

An Acute, Severe Axonal Sensorimotor Polyneuropathy in the Setting of Nitrous Oxide Abuse

The Neurohospitalist
2020, Vol. 10(4) 293-296
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1941874420910648
journals.sagepub.com/home/NHO



Jules C. Beal, MD^{1,2} , Yishan Cheng, MD¹, Sabiha Merchant, MD^{1,2}, and Reza Zarnegar, DO³

Abstract

Nitrous oxide, often used as an anesthetic agent, is also increasingly a drug of abuse due to its euphoric and anxiolytic effects. Frequent exposure to nitrous oxide can lead to neurologic complications, including B12 deficiency and resultant subacute myeloneuropathy, as well as direct neurotoxicity. A clinical presentation of acute sensorimotor polyneuropathy mimicking Guillain-Barré syndrome after chronic nitrous oxide abuse has been reported only rarely. Here we present a 17-year-old previously healthy girl presented with 10 days of progressive ascending sensory loss and weakness in the legs. She admitted to heavy nitrous oxide abuse over a period of a year or more. Laboratory evaluation was significant for normal vitamin B12 level with elevated homocysteine. A magnetic resonance imaging (MRI) of her spine showed abnormal signal involving the bilateral dorsal columns. Nerve conduction studies were suggestive of severe axonal sensorimotor polyneuropathy. This patient demonstrates concurrent multifactorial neurologic injury as a result of nitrous oxide abuse. She had a functional vitamin B12 deficiency as indicated by the elevated homocysteine, leading to a subacute combined degeneration that was evident on the MRI. In addition, she had evidence of direct neurotoxicity leading to axonal injury and sensorimotor polyneuropathy reminiscent of Guillain-Barré syndrome. This clinical picture is a serious but seldom reported possible complication if nitrous oxide abuse and should be considered in patients presenting with a clinical picture suspicious for Guillain-Barré syndrome or its variants.

Keywords

neurotoxicity syndromes, nitrous oxide, Guillain-Barré syndrome, autoimmune diseases of, the nervous system, polyneuropathies, neuromuscular diseases

Introduction

Nitrous oxide (N₂O), also called “laughing gas,” is often used medically as an anesthetic agent but can be used recreationally for its euphoric and anxiolytic effects. It can produce hallucinations, dissociation, dizziness, and loss of balance. The onset is rapid, within seconds, and the effects wear off within minutes. Recreational inhalation of N₂O, sometimes referred to as “whippets,” is reported to be increasing.^{1,2} In the United States, the lifetime prevalence of recreational N₂O abuse may be as high as 29%.² Chronic N₂O exposure is known to cause neurotoxicity. Most commonly seen is a predominant sensory subacute myeloneuropathy involving the dorsal columns of the spinal cord,¹ though peripheral neuropathies and neuropsychiatric symptoms have also been reported.^{3,4} “Pseudo” Guillain-Barré syndrome in the context of N₂O abuse has rarely been reported.⁵ Here, we report an adolescent girl with chronic heavy N₂O abuse who presented with progressive ascending weakness of the lower limbs, areflexia, and sensory loss, resembling Guillain-Barré syndrome.

Case Report

A 17-year-old girl with no prior medical problems presented to the emergency department with 10 days of progressive leg weakness and numbness. She reported gradual onset of progressive sensory loss involving both legs ascending to the level of the abdomen, with accompanying tingling sensation on the plantar surface of both feet. Five days prior to presentation, she noticed weakness in both legs which progressed to

¹ Division of Pediatric Neurology, Weill Cornell Medicine, New York, NY, USA

² Department of Pediatrics, New York-Presbyterian Queens Hospital, Flushing, New York, NY, USA

³ Department of Neurology, Weill Cornell Medicine and New York-Presbyterian Queens Hospital, Flushing, New York, NY, USA

Corresponding Author:

Jules C. Beal, Division of Pediatric Neurology, 56-45 Main Street, Flushing, NY 11355, USA.

Email: jcb9023@med.cornell.edu

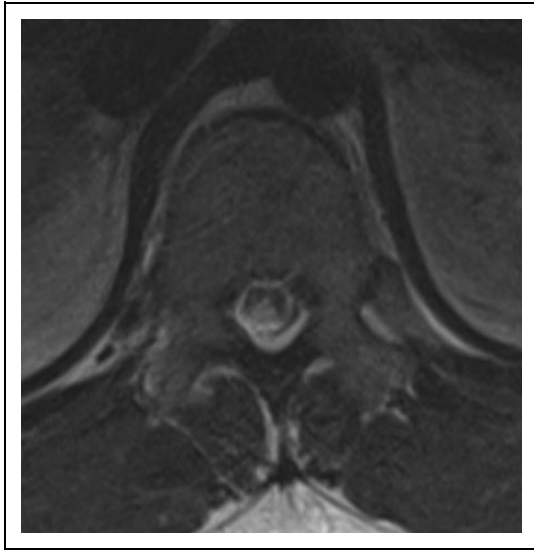


Figure 1. Spine magnetic resonance imaging.

the point that she was unable to walk and had to crawl to the bathroom at home. There was no involvement of the upper extremities. There was no urinary or bowel incontinence, no respiratory symptoms, and no dysphagia or drooling. Examination was significant for weakness in both legs which was more severe in the left, impaired sensation to light touch throughout the legs to the level of the umbilicus, impaired vibratory sensation to the level of the mid-thighs, and impaired proprioception in the feet. Reflexes were absent at the ankles and patellae bilaterally. Strength, sensation, and reflexes in the arms were normal. Mental status and cranial nerves were normal. On further history, the patient admitted to chronic heavy abuse of N₂O “whippets” over a period of a year or more, using between 100 and 200 or at times even more than a thousand N₂O cartridges per day.

Laboratory evaluation revealed a normal serum vitamin B12 level of 408 pg/mL (normal range 211-945 pg/mL) and an elevated homocysteine level of 81.2 μmol/L (normal range 2.5-15 μmol/L). Other laboratory evaluations, including complete blood count, electrolytes, liver function tests, hemoglobin A1C, antinuclear antibodies, syphilis screening, and HIV screening were unremarkable. Lumbar puncture was deferred. An magnetic resonance imaging of the thoracic and lumbar spine with and without contrast revealed diffuse abnormal signal involving the bilateral dorsal columns on T2 and short-TI inversion recovery (STIR) images (Figure 1).

Nerve conduction studies showed absent tibial motor responses bilaterally, absent right peroneal motor response, and severely reduced left peroneal motor response. The sural sensory responses were absent bilaterally. In the upper extremities, the median and ulnar sensory responses were severely reduced in amplitude but with normal motor responses. Needle electromyography (EMG) did not show clear abnormalities. The overall picture was consistent with a severe axonal

sensorimotor polyneuropathy in the lower extremities as well as a sensory neuropathy in the upper extremities (Table 1).

The patient was treated with vitamin B12 repletion and physical therapy. A psychiatry evaluation leads to a diagnosis of previously unrecognized major depressive disorder, for which she was self-medicating by abusing whippets. She gradually regained strength and sensation in her legs over a period of weeks and was discharged to a subacute rehabilitation facility with mental health services.

Discussion

Chronic N₂O exposure leads to inactivation of vitamin B12 and a functional B12 deficiency. This can result in subacute combined degeneration (SCD), a myeloneuropathy involving the dorsal columns of the spine leading to subacute onset of predominantly sensory symptoms including impaired vibratory sensation, impaired proprioception, and paresthesias. Subacute combined degeneration is the most common neurologic manifestation of N₂O toxicity.⁶ Vitamin B12 deficiency can also lead to megaloblastic anemia, which may be quite marked, although this was not seen in our patient. It is important to note that a functional B12 deficiency can be present even with a normal serum B12 level, and therefore, other biomarkers must also be checked when B12 deficiency is suspected. It is not uncommon for individuals with chronic N₂O exposure to have normal B12 levels but elevated homocysteine and/or methylmalonic acid, as seen in our patient.⁷

There is also evidence that N₂O can have direct neuronal toxicity independent of B12 involvement.⁶ Paresthesias, disorders of equilibrium, gait abnormalities, weakness, and ataxia have all been described in 10% or more of individuals with N₂O exposure in a recent meta-analysis.⁷ Progressive ascending sensorimotor neuropathy reminiscent of Guillain-Barré syndrome as a consequence of N₂O exposure, as seen in our patient, has been reported only rarely.^{3,5,8}

Our patient presented with simultaneous, multifactorial neurologic dysfunction. She had myelopathy in the setting of functional B12 deficiency as evidenced by her spinal imaging findings, pattern of sensory loss, and elevated homocysteine. Additionally, she had direct neuronal injury leading to progressive weakness and loss of deep tendon reflexes, mimicking Guillain-Barré syndrome, which was apparent on electrodiagnostic studies. In order to understand the presentation and examination findings in this patient, it was important to recognize both pathophysiologic processes as neurotoxic consequences of N₂O use. Their concurrent presentation in this patient is unusual.

The exact risk factors for developing this kind of severe neurotoxicity after N₂O exposure are not clear. Certainly patients with B12 deficiency at baseline are at increased risk of developing SCD.⁶ There also may be certain congenital disorders that predispose to N₂O toxicity; adverse outcomes were reported in a child with methylenetetrahydrofolate reductase (MTHFR) deficiency who was exposed to N₂O for

Table 1. Nerve Conduction Studies.

Motor Nerves						
Nerve/Sites		Latency (ms)	Amplitude (mV)	Segments	Distance (mm)	Velocity (m/s)
Left Median—APB						
Wrist		3.8	8.3	Wrist—APB	80	
Elbow		8.1	7.9	Elbow—Wrist	220	50.9
Left Ulnar—ADM						
Wrist		3.2	8.9	Wrist—ADM	80	
B.Elbow		7.5	8.4	B.Elbow—Wrist	220	50.9
A.Elbow		9.6	8.3	A.Elbow—B.Elbow	110	51.5
Left peroneal—EDB						
Ankle		6.0	0.3	Ankle—EDB		
Right peroneal—EDB						
Ankle		NR	NR	Ankle—EDB		
Left tibial—AH						
Ankle		NR	NR	Ankle—AH		
Right tibial—AH						
Ankle		NR	NR	Ankle—AH		
Sensory Nerves						
Nerve/Sites	Rec. Site	Latency (ms)	Amplitude (μ V)	Segments	Distance (mm)	Velocity (m/s)
Left sural—ankle						
Calf	Ankle	NR	NR	Calf—Ankle	140	NR
Right sural—ankle						
Calf	Ankle	NR	NR	Calf—Ankle	140	NR
Left median—wrist—digit II						
Wrist	Dig II	2.97	3.5	Dig II—Wrist	130	44
Left ulnar—wrist—digit V						
Wrist	Dig V	2.55	3.5	Dig V—Wrist	110	43

Abbreviations: AH, abductor hallucis; ADM, abductor digiti minimi; APB, abductor pollicis brevis; EDB, extensor digitorum brevis; NR, no response.

surgical anesthesia, for example.^{6,9} It is possible that cumulative exposure or high doses of N₂O may have played a role in this patient's more extensive neurotoxicity. A recent meta-analysis examining 76 individuals with regular N₂O exposure found a median use of 25 cartridges per day, with an interquartile range of 8 to 85 cartridges per day, and a high incidence of neurologic complications (80% or more) in this population.⁷ By comparison, our patient reported significantly higher use of one to two hundred, and at times up to a thousand or more, cartridges per day.

Conclusion

Vitamin B12 deficiency and resultant myeloneuropathy are well described consequences of chronic N₂O exposure. Other neurotoxicity has also been described, independent of B12 status, causing paresthesias, disorders of equilibrium, gait abnormalities, weakness, and ataxia, among other symptoms. Acute sensorimotor polyneuropathy mimicking Guillain-Barré syndrome is a serious but less commonly described clinical presentation of N₂O abuse that is important to recognize. This presentation can occur either independently or

concurrently with the more typical myelopathy. Possible N₂O exposure should be considered in the differential diagnosis for patients presenting with a clinical picture suspicious for Guillain-Barré syndrome. Additionally, further investigation into possible dose-dependent effects of N₂O exposure may be warranted.


Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Jules C. Beal, MD  <https://orcid.org/0000-0003-4748-9248>

References

1. Amsterdam JV, Nabben T, den Brink WD. Recreational nitrous oxide use: prevalence and risks. *Regul Toxicol Pharmacol*. 2015; 73(3):790-796.

2. Kaar SJ, Ferris J, Waldron J, Devaney M, Ramsey J, Winstock A. Up: the rise of nitrous oxide abuse. An international survey of contemporary nitrous oxide use. *J Psychopharmacol*. 2016;30(4):395-401.
3. Hirvioja J, Joutsa J, Wahlsten P, Korpela J. Recurrent paraparesis and death of a patient with 'whippet' abuse. *Oxf Med Case Reports*. 2016;2016(3):41-43.
4. Sethi NK, Mullin P, Torgovnick J, Capasso G. Nitrous oxide 'whippet' abuse presenting with cobalamin responsive psychosis. *J Med Toxicol*. 2006;2(2):71-74.
5. Tatum WO, Bui DD, Grant EG, Murtagh R. Pseudo-Guillain-Barre syndrome due to 'whippet'-induced myeloneuropathy. *J Neuroimaging*. 2010;20(4):400-401.
6. Sanders C, Weimann J, Maze M. Biologic effects of nitrous oxide: a mechanistic and toxicologic review. *Anesthesiology*. 2009;109(4):707-722.
7. Oussalah A, Julien M, Levy J, et al. Global burden related to nitrous oxide exposure in medical and recreational settings: a systematic review and individual patient data meta-analysis. *J Clin Med*. 2019;8(4):pii:E551. doi:10.3390/jcm8040551.
8. 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;51(4):614-616.
9. Selzer RR, Rosenblatt DS, Laxova R, Hogan K. Adverse effect of nitrous oxide in a child with 5,10-methylenetetrahydrofolate reductase deficiency. *N Engl J Med*. 2003;349(1):45-50.