

Rapid-Onset Subacute Combined Degeneration After Short-Term, High-Dose Nitrous Oxide Use

JACOB MICHALIK, DO; NEAL MADHANI, MD

ABSTRACT

Recreational nitrous oxide (N_2O) use has risen in recent years and is increasingly accessible in high-volume cartridges and canisters. N_2O oxidizes cobalamin and functionally inhibits methionine synthase disrupting methylation pathways essential for myelin maintenance and DNA metabolism. Serum vitamin B12 levels may be normal despite functional deficiency, making markers such as homocysteine and methylmalonic acid helpful to confirm the diagnosis. Clinical manifestations range from peripheral neuropathy and megaloblastic anemia to subacute combined degeneration (SCD), a demyelinating myelopathy classically involving the dorsal columns (and sometimes corticospinal tracts). Although SCD is often associated with chronic exposure, brief but high-dose use may precipitate rapid neurologic decline. Early recognition and prompt parenteral vitamin B12 replacement may reduce the risk of irreversible deficits.

KEYWORDS: Subacute Combined Degeneration; Nitrous Oxide; Functional b12 deficiency

CASE PRESENTATION

A 40-year-old man with polysubstance use (cocaine, nitrous oxide), suicidal ideation, and substance-induced psychosis presented with three days of progressive distal numbness and tingling in the hands and feet, generalized weakness, and gait instability after inhaling one full N_2O canister daily for three consecutive days. Symptoms began after the initial exposure and persisted, accompanied by nausea and bilious emesis. He denied chest pain, dyspnea, bowel or bladder dysfunction, and fever. He was afebrile and hemodynamically stable; cardiopulmonary and abdominal examinations were unremarkable. Neurologic examination demonstrated decreased distal sensation to bilateral hands and feet, diffuse weakness, and an ataxic gait without a focal motor deficit. Serum vitamin B12 was decreased at 156 pg/mL (normal range: ≥ 200 pg/mL) with elevated homocysteine at 204 $\mu\text{mol/L}$ (normal range ≤ 13 $\mu\text{mol/L}$) consistent with functional cobalamin depletion. The urine toxicology screen resulted with a presumptive positive for cocaine. Brain magnetic resonance imaging (MRI) was normal. Cervical spine

MRI demonstrated non-enhancing T2-weighted and short tau inversion recovery (STIR) hyperintensity within the dorsal columns from C1 to C5, consistent with SCD. Poison control recommended serial electrocardiograms and corrected QT interval (QTc) monitoring, as well as initiation of high-dose parenteral vitamin B12 therapy. He received intramuscular cyanocobalamin 1,000 mcg daily for 10 days, was counseled to stop N_2O , was evaluated by neurology, and by psychiatry. Psychiatry found no evidence of imminent risk of harm to himself or others and no concerning symptoms warranting psychiatric hospitalization. Neurology recommended maintaining a B12 level above 500 pg/mL and physical therapy (PT)/occupational therapy (OT) consultation. On evaluation by PT/OT, the patient displayed persistent gait instability warranting discharge to an inpatient rehabilitation facility. Improvement in persistent deficits appreciated at rehabilitation facility and patient was subsequently discharged home with outpatient neurology follow-up arranged in two to three weeks.

DISCUSSION

Nitrous oxide (N_2O) can rapidly inactivate cobalamin through oxidation of the cobalt ion resulting in irreversible inhibition of methionine synthase and disruption of methylation-dependent myelin maintenance [Figure 1].¹ This biochemical interference impairs DNA synthesis and leads to accumulation of homocysteine and methylmalonic acid, producing a functional vitamin B12 deficiency even when serum B12 concentrations appear normal.² The downstream consequence is defective myelin formation and progressive

Figure 1. Methionine–homocysteine cycle showing B12-dependent conversion inhibited by nitrous oxide and its role in methylation.

N_2O = Nitrous Oxide

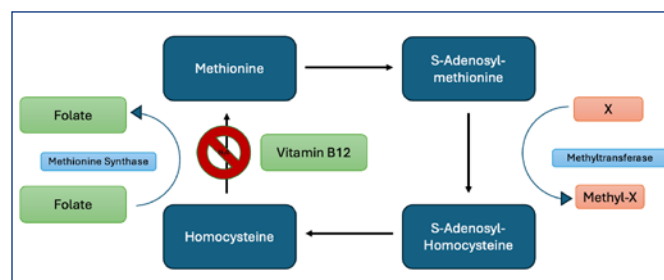
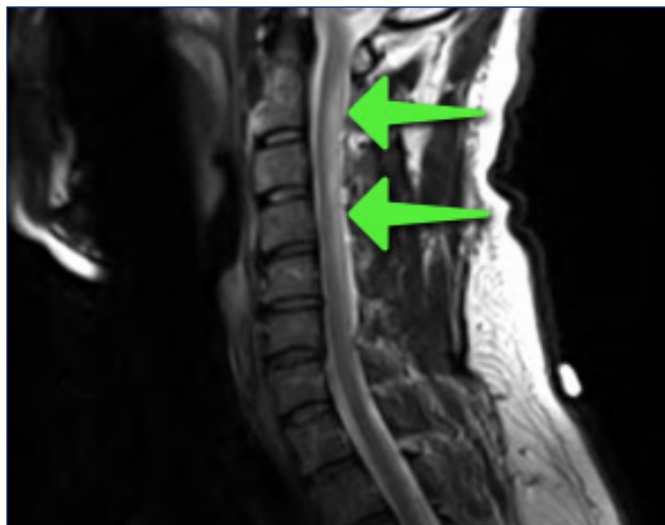


Figure 2. Non-enhancing hyperintense signal in the dorsal column of cervical spine from C1–2 & C5 consistent with subacute combined degeneration (SCD).



demyelination of the dorsal and lateral columns of the spinal cord.³ Radiographically, this manifests as the characteristic symmetric T2 hyperintensity within the posterior columns on MRI often described as an “inverted V” pattern.⁴ In this case, MRI of the cervical spine [Figure 2] demonstrated non-enhancing T2-weighted and short tau inversion recovery (STIR) hyperintensity within the dorsal columns from C1 to C5 consistent with subacute combined degeneration. This mechanism has increasingly been implicated in SCD associated with recreational N₂O use, particularly among younger individuals without traditional nutritional or malabsorptive risk factors.⁵

The differential diagnosis for acute or subacute distal paresthesias and gait ataxia is broad, and includes acute inflammatory demyelinating polyneuropathy, transverse myelitis, multiple sclerosis, copper deficiency myelopathy, and compressive or structural spinal cord lesions. Distinguishing N₂O-induced SCD from these entities requires careful integration of clinical history, imaging, and laboratory findings.⁶ A history of recent or chronic N₂O exposure is a critical diagnostic clue and may not be volunteered unless specifically elicited. Nitrous oxide-associated SCD is typically associated with prolonged or chronic exposure over weeks to months. While this patient described use over a three-day period, the extent of prior nitrous oxide use remains unclear. Acute nitrous oxide use may have precipitated symptoms in the setting of underlying chronic exposure. From a diagnostic standpoint, the combination of dorsal column predominant signal abnormalities on MRI and biochemical evidence of cobalamin dysfunction (particularly elevated homocysteine and methylmalonic acid levels) strongly supports the diagnosis. Notably, reliance on serum B12 alone may be misleading, as levels can be normal or only mildly reduced despite

significant functional deficiency. In this case, the presence of classic dorsal column imaging findings [Figure 2] together with laboratory evidence of impaired cobalamin metabolism supported SCD related to N₂O exposure rather than an inflammatory, autoimmune, or compressive etiology.

Clinically, dorsal column involvement manifests as distal paresthesias, impaired vibration, impaired proprioception, and sensory ataxia frequently resulting in gait instability and increased fall risk.⁷ As disease progression extends to the lateral corticospinal tracts, patients may develop weakness, spasticity, hyperreflexia, bladder incontinence, and fecal incontinence, reflecting upper motor neuron involvement. In some cases, peripheral neuropathy coexists, further contributing to sensory deficits and functional impairment.⁸ Neuropsychiatric symptoms, including mood changes and cognitive impairment, have also been reported, reflecting the broader systemic impact of cobalamin dysfunction. Importantly, the severity of neurologic impairment does not always correlate with the duration of exposure. Even relatively short intervals of high-intensity N₂O use can precipitate clinically significant neurologic injury.⁹ This underscores the potential for acute toxicity, in addition to the more traditionally recognized chronic exposure paradigm.

The rising prevalence of recreational N₂O use often through easily accessible “whippits” or commercial cartridges has led to an increasing number of reported neurologic complications. This trend highlights the importance of maintaining a high index of suspicion in patients presenting with otherwise unexplained neurologic symptoms. Clinicians should specifically inquire about inhalant use when evaluating patients with paresthesias, ataxia, or macrocytosis, as early identification of exposure can expedite diagnosis and management. Additionally, clinicians should maintain suspicion for nitrous oxide misuse in patients presenting with hypoxia, altered mental status, or respiratory failure, as inhalation can cause asphyxiation from oxygen displacement. Recommended laboratory evaluation includes serum vitamin B12, homocysteine, and methylmalonic acid levels which together provide a more accurate assessment of functional cobalamin status. Neuroimaging (particularly MRI of the cervical and thoracic spine) is valuable for confirming dorsal column involvement and excluding alternative diagnoses.

Prompt recognition and treatment are critical, as early intervention may halt disease progression and improve neurologic outcomes. Management consists of immediate cessation of N₂O exposure and initiation of parenteral vitamin B12 supplementation (typically with high-dose intramuscular cyanocobalamin). While some patients experience partial or even substantial recovery, neurologic deficits may persist, particularly in cases of delayed treatment or severe initial presentation. Rehabilitation services, including physical and occupational therapy, may be necessary to address residual functional impairments.

This case highlights the importance of recognizing N₂O-induced functional vitamin B12 deficiency as a reversible but potentially debilitating cause of subacute combined degeneration. It reinforces the need for targeted history-taking, appropriate biochemical evaluation, and early treatment to mitigate long-term neurologic sequelae. As recreational N₂O use continues to increase, awareness of its neurologic risks will be essential for timely diagnosis and optimal patient outcomes.¹⁰

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Authors

Jacob Michalik, DO, Kent Hospital, Warwick, Rhode Island.
Neal Madhani, MD, Kent Hospital, Warwick, Rhode Island.

Disclosures

None

Correspondence

Jacob Michalik, DO
Emergency Medicine Program
Kent Hospital
455 Gate Rd., Warwick, RI 02886
jmichalik@carene.org