

Missing a case of nitrous oxide toxicity

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Abstract: Nitrous oxide is a highly lipid-soluble molecule, which can produce euphoria and calming effects through noncompetitive antagonism of the N-methyl-D-aspartate (NMDA) glutamate receptor and agonism of the γ -aminobutyric acid (GABA) A receptor. It can also produce toxicities likely through inactivation of methylcobalamin (vitamin B12) with subsequent neurological, psychiatric, and other sequelae that may be mistaken for other clinical entities. We present a classic presentation of nitrous oxide toxicity, which was missed and urgently referred to infectious diseases with concerns for an infectious neuromyelitis. Knowing the constellation of symptoms and findings and maintaining a high index of suspicion are key to diagnosing nitrous oxide toxicity, which can otherwise easily be missed. Cessation of use, B12 supplementation, and supportive measures such as occupational and physical therapy are helpful for maximizing long-term beneficial outcomes.

Keywords: nitrous oxide toxicity, substance toxicity, substance use

Received: 10 February 2022; revised manuscript accepted: 13 May 2022.

Introduction

Nitrous oxide has long been used for its euphoric effect, with so-called ‘laughing gas parties’ going back to 1799.¹ This highly lipid-soluble molecule rapidly crosses the blood–brain barrier to produce a rush of euphoria followed by lethargy, acting at least partially through noncompetitive antagonism of the N-methyl-D-aspartate (NMDA) glutamate receptor.² There may also be some indirect agonist effects on the γ -aminobutyric acid (GABA) A receptor.² In some cases, hypoxia may also play a role in intoxication. Unlike many other intoxicating substances, the use of inhalants, including nitrous oxide, tends to peak in early adolescence and decline thereafter and has a slight female predominance in use.³ The toxicities associated with nitrous oxide use are generally categorized into three types: psychiatric, neurologic, and other medical manifestations.⁴ The exact mechanisms of these toxicities are not fully understood but involve nitrous oxide oxidizing the cobalt ion in methylcobalamin, leading to the loss of function of this vitamin coenzyme. This may lead to impaired synthesis of neuronal myelin and DNA, directly leading to neurotoxicity and indirect damage to

a variety of cells by increasing homocysteine levels.⁴ We present a case of nitrous oxide toxicity missed, with the patient coming into care for concern for an infectious process.

Case presentation

The patient was a 23-year-old woman who presented *via* urgent referral to an outpatient infectious diseases clinic for follow-up after a recent hospitalization for multiple neurological symptoms. Her cerebral spinal fluid (CSF) herpes simplex virus-1 (HSV-1) polymerase chain reaction (PCR) testing returned positive after discharge. She did not have any known history of oral or genital herpes. Her other medical history was notable for generalized anxiety disorder, intermittent migraine headaches, and polysubstance use without a formally diagnosed specific substance use disorder. She reported a family history of a maternal aunt with unhealthy alcohol use but did not know any more specifics of this. She endorsed the personal sporadic use of multiple substances at different points in life, without regular use of any of these aside from marijuana. Despite not using any substance regularly, she had experiences significant consequences from

Ther Adv Infect Dis

2022, Vol. 9: 1–6

DOI: 10.1177/
20499361221104377

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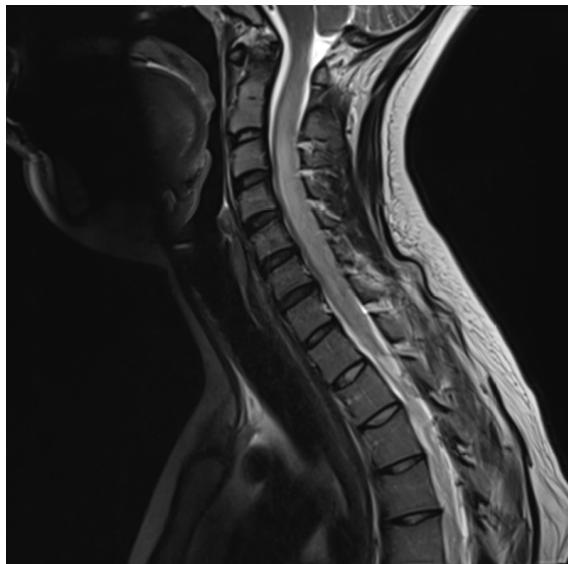


Image 1. Early sagittal T2-weighted MRI.

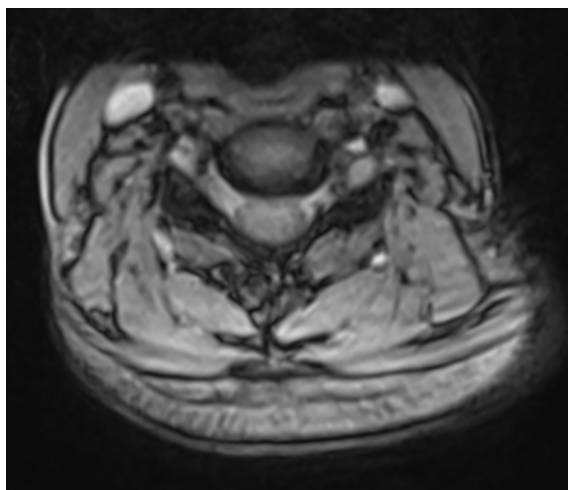


Image 2. Early axial T2-weighted MRI.

the use of multiple substances. She reported involvement with a sobriety court for the last 2 years secondary to an operating while intoxicated (OWI) charge related to alcohol use. Review of the available medical record also revealed two hospitalizations in the last 4 months for accidental overdoses requiring intubation. Toxicology from the first hospital stay showed the presence of fentanyl, cocaine, and alcohol, with the second hospitalization being related to the use of gamma-hydroxybutyrate (GHB) and benzodiazepines.

Around 1 month prior to the second overdose-related hospitalization, she began experiencing weakness and tingling in her feet in addition to difficulties with balance. After the overdose, the tingling started in her hands. She also began having discoordination of her hands and legs, resulting in dropping things, off-balanced gait, and tripping frequently. An outpatient magnetic resonance imaging (MRI) of the cervical spine done around 2 months into this process showed diffuse edema of the cervical spinal cord, extending into the visualized thoracic spine as well. This was focused around the central and dorsal spinal cord with relative sparing of the ventral and lateral white matter tracts. Sagittal and axial views of this can be seen in Images 1 and 2, respectively. Her symptoms continued to worsen, and she also began having loss of sensation in her hands and feet. Repeat imaging by MRI, including her brain and entire spinal column, was done around 4 weeks later. This revealed extensive abnormalities focused on the dorsal columns involving most of the cervical and thoracic spinal cord, as seen in Images 3 (sagittal) and 4 (axial). No abnormalities were noted in the brain. Secondary to her MRI findings and progressive ataxia, with resultant difficulty walking, she was hospitalized for further evaluation.

The neurology service saw her while she was in the hospital. Her exam revealed symmetric reduction in vibratory sensation in the distal upper and lower extremities. Sensation to pain and touch was also reduced in a similar distribution. She demonstrated ataxia on finger-to-nose testing without dysmetria. She had a mildly wide-based gait. Her Romberg test was positive. Complete blood count demonstrated anemia to 10.2 g/dL with a mean cell volume of 105.9 fL. HIV and Lyme disease serologies were negative. Vitamin B12 levels were low-normal at 308 pg/mL. Folate, vitamin B1, vitamin E, and copper levels were also checked and were within normal limits. A lumbar puncture was performed. The initial CSF tube showed around 1900 red blood cells/uL, which dropped to 6 by the fourth tube. There were 2 white blood cells/uL, with a normal differential. Her CSF glucose was normal, and the protein level was 61 mg/dL, just above the laboratory reference normal range. No definitive diagnosis was made, and she was discharged to follow-up with outpatient neurology, physical therapy, and occupational therapy. After discharge, CSF testing for angiotensin-converting

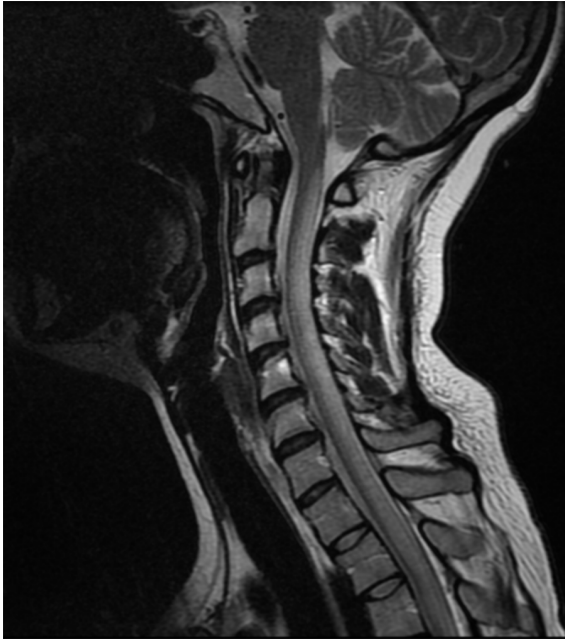


Image 3. Late sagittal T2-weighted MRI.

enzyme, enterovirus, and varicella-zoster virus returned normal. However, HSV-1 was detected by qualitative PCR. Her primary care put her urgently on valacyclovir and referred her to the infectious diseases clinic.

On evaluation, she denied any new symptoms, including neck stiffness or headache. She reported no fevers, chills, or sweats. No skin changes or sores on her mucosal membranes were noted. She did discuss that around 2 weeks prior to the onset of her initial symptoms, and she had begun to use nitrous oxide, in the form of inhaled "Whip-Its," heavily and daily. She specifically noted that the tingling sensations in her hands and feet would acutely worsen while intoxicated. Assuming her symptoms were secondary to her use of nitrous oxide, she stopped using this around 1 week prior to hospitalization.

On review of her MRI findings, it lacked any abnormalities of the brain or meninges. Her lumbar puncture results, though initially showing a significant number of red blood cells potentially consistent with a herpes simplex infection of the central nervous system, subsequently showed only a minimal elevation of red blood cells without any abnormality in number or type of white blood cells. She also lacked likely symptoms consistent with herpes simplex infection. As such, her

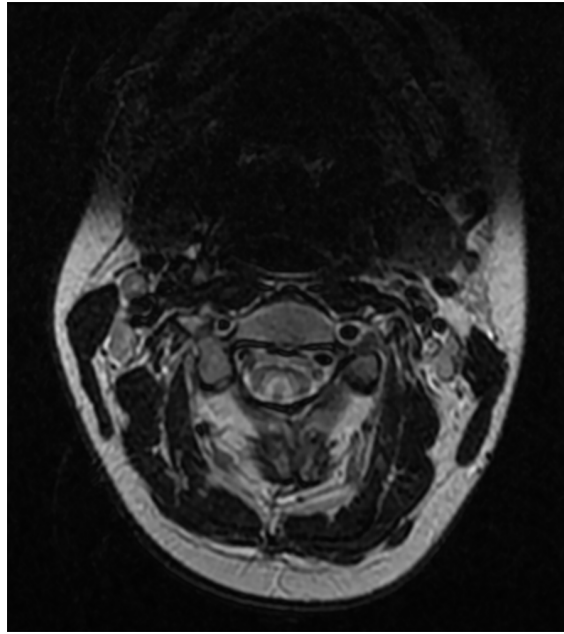


Image 4. Late axial T2-weighted MRI.

HSV-1-positive testing was presumed to be unrelated to her symptoms and likely a false positive. Her valacyclovir was stopped. Testing was sent for a repeat HIV and syphilis and both were negative. She was started on vitamin B12 supplementation. A 2-month follow-up showed an improvement in all of her symptoms, though some tingling in her hands and feet persisted. Her MRI findings showed significant improvement, and her prior macrocytic anemia had resolved. Multiple subsequent toxicology reports showed the presence of non-prescribed benzodiazepines.

Discussion

This case demonstrates multiple interesting points. Toxicity from nitrous oxide use can have varied presentations, potentially being mistaken for multiple other entities, infectious or otherwise. Neurological sequelae are the most commonly reported toxicity from nitrous oxide use.⁴ Symptoms often include 'numbness' or 'weakness'. Gait disturbances, loss of coordination, changes in mentation, and loss of bowel and bladder control may also be seen.⁴ The use may result in myelopathy, peripheral and polyneuropathies, myeloneuropathy, or, as in this case, subacute combined degeneration of the spinal cord⁴ similar to that seen with vitamin B12 deficiency, which is most commonly from pernicious anemia or dietary deficiency. Notably, vitamin B12 levels may be low, but, as in this case, this is not always true.

Mechanistically, recurrent nitrous oxide use may result in a functional B12 deficiency secondary to oxidation of the cobalt ion within the molecule.² This renders the vitamin unable to function as the coenzyme to methionine synthase, with resultant impairment in the methionine production necessary for the synthesis of DNA, RNA, myelin, and catecholamines.² Deficiencies in vitamin E and copper can present similarly.^{5,6} Given the often affected areas, such as the dorsal columns in this patient, this may also mimic infections such as syphilis, appearing similar to tabes dorsalis. Notably, though concern for HSV encephalitis or meningitis was what led to this patient being seen in an infectious diseases clinic, the neurological symptoms associated with these infections do not typically significantly overlap with symptoms of nitrous oxide toxicity. Herpes infections of the central nervous system are more often acute in onset and associated with infectious symptoms, such as fever. Headache with or without associated neck pain would be common with HSV infections but not nitrous oxide toxicity. Certainly focal neurological deficits may occur in either entity and potentially overlap, and with a positive HSV PCR test, this diagnosis would need to be considered.

Psychiatric manifestations of nitrous toxicity include acute hallucinations and delirium.⁴ Delusions, often of a paranoid nature, panic, acute mania, and grandiosity have been described.⁴ The development of chronic neurocognitive dysfunction and depression has also been documented. Loss of functional vitamin B12, particularly if chronic, may account for some of these findings. Notably, hypomania, though not seen in this case, has been described with HSV-1 encephalitis as well, again adding some potential overlap of symptoms with nitrous oxide toxicity.⁷

Other medical complications include pneumothorax and emphysema, likely as a consequence of repeated inhalation and the method of inhalation, frostbite from inhalation of nitrous oxide in its pressurized liquid form,⁸ and macrocytic anemia, as seen in this case, from a functional B12 deficiency. There has also been documented decreased immune function, with worsened neutrophilic chemotaxis and decreased monocyte count.² Concerns have been raised about potential cardiac toxicity resulting from

chronically elevated homocysteine levels.² Homocysteine is the precursor to methionine, which builds up the absence of functioning methionine synthase. Deaths associated with nitrous oxide use are most frequently a result of hypoxia, when the source of nitrous oxide is not detached when the person loses consciousness, or by cardiac arrhythmia.

In general, the use of inhalants, including nitrous oxide, becomes increasingly rare with older age in the United States, with peak use being among adolescents.³ There are notable exceptions to this. Inhalant use among military recruits is frequent. It is the third most common class of intoxicant used in this group, after alcohol and marijuana.⁹ Proposed reasons for this include the low cost, high availability, and lack of detection of these substances on standard drug tests.⁶ Notably, this patient was involved in drug court, where detection avoidance may have been important. Nitrous oxide has also become increasingly popular as a club drug, particularly in Northwestern Europe.¹⁰

Nitrous oxide likely produces its effects primarily through antagonism of the NMDA glutamate receptor with some potential agonism of the GABA_A receptor.² Opposing the effects of the excitatory neuropeptide glutamate and increasing the calming effects of the GABA_A receptor produces a sedating and anxiolytic effect. Alcohol similarly exerts much of its effect through agonism of the GABA_A receptor with some antagonism of the NMDA receptor.¹¹ GHB, largely exerting its effects through its own GHB receptor, also acts on the GABA_B receptor.¹² Benzodiazepines also exert effects on the GABA_A receptor.¹³ Notably, this patient reported a familial history of problematic alcohol use, potentially suggesting a genetic component to her use of substances. Prior studies have found that some single nucleotide polymorphisms in the gene responsible for encoding the GABA_A $\alpha 2$ subunit may provide an inherited predisposition for the subjective experience of drinking alcohol to be more pleasant and be associated with a higher risk of developing problematic use of alcohol.^{14,15} The mechanistic role of this receptor in the effects of other substances may suggest a genetic role in the experiences of those as well. Given the role of the NMDA receptor in producing nitrous oxide intoxication, acamprosate, which modulates

activity at the NMDA receptor, also seems worth exploring further as a potential therapeutic option for treating chronic nitrous oxide use.

Conclusion

Overall, toxicity from nitrous oxide use can have variable presentation that may be mistaken for other clinical entities. Given the difficulty of detecting inhalant use in general medical practice, having a high index of suspicion when someone presents with signs consistent with acute or chronic inhalant use is essential to identifying and properly managing these conditions. This person underwent significant testing and delayed diagnosis based on a lack of early identification of substance use despite a history of irregularly regular polysubstance use. Screening broadly for substance use with validated verbal screening tools may assist in identifying use, particularly when short-acting substances may be difficult to detect in toxicological studies. Clinicians should be aware of the constellations of signs and symptoms that could indicate nitrous oxide use, including neurological, psychiatric, and laboratory manifestations. Cessation of use can assist in early recovery. Vitamin B12 supplementation and supportive measures like physical and occupational therapy may improve long-term outcomes.

Ethics approval and consent to participate

This case report did not require ethical board approval.

Consent for publication

The patient provided verbal consent for her case to be presented for this publication.

Author contributions

Paul Trowbridge: Writing – original draft; Writing – review & editing.

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Acknowledgements

None

Funding

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

Conflict of interest statement

The authors declare that there is no conflict of interest.

Availability of data and materials

There are no additional data for this article.

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