Subacute Combined Degeneration of the Spinal Cord From Nitrous Oxide Abuse

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ABSTRACT

Introduction: The recreational use of nitrous oxide is surging in popularity, with nearly 13 million Americans aged 12 and older reported to have misused it, according to a 2019 survey by the Substance Abuse and Mental Health Services Administration. Prolonged use has been linked to significant neurological deficits, potentially leading to lifelong issues if not treated early.

Case Presentation: We present a case of a 38-year-old male with significant neurologic deficits attributed to prolonged nitrous oxide abuse, resulting in subacute combined degeneration of the spinal cord. This condition is characterized by demyelination of dorsal and lateral columns.

Discussion/Conclusions: The growing recreational use of nitrous oxide, facilitated by its easy availability and lack of regulation, highlights the importance of clinician vigilance in managing associated risks. Neurological symptoms from vitamin B12 deficiency are particularly worrisome. Early intervention is crucial to prevent potential long-term consequences.

INTRODUCTION

Vitamin B12 is a necessary coenzyme in biochemical processes in the human nervous system. It plays a crucial role in the formation of the myelin sheath, insulating neurons and allowing for efficient transmission of impulses down their axons.[1] Deficiencies in vitamin B12 can lead to loss of neuronal myelination, resulting in motor and sensory neurological symptoms.[1] A well-balanced diet will provide adequate vitamin B12 as it is naturally found in fish, meat, eggs, and dairy products.

Nitrous oxide is a colorless and odorless gas that has a long history of medical use for anesthesia and anxiolytic purposes.[2] It also has been used as a recreational substance for many decades, producing a short-lived euphoria (around 1 minute) when inhaled.[2] Street names for nitrous oxide include laughing gas, nitro, NOS, nangs, whippets, hippy crack, canisters, and balloons. It remains legal and loosely regulated in many countries, including the United States, where it is readily available in stores and online. It is often sold under the guise of use in the food industry as a propellant and bacteriostatic agent in whipped cream and is available in small single-use canisters or larger bottles that can hold multiple "doses." Statutes on possession limits and intentional inhalation differ depending on local jurisdictions. As of 2020, the National Survey on Drug Use and Health reported a 4.7% lifetime prevalence in those 12 years old and older of recreational nitrous oxide in the US.[3]

The detection of nitrous oxide use is usually not feasible in a clinical setting due to its short half-life in the blood (5 minutes).[4] It is not commonly reported on serum or urine drug screens. Clinicians should instead focus on taking a thorough substance use history, especially in patients who present with neurological findings. Clarifying the quantity and duration of use is important as there is a dose-dependent relationship with adverse neurological effects.[5]

Vitamin B12 Measurement

Vitamin B12 levels are most commonly measured using a chemiluminescence assay; however, this does not always reflect actual total body B12 stores but rather the protein-bound B12 in the serum.[6] It is possible to have B12 deficiency despite having a normal value on a serum B12 assay. Therefore, other biomarkers in the cyanocobalamin metabolism pathway are used to help quantify actual B12 stores. Methylmalonic acid (MMA) is a useful test and

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may be elevated in a setting of true B12 deficiency, as B12 is a necessary cofactor for its conversion to succinyl-COA.[6] MMA can be a useful test when serum B12 levels are normal but suspicion of deficiency remains high.

Nitrous Oxide Mechanism of Reducing B12

Vitamin B12 plays a crucial role in cellular DNA production by serving as a co-factor for enzymes of methionine synthase and methyl-malonyl CoA mutase. Methionine synthase carries out the conversion of homocysteine to methionine. Methionine is then converted to S-adenosyl methionine, which serves as a methyl group donor to myelin basic protein (MBP). Without methylation of MBP, the myelin sheath is more susceptible to damage. The second enzyme, methyl-malonyl CoA mutase, is directly involved in myelin production. Therefore, B12 deficiency may impair new myelin production and leave existing myelin more prone to insult.[6]

B12 deficiency in nitrous oxide poisoning has a unique mechanism as it represents a functional deficiency. Nitrous oxide acts on the cobalt atom in vitamin B12, causing it to become irreversibly inactivated and unable to serve as a cofactor in the processes described above.[6] The risk of neurologic symptoms from nitrous oxide abuse is dose-dependent and more likely to occur with long-term use.[5]

Subacute Combined Degeneration

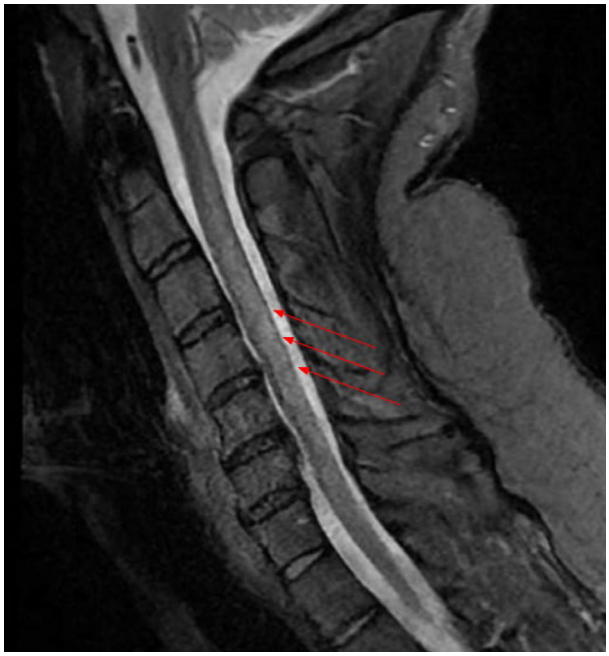
Subacute combined degeneration is a neurological syndrome that arises as a complication of vitamin B12 deficiency. The signs and symptoms stem from demyelination of neurons in the spinal cord.[6] Subacute combined degeneration is preferential to the dorsal and lateral columns of the spinal cord, and the clinical syndrome presents accordingly. Involvement of the dorsal column leads to paresthesias (often the earliest sign) and impaired proprioception and vibratory sensation. Both the upper and lower extremities can be affected. Balance also may be impaired secondary to proprioception. The lateral column carries the corticospinal tract, which is responsible for motor function of the limbs. Demyelination at this site can manifest as muscle weakness, and upper motor neuron signs, such as spasticity and hyperreflexia, may be present.[6] Normocytic or macrocytic anemia also may be present; therefore, the absence of macrocytic anemia does not rule out subacute combined degeneration.[7]

Prognosis

Generally speaking, treatment of subacute combined degeneration with B12 replacement will arrest the progression of the disease and lead to partial reversal of the neurological complications. A small retrospective review of 57 patients showed that 86% of patients had symptom improvement with B12 replacement, but only 14% had complete resolution of their symptoms.[8]

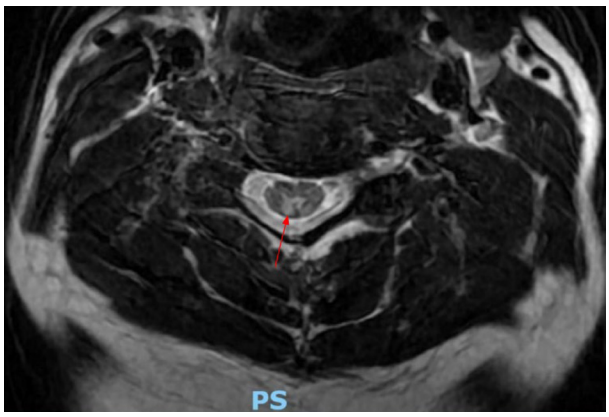
We present a case of a patient with significant neurologic deficits attributed to prolonged nitrous oxide abuse, resulting in subacute combined degeneration of the spinal cord.

Figure 1. Magnetic Resonance Imaging of the Dorsal Spine



Hyperintense T2 signal in the dorsal spinal column extending over several levels of the cervical spine.

Figure 2. Magnetic Resonance Imaging of the Cervical Spine



Classic subacute combined degeneration findings of hyperintense T2 signal affecting the dorsal columns.

CASE PRESENTATION

A 38-year-old male with a past medical history of polysubstance abuse presented to the hospital with altered mental status, psychosis, and generalized weakness. He reported using nitrous oxide multiple times daily over the past several months. He also used recreational cannabis during that time period. He had a history of alcohol dependence with previous withdrawal seizures, but he was not using alcohol in the months leading up to his presentation. Initially, the patient's altered mentation, agitation, and psycho-

sis prevented a comprehensive neurological evaluation. He experienced visual hallucinations and was very irritable for the first few days of his hospitalization, which led to the administration of antipsychotic medications. As his mentation cleared, his weakness became more apparent, and a neurological workup was initiated. Imaging and laboratory workup were performed over the course of his hospitalization. His vitamin B12 on admission was low at 204 (reference range 232-1245) and MMA was significantly increased at 14.37 (reference range 0.00-0.40). He had a mild normocytic anemia with a hemoglobin of 11.7 and a mean corpuscular volume of 94.9 (reference 81.5-99.0).

Neurological exam performed on day 6 of hospitalization was significant for bilateral lower extremity weakness, impaired vibration and proprioception below the waist, and patellar and achilles hyperreflexia. His sensory deficits were symmetric and in a graded fashion proximal to distal. He had a positive Babinski sign and multiple beat clonus in his bilateral ankles. There were findings of upper extremity weakness as well, with 3/5 strength of intrinsic finger muscles and 4/5 wrist extension and grip. He had no cranial nerve deficits, dysarthria, ataxia, or dysmetria.

The patient's symptoms were suspicious for a spinal cord etiology, prompting cervical and thoracic spine magnetic resonance imaging (MRI). The MRI revealed an abnormal T2 hyperintense signal in the dorsal spinal cord consistent with subacute degeneration seen in nitrous oxide abuse (Figures 1 and 2). The patient initially required a mechanical lift for transfer. He was able to stand for short periods of time but could not ambulate and needed assistance with activities of daily living, including dressing and toileting.

Follow-up and Outcome

The patient was treated with intravenous B12 at a dose of 1000 mcg every other day along with high-dose folic acid (4 mg daily). He worked intensively with physical and occupational therapy. Over the course of 6 weeks, he gradually regained both motor and sensory function. At the time of his discharge, he was able to ambulate with the assistance of a 4-wheeled walker and subjectively regained most of his lower extremity sensation. His upper extremities improved more quickly and, at discharge, he had full use and normal sensation. Additionally, his serum B12 levels measured above the upper limit of normal and his MMA had normalized. He was discharged on 1000 mcg of oral B12 and 800 mcg of folic acid daily and was set up with outpatient neurology, physical therapy, and addiction medicine.

The patient was discharged from physical therapy after approximately 3 months due to financial constraints. He did show improvements in lower extremity strength during the course of physical therapy, ambulating with a cane at the time of discharge rather than a 4-wheeled walker and able to independently perform activities of daily living. He self-increased his oral B12 to 2000 mcg once a week, which was continued due to patient preference and low risk for toxicity. Additionally, he continues to take folic acid 800 mcg daily and is actively working with addiction medicine for his polysubstance abuse.

DISCUSSION

Subacute combined degeneration of the spinal cord (SCD) is a demyelinating condition of the dorsal and lateral columns of the spinal cord commonly seen in vitamin B12 deficiency. Due to nitrous oxide's effect on vitamin B12 activation, nitrous oxide misuse is a rare, yet possible cause of SCD. Patients with SCD may present with numbness, weakness, impaired vibration and proprioception, psychosis, normocytic or macrocytic anemia, and upper motor neuron symptoms.[9] Additionally, in patients with polysubstance abuse, as seen in this case, symptoms initially may be masked by substance intoxication making diagnosis challenging. Given the rise in recreational use of nitrous oxide, it is now essential to include questions about this substance in drug screenings. Important questions to ask include the quantity and duration of misuse as there is a dose-dependent relationship with adverse neurologic effects.[5] A thorough social history can help identify medical issues related to B12 deficiency and potentially prevent SCD if patients are educated properly.

Diagnostic workup includes a thorough neurologic examination, metabolic panel, complete blood cell count, B12 and methylmalonic acid, and MRI of the spinal cord. Of note, testing for nitrous oxide misuse is challenging as it does not commonly appear on urine or serum drug tests due to its short half-life.[4] Once a diagnosis is made, treatment typically involves aggressive supplementation of B12 to prevent irreversible neurological deficits and intensive physical therapy. Recommended dosing regimens in the acute setting include parenteral 1000 mcg of vitamin B12 every other day for at least 2 weeks, followed by B12 injections 3 times weekly for another 2 weeks. While parenteral administration is strongly preferred, oral 1000 – 2000 mcg daily B12 supplementation may be used as an alternative.[7] For reversible causes of B12 deficiency (ie, drug-induced), supplementation is required only until the deficiency is corrected and offending substance stopped.[6]

CONCLUSIONS

We present a case involving a patient with polysubstance abuse who presented with a complex combination of vague neurological symptoms, psychosis, and altered mentation. Upon further examination and history, it was discovered that he had recently misused nitrous oxide, leading to symptoms consistent with SCD. Although rare, SCD has been associated with nitrous oxide misuse. Key factors in reaching an accurate diagnosis included considering the patient's age and social history, conducting a thorough neurological examination, and understanding that normocytic anemia does not exclude B12 deficiency/inactivation. Early intervention, as this case highlights, is crucial to prevent potential long-term, life-changing consequences.

This case emphasizes the potential severity of SCD from nitrous oxide abuse, as this patient's neurological symptoms were more severe than most contemporary case reports on this condition. It also highlights the importance of including screening for nitrous oxide misuse when taking a patient's substance use history, especially in patients with neurological symptoms.

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