Not a Laughing Matter: When Nitrous Oxide Causes Functional Vitamin B12 Deficiency

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ABSTRACT

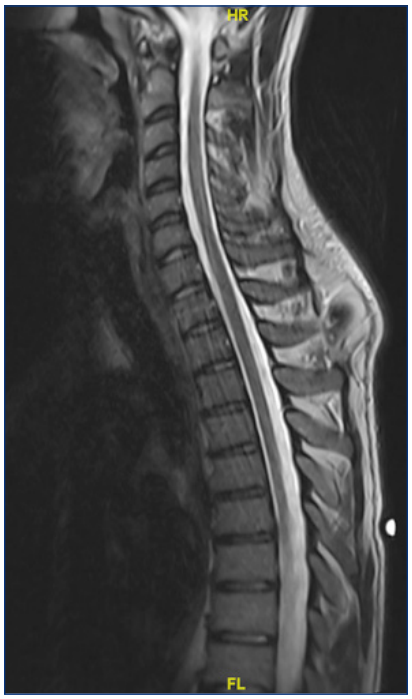
Subacute combined degeneration (SCD) is an acquired neurologic complication from prolonged vitamin B12 deficiency. As a result of dorsal and lateral spinal cord column degeneration, patients present with a range of neurological symptoms, including paresthesias, ataxia, and muscle weakness. Without prompt treatment, irreversible nerve damage occurs. Here we present a young man who developed progressive ascending paresthesias and lower extremity weakness after escalated nitrous oxide use. This case highlights the importance of considering SCD from nitrous oxide toxicity when patients present with progressive ataxia, paresthesia, and lower extremity weakness.

KEYWORDS: Nitrous oxide use, functional cobalamin deficiency, subacute combined degeneration

INTRODUCTION

Nitrous oxide (N_2O), or "laughing gas," is a commonly used anesthetic and analgesic in medical and dental procedures. It is also widely used as a mixing and foaming agent in the culinary arts and as a fuel booster in the motor industry.[1] Due to its euphoric effects, easy accessibility for nonmedical purposes, and relatively cheap cost, it has become a popular recreational drug. The U.S. Department of Health and Human Services' National Survey on Drug Use and Health found a 4.5–5.1% lifetime prevalence of recreational N_2O use in the United States among individuals aged 12 and older.[2] N_2O exposure can lead to many symptoms due to its impact on the metabolism of vitamin B12 (cobalamin), specifically by inactivating vitamin B12 through irreversible oxidation. In this report, a 23-year-old male developed progressive disabling neurologic symptoms following heavy N_2O use with spinal imaging consistent with SCD, but biochemical findings suggestive of only functional cobalamin deficiency.

Figure 1. T2-weighted sagittal MRI view demonstrating abnormal signal in the dorsal columns of the cervical spine.



CASE PRESENTATION

A 23-year-old male with a past medical history of depression and polysubstance use presented with a week-long history of ascending bilateral lower extremity paresthesia, progressive lower extremity weakness, and multiple falls. In the preceding months, he had no illnesses, had not received any vaccinations, and had eaten a balanced diet with no dietary restrictions. The patient had a history of intermittent N_2O use, which had recently escalated to inhaling multiple liters of N_2O daily. He estimated he had spent over $10,000 in the past 90 days leading us to infer his total consumption was between 300 to 500L. The patient self-administered multiple cobalamin tablets in the days prior to presenting to the Emergency Department, as a friend experienced similar symptoms from a cobalamin deficiency. However, he had no symptomatic improvement following oral supplementation.

On presentation, neurological examination was remarkable for: bilateral foot drop, diminished sensation to light touch, impaired proprioception in his bilateral lower extremities, positive Romberg sign, and ataxic wide-based gait. No neurologic deficits in upper extremities. His physical examination was otherwise unremarkable.

Routine blood tests revealed a white blood cell count of 7.2 x 10^9/L, hemoglobin of 14.4 g/dL, and mean cell volume of 94.6 fL, which were all within normal limits. Vitamin B12 level was 623 pg/mL (normal 211–911 pg/mL), but both homocysteine and methylmalonic acid (MMA) levels were markedly elevated to 104.8 umol/L (normal 5–13.9 umol/L) and 3.66 umol/L (normal 0–0.4 umol/L) respectively. Inflammatory serum markers were within normal limits, including the C-reactive protein

and the erythrocyte sedimentation rate. Thyroid stimulating hormone was within normal limits six months prior and was not rechecked on admission. Human immunodeficiency virus, hepatitis serologies, treponemal antibodies, and other vitamin levels, including folic acid, were not checked. Magnetic resonance imaging (MRI) of the cervical, thoracic, and lumbar spine with and without contrast was notable for T2 hyper-intensities predominantly involving the dorsal columns of the cervical cord (**Figure 1**), with questionable areas of patchy involvement in the thoracic cord. Given the clinical suspicion of SCD from his substantial N_2O use, a lumbar puncture was not performed.

He received one intramuscular injection of Vitamin B12 1000 mcg, was counseled to cease N_2O inhalation, and was discharged home with oral cobalamin supplements (100 mcg/day) and appointments for physical therapy and neurology follow-up.

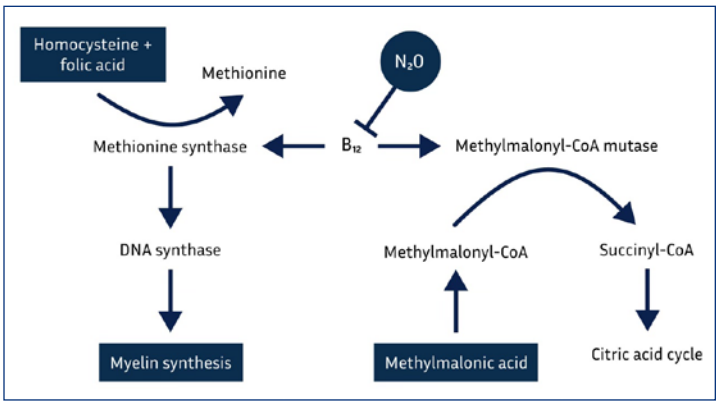
One week later, the patient was readmitted to the hospital after multiple falls at home. Since leaving the hospital, he had wholly abstained from ongoing N_2O use and was compliant with his cobalamin supplementation. In addition to his persistent lower extremity symptoms, he had new complaints of cognitive slowing, headaches, upper extremity weakness, and hand paresthesias. Repeated neurological examination found decreased sensation to light touch in both distal upper and lower extremities, persistent bilateral foot drop, and mildly decreased strength (4 out of 5) in elbow flexion, finger flexion, and abduction.

Labs on readmission revealed normal Vitamin B12 levels again. Homocysteine and MMA remained elevated but dramatically improved to 19.8 umol/L and 0.96 umol/L, respectively, suggesting methionine metabolism and B12 cofactor activity was normalizing. However, as he was clinically more symptomatic, his cobalamin supplementation was increased to 1000 mcg daily, and he was started on Gabapentin 300mg nightly for his neuropathic pain and paresthesias. The patient was discharged to an inpatient rehabilitation facility. After three weeks of intensive physical and occupational therapy and daily oral and weekly intramuscular cobalamin supplementation, his cognition and motor skills had improved but not yet normalized. He was able to ambulate with a quad cane for short distances independently but continued to require a rolling walker for longer excursions due to his persistent ataxic gait and foot drop.

DISCUSSION

This case underscores the importance of eliciting a comprehensive substance use history and recognizing chronic N_2O use as a cause of functional cobalamin deficiency to prevent disabling neurologic consequences. Serum cobalamin deficiency develops in adults from inadequate dietary intake, gastrointestinal malabsorption, parasitic infection, or adverse drug effect.[3] Unlike true cobalamin deficiency, functional cobalamin deficiency occurs because of the body's inability to utilize cobalamin due to impaired intracellular transport or cellular processing. In the case of N_2O inhalation, N_2O irreversibly oxidizes the cobalt ion in cobalamin, rendering it inactive. This inactivation disrupts the normal metabolism and causes the accumulation of homocysteine and MMA (**Figure 2**). Demyelination occurs from both high breakdown of myelin from direct MMA toxicity and reduced myelin synthesis from decreased methionine stores.[4,5] As a result of dorsal and lateral spinal cord degeneration, patients typically present with weakness, ataxia, paresthesias, and falls, as well as a range of psychiatric complaints, including memory impairment and paranoia.[1] SCD most frequently occurs after prolonged recreational N_2O exposure. However, there have been reports of SCD developing after minimal N_2O exposure, including only 30 minutes of N_2O anesthesia, in patients with subclinical B12 deficiency.[6]

Figure 2. Role of B12 in Methylmalonic Acid and Homocysteine metabolism



Diagnosis of functional cobalamin deficiency requires a high degree of clinical suspicion as serum B12 levels are normal. To detect B12 deactivation, look for elevated MMA and homocysteine levels. Megaloblastic changes in the bone marrow with or without anemia are a known complication of cobalamin deficiency. However, as with this case, most patients with only biochemical evidence of cobalamin deficiency present with MCV and hemoglobin within the reference range.[7] Imaging is required to diagnose subacute combined degeneration and to rule out other possible demyelinating etiologies, including multiple sclerosis or transverse myelitis.[8] In SCD, MRI shows T2 hyper-intensities confined to the dorsal column in the cervical and thoracic spinal cord without post-contrast enhancement.[5,9]

In cases of N_2O-induced functional cobalamin deficiency, treatment consists of abstinence from N_2O and cobalamin supplementation. There are no established treatment guidelines. Review of the literature reveals a wide range of supplementation, from daily high-dose parenteral therapy to intermittent oral supplementation.[6,10,11] While the progression of neurologic deficits frequently arrests shortly after

initiation of cobalamin therapy, in this case stabilization of neurologic symptoms required increasing the daily cobalamin dose to 1000 mcg PO. On discharge, the patient's overall functional capacity remained below baseline. Recovery from SCD is often protracted and incomplete. An observational study of 57 cases of SCD found that while 49 patients (86%) improved, only eight (14%) achieved complete clinical resolution.[12] This patient required several weeks of intensive physical rehabilitation with ongoing ataxic gait and foot drop at time of discharge from physical therapy. Overall, this case report underscores the foundational importance of a detailed patient history and comprehensive diagnostic approach. In retrospect, higher cobalamin dosing after index hospitalization likely would have prevented the progression of his symptoms and subsequent readmission.

CONCLUSION

This case report emphasizes the critical need for early recognition of SCD and functional cobalamin deficiency in the setting of N_2O use. When serum cobalamin is normal, elevated homocysteine and MMA are indicative of cobalamin inactivation. Adequate cobalamin dosing is needed to prevent SCD symptom progression and re-admission. In this case, 1000 mcg was sufficient to halt neurologic symptoms. Further studies are needed to develop standardized protocols to treat functional cobalamin deficiencies. Given the complexity of managing the underlying substance use disorder and the debilitating resultant neurologic symptoms, a comprehensive and individualized treatment approach is recommended.

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Acknowledgments

We would like to thank Idiris Mohamed, Director of Idrees Studios, for his help in creating the diagram used in the discussion section of this paper.

Disclosures

No conflict of interest or financial disclosures.

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