Diagnostic Challenges and Key Insights of Nitrous Oxide Neuropathy: A Case Series

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Abstract

Nitrous oxide (N_2O) is increasingly misused due to its easy availability. Chronic misuse causes irreversible oxidation of cobalamin which results in vitamin B12 deficiency and impaired myelination leading to neurological complications. We present two cases highlighting diagnostic challenges consisting of a 34-year-old male and a 52-year-old, both initially misdiagnosed as chronic inflammatory demyelinating polyneuropathy (CIDP). They were eventually diagnosed as N_2O-induced neuropathy based on lab testing and electrodiagnostic findings. Clinicians should maintain a high suspicion of N_2O misuse in unclear neuropathies. Early recognition with prompt and sustained vitamin B12 supplementation is crucial for preventing irreversible neurological damage and avoiding unnecessary immunotherapy.

Introduction

Nitrous oxide (N_2O), also known as laughing gas, is an anesthetic agent frequently utilized in medical and dental procedures. Recreational use of N_2O has increased, particularly among young adults, due to its short-acting euphoric and dissociative effects. It is most commonly inhaled from whipped cream chargers («whippets»), balloons filled from gas canisters, or directly from medical-grade cylinders, often accessed via online or over-the-counter sources.[1] N_2O misuse is an emerging public health concern, increasingly identified for causing significant neurotoxicity. Chronic exposure to N_2O leads to vitamin B12 deficiency through irreversible oxidation of cobalamin, impairing myelin synthesis and resulting in peripheral neuropathy and myelopathy.[2,3] Despite rising awareness, clinical differentiation of N_2O-induced neuropathy from inflammatory or autoimmune conditions, such as chronic inflammatory demyelinating polyneuropathy (CIDP), remains challenging and often delays accurate diagnosis and effective treatment.[4] While vitamin B12 supplementation remains central to management, variability in neurological recovery highlights ongoing clinical challenges.[5]

We present two illustrative cases highlighting these diagnostic challenges. The first case involves a 34-year-old male initially suspected of CIDP due to sensory and motor deficits, subsequently diagnosed with N_2O-induced neuropathy. The second case involves a 52-year-old female with subacute painless bilateral foot drop who underwent Intravenous Immunoglobulin (IVIG) therapy without improvement before identification of the toxic etiology. Both cases highlight the critical need for timely recognition of N_2O abuse to initiate appropriate treatment and avoid unnecessary interventions.

Case Presentation

Case 1

A 34-year-old male presented with progressive tingling and numbness that started in the feet and ascended to the knees approximately two weeks following a viral illness. Symptoms evolved over several months, resulting in frequent falls and balance impairment, particularly in low-light conditions. He denied upper extremity weakness, dysphagia, or respiratory issues. His medical history was notable for chronic back pain, prior alcohol dependence, and recreational inhalation of nitrous oxide gas for an unknown duration.

On examination, strength was intact except for mild bilateral weakness of the great toe extensors. Vibration sense was absent up to the knees bilaterally, and proprioception was impaired at the toes. Deep tendon reflexes were absent at the knees and ankles but preserved in the upper extremities. Gait was wide-based, with mild difficulty performing tandem and heel walking. Romberg sign was positive.

Previous nerve conduction studies (NCS) and electromyography (EMG) indicated possible demyelinating neuropathy based on prolong latencies and slow conduction velocities. However, this initial external study did not meet formal EAN/PNS electrophysiological criteria for demyelination upon closer review. Two months later repeat testing at our institution confirmed axonal sensory-motor polyneuropathy. Vitamin B12 was markedly reduced (123 pg/mL, normal: 180-950 pg/mL), with elevated methylmalonic acid (1.66 µmol/L, normal: <0.40 µmol/L). X-ray of the cervical spine was performed and that reported mild degenerative changes. Magnetic resonance imaging (MRI) of the lumbar spine showed mild degenerative changes but no significant stenosis or dorsal column signal.

The patient was diagnosed with N_2O-induced neuropathy with vitamin B12 deficiency. Treatment included cessation of N_2O, 1000 mcg of intramuscular vitamin B12 weekly for four weeks, followed by monthly 1000 mcg injections as maintenance, and ongoing physical therapy. During the last follow-up at the end of January

2025, the patient reported reduced tingling sensation with improved vibration, proprioception and balance following continued abstinence from N_2O.

Case 2

A 52-year-old female with a history of hypothyroidism, breast cancer, Sjogren's syndrome, depression, and prolonged laughing gas use abused whippet canisters for months, consuming up to 200-300 canisters per day at some point in 2022. She presented with relatively simultaneous, painless subacute bilateral foot drop. She described numbness on the soles, impaired balance, and difficulty climbing stairs but denied significant foot pain. Her medical history included multiple hospitalizations for toxic encephalopathy, anemia, and leukopenia. The episodes of toxic encephalopathy, including one with visual hallucinations, were presumed to be secondary to nitrous oxide use and responded to cessation of exposure and vitamin B12 supplementation. Initially, she was evaluated by a neurologist outside our hospital, who performed an NCS/EMG, which there was mention of temporal dispersion on bilateral peroneal nerves. This raised the suspicion of CIDP, and she was started on steroids followed by IVIG, which resulted in no clinical improvement. Blood work at the time showed leukopenia. Three days post-IVIG, she developed a rash involving both lower extremities and torso, leading to us for further workup.

Neurological examination revealed severe bilateral weakness in ankle dorsiflexion (Medical Research Council scale 1/5) and complete loss of toe extension. Vibratory sensation was absent at the toes, with reduced proprioception at the great toes. Reflexes were hyperactive at the knees but absent at the ankles. Her gait was wide-based with bilateral steppage pattern and an inability to heel-toe walk.

Repeated EMG/NCS study in our hospital a month later demonstrated length-dependent pure motor axonal neuropathy, suggesting that the abnormal large fiber sensory findings were likely due to dorsal column involvement. MRI of the cervical spine identified severe central canal stenosis at C4-C5 and C5-C6 level with associated increased cord signal. These findings could potentially explain the brisk lower extremity reflexes and features of sensory ataxia, given the normal peripheral sensory nerve conduction studies. However, they are insufficient to fully account for the motor-predominant bilateral foot drop, suggesting a concurrent peripheral process. MRI of the lumbar spine revealed mild degenerative disc disease at L3–L5 with mild spinal and foraminal stenosis, but no significant compressive pathology to explain the bilateral foot drop. Laboratory studies confirmed vitamin B12 deficiency (111 pg/mL, normal 180-950 pg/mL), leukopenia (white blood count: 2.0/ µL, normal: 4.50-11.00 10^3/ µL) and anemia (Hemoglobin: 9.4 g/dL, normal: 12.0-15.0 g/dL), (MCV 92fL, normal 80-100 fL).

Cerebrospinal fluid (CSF) analysis showed mild chronic inflammatory changes (total nucleated cells 10, normal: <5/ µL; lymphocytes predominant, 91%, and total protein 31 mg/dL, normal: 15-45 mg/dL) however, these were considered to be related to recent IVIG treatment. Dermatology considered a possible leukocytoclastic vasculitis, however not confirmed on a biopsy. The rash improved in few days indicating an adverse reaction to IVIG treatment. A nerve and muscle biopsy were also performed and reported mixed axonal and myelin sheath loss without any evidence of inflammation nor signs of vasculitis. Recognition of N_2O-induced neuropathy prompted initiation of 1000 mcg of intramuscular vitamin B12 weekly for four weeks, followed by monthly 1000 mcg injections. Following two-week period of supplementation, mild improvement in balance and ambulation were seen, though severe foot drop persisted, necessitating ongoing physical therapy, orthotic support, and further diagnostic evaluations. Table 1 summarizes and compares key clinical characteristics, diagnostic findings, treatments, and clinical outcomes of the two patients in this case series.

Discussion

This case series demonstrates diagnostic challenges caused due to N_2O-induced neuropathy which is an increasingly prevalent yet often unrecognized clinical entity. Misuse of N_2O often sourced from medical supplies, whipped cream dispensers, or recreational use, disrupts vitamin B12 metabolism. This disruption can lead to severe neurologic deficits resembling inflammatory and autoimmune neuropathies, which frequently leads to delayed or inappropriate treatment.[6,7]

Our two cases presented with the diagnostic complexity associated with N_2O neuropathy. Case 1 was initially misdiagnosed with CIDP, and Case 2 underwent unsuccessful treatment with steroids and IVIG. In both cases, the initial electrodiagnostic studies performed at outside institutions suggested demyelinating features, which on further review did not meet the formal EAN/PNS criteria for demyelinating neuropathy. Therefore, repeat studies were performed at our center, which demonstrated axonal sensorimotor and motor axonal neuropathies, respectively. Both cases presented with progressive motor and sensory deficits with ataxia manifested as impaired coordination and balance, with lab tests showing severely reduced vitamin B12 levels. Coexisting autoimmune conditions such as Sjogren's syndrome, as seen in Case 2, can significantly complicate the diagnostic landscape. Sjogren's is associated with a spectrum of neuropathies, most commonly presenting as distal symmetric sensory neuropathy, painful small fiber neuropathy, or sensory ganglionopathy. Less commonly, it may mimic vasculitic neuropathies or even present with overlapping motor symptoms. In our patient, the presence of leukopenia, skin rash, and chronic inflammatory CSF findings raised concern

Table 1. Comparative Summary of Clinical Features, Diagnostics, Treatments, and Outcomes in Two Patients with N_2O-Induced Neuropathy.

Characteristic	Case 1	Case 2
Age and Sex	34-male	52-female
Clinical Presentation	Ascending numbness, tingling, gait imbalance, frequent falls	Bilateral simultaneous painless foot drop, gait imbalance, numbness, balance issues
Onset & Duration	January 2024, progressive over several months	November 2024, subacute progression
Neurological Examination	Mild distal lower limb weakness, absent vibration at knees, proprioception impaired at toes, absent knee and ankle reflexes, wide-based gait	Severe distal lower limb weakness, absent vibration/proprioception at toes, hyperreflexia proximally, absent ankle reflexes, bilateral steppage gait
Relevant Medical History	Chronic back pain, previous alcohol dependence, recreational N_2O use	Breast cancer (chemotherapy/radiation), hypothyroidism, Sjogren's syndrome, chronic N_2O abuse
Vitamin B12 & MMA Levels	Vitamin B12: 123 pg/mL; MMA: 1.66 µmol/L	Vitamin B12: 111 pg/mL; MMA: 0.45 µmol/L
EMG/NCS Findings	Sensorimotor axonal neuropathy	Length-dependent pure motor axonal neuropathy
MRI Findings	Mild degenerative lumbar spine changes, No posterior column signal changes	Cervical stenosis with hazy increased cord signal. No spinal cord signal changes on lumbar MRI. (Figure 1)
Initial Diagnosis	CIDP	CIDP, small vessel vasculitis
Treatment Received	Vitamin B12 supplementation, cessation of nitrous oxide, physical therapy	Steroids, IVIG (no response), vitamin B12 supplementation, planned orthotic support
Clinical Outcomes	Significant symptomatic improvement, improved balance, mild residual symptoms	Modest improvement in balance and ambulation, persistent severe foot drop, ongoing evaluation

for autoimmune or vasculitic neuropathy. However, the electrophysiological pattern of a pure motor axonopathy, muscle and nerve biopsy findings, combined with a known history of nitrous oxide abuse and vitamin B12 deficiency, favored a toxic-metabolic etiology. This underscores the importance of integrating autoimmune markers with clinical, electrodiagnostic, and histopathologic data to avoid misclassification and unnecessary immunotherapy.[8]

Emerging literature highlights the mechanism by which N_2O remains stored in the body, contributing to ongoing neurological damage despite cessation of exposure. N_2O can bind intracellularly in a stabilized form known as dinitrosyl iron (II) complexes with protein thiols.[9] These complexes serve as reservoirs, thus gradually releasing N_2O-derived reactive species over the period of time. Such slow release can perpetuate vitamin B12 deficiency and subsequent neurotoxicity, explaining persistent symptoms and potential relapse after premature discontinuation of vitamin B12 supplementation.[9]

Given this pathophysiology, prolonged and adequately dosed vitamin B12 supplementation is essential. In our series, both patients received 1000 mcg of intramuscular vitamin B12 weekly for four weeks as part of the induction phase, followed by monthly 1000 mcg injections for

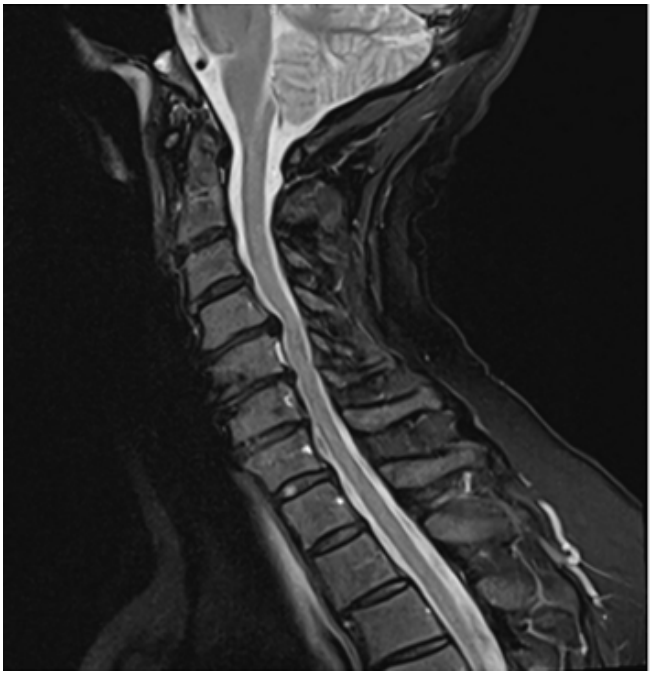

Fig 1: MRI C-spine sagittal view, STIR sequence. Showing cervical stenosis and hazy increased signal at the level of C4-5 C5-6 that might be due early myelomalacia.

maintenance, but in case 2 due to more advanced disease and delayed recognition, recovery was limited. Previous literature suggests that therapy should be continued for at least 6–12 months, and sometimes longer, based on clinical and biochemical response. Premature cessation may risk relapse due to continued oxidative inactivation of cobalamin by intracellularly stored N_2O complexes.[2,4] Our case series emphasizes this point, as seen in Case 1, where the patient who received consistent supplementation and ceased N_2O use early experienced marked clinical improvement. Conversely, the Case 2 patient, who had prolonged exposure and delayed diagnosis, showed minimal improvement which is likely due not only to the need for sustained long-term therapy but also to the greater severity of her initial neurological presentation including profound bilateral foot drop and pure motor axonopathy, compared to the milder, more sensory-predominant deficits observed in Case 1.

The diagnostic complexity in both cases highlights the potential overlap between nitrous oxide (N_2O) misuse and autoimmune conditions. N_2O-induced neuropathy, resulting from functional vitamin B12 inactivation, may mimic autoimmune neuropathies like Guillain-Barré syndrome, including features such as motor weakness and areflexia. Reports of positive anti-ganglioside antibodies in some cases suggest a possible immune-mediated component. In patients with underlying autoimmune disorders like Sjögren's syndrome, this overlap can complicate diagnosis.[8] Clinicians should consider N_2O-induced neuropathy in patients with acute or subacute neuropathic symptoms and relevant exposure history to avoid misdiagnosis and inappropriate treatment.[10] N_2O-induced neurotoxicity is classically associated with subacute combined degeneration of the spinal cord, primarily affecting the posterior columns, leading to sensory ataxia and proprioceptive loss. This myelopathic pattern is well documented and often visible as hyperintense signal changes in the dorsal cord on MRI.[3] However emerging evidence, including the present case series demonstrates that N_2O can also produce isolated peripheral neuropathies, particularly axonal or motor-predominant forms, even in the absence of spinal cord signal changes. This variability in localization complicates the clinical picture and may delay diagnosis if N_2O toxicity is not considered early. This case series also highlights the interplay between N_2O-induced neuropathy and coexisting autoimmune conditions, further complicating diagnosis and management. Notably, a significant proportion of patients with N_2O-induced neuropathy may have normal or borderline serum vitamin B12 levels despite functional deficiency. This occurs due to oxidation of cobalamin by N_2O, impairing its cofactor activity without reducing total serum levels. A systematic review by Oussalah et al. reported that approximately 30% of patients with N_2O-related toxicity had normal serum vitamin B_{12} concentrations, despite exhibiting clinical signs of deficiency.[11] In such cases, testing methylmalonic acid (MMA) and homocysteine provides more sensitive indicators of functional B12 status. Elevated levels of MMA or homocysteine should prompt consideration of N_2O-related neurotoxicity even when serum B12 appears normal, to avoid missed or delayed diagnosis.[3] Our clinical findings expand current understanding by illustrating real-world challenges clinicians face, particularly regarding the duration and monitoring of B12 therapy to mitigate relapse risk.

In conclusion, this case series demonstrates the importance of maintaining a high clinical suspicion for N_2O-induced neuropathy in patients presenting with idiopathic peripheral neuropathy, particularly those non-responsive to immunotherapy. Clinicians should recognize the potential for prolonged biological storage of N_2O in the form of stable dinitrosyl iron complexes, necessitating extended vitamin B12 supplementation for at least 6–12 months to prevent relapse. Additionally, comprehensive history taking regarding recreational substance use remains important for timely and accurate diagnosis.

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