PMID: 25297001.
5. **Pugliese RS, Slagle EJ, Oettinger GR, Neuburger KJ, Ambrose TM**. Subacute combined degeneration of the spinal cord in a patient abusing nitrous oxide and self-medicating with cyanocobalamin. *Am J Health Syst Pharm*. 2015 Jun 1;72(11):952-7. doi: 10.2146/ajhp140583. PubMed PMID: 25987690.

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