Clinical Reasoning:

A 27-year-old man with unsteady gait

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SECTION 1

A 27-year-old man presented to our hospital's emergency department (ED) with an abnormal gait, paresthesias of the lower extremities, and lower back pain that had progressed over 2 weeks. He reported no medical history and a family history notable only for poor folic acid absorption in his father (etiology unknown).

The patient's symptoms began with lower back pain followed by numbness of his lower extremities involving both feet and his right leg almost to the knee. Next, he developed difficulty with ambulation and minimal tingling of his fingertips bilaterally. His difficulty walking worsened, and he fell, sustaining an abrasion to his right forearm that prompted him to go to an outside ED. Prior to that fall there had been no trauma. MRI of the lumbar spine was performed; he was diagnosed with lumbar polyradiculopathy and referred for orthopedic evaluation. From available records of the outside ED, the suspected etiology of the lumbar polyradiculopathy is unclear. He was prescribed cyclobenzaprine 10 mg twice daily and a rapid methylprednisolone taper but reported no improvement with these medications. Five days later, he sought neurologic evaluation, and was referred directly to our ED for a more complete evaluation.

Upon arrival, his temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation were all normal. His fingerstick glucose was 92 mg/dL. On physical examination, he appeared well, in no apparent distress. He was awake and alert, with normal cognition. Cranial nerves II–XII were intact. His muscle bulk and tone were normal, and his strength was full with the exception of bilateral hip flexion (4+/5) and bilateral great toe extension (4/5). Sensation was intact to light touch and pinprick, but severely decreased to vibration and joint position sense at the toes (see video 1 at Neurology.org), ankles, knees, and hips. The Romberg test was positive. No clear sensory level could be identified. All sensation was intact in the hands bilaterally. His deep tendon reflexes were exaggerated throughout his upper and lower extremities, and Babinski sign was present bilaterally. He had a hesitant, wide-based, ataxic gait (see video 2).

Questions for consideration:

1. Where would you localize his lesion?
2. What is the differential diagnosis for his presentation?

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Supplemental data
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SECTION 2

The patient's symptoms and examination are most consistent with injury to the spinal cord, with preferential involvement of the dorsal columns. The absence of sensory abnormalities in the upper extremities suggests a lesion at the T2 level or below, although hyperreflexia in the upper extremities points more rostral. His lower extremity weakness also suggests involvement of the corticospinal tracts.

The differential diagnosis for the patient's clinical findings includes cyanocobalamin (B₁₂) deficiency, copper deficiency, nitrous oxide (N₂O) toxicity, HIV vacuolar myelopathy, and neurosyphilis as the most common processes preferentially affecting the dorsal columns. Less likely considerations include other nutritional deficiencies such as folic acid or tocopherols (vitamin E); infectious processes such as herpes virus myelitis or a spinal epidural abscess; demyelinating disease such as multiple sclerosis, neuromyelitis optica, or transverse myelitis; inflammatory conditions such as neurosarcoidosis; neoplastic disease (for example, spinal cord astrocytoma and ependymoma); and neurovascular causes such as compression from an arteriovenous malformation, or slow venous hemorrhage.

The patient's laboratory analysis was notable for a cyanocobalamin concentration of 122 pg/mL (normal, 214–1,070 pg/mL) with hemoglobin of 13.5 g/dL, hematocrit of 41.7%, and mean corpuscular volume of 97.8 fL. Folate concentration was >20 ng/mL (normal, >5.2 ng/mL). His erythrocyte sedimentation rate was 35 mm/h and C-reactive protein 6 mg/L (normal, 0–10 mm/h and 0–9 mg/L, respectively). His rapid plasma reagin test was negative. His homocysteine concentration was elevated at 99.4 μmol/L (normal, 5.5–16.2 μmol/L); methylmalonic acid level was not tested. Given his low B₁₂ concentration, he underwent testing for pernicious anemia: intrinsic factor was negative and his parietal cell immunoglobulin G antibodies were 1.4 units (normal, 0–24.9 units). Celiac antibodies were negative. Serum copper and zinc testing resulted as 95 and 96 μg/dL, respectively (normal, 70–140 μg/dL and 60–120 μg/dL, respectively). He underwent MRI of the cervical and thoracic spine (figure).

Question for consideration:

1. Which diagnoses should be at the top of the differential?

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Figure The patient's cervical spine MRI

(A) MRI short tau inversion recovery sagittal image of the lower cervical and upper thoracic spine shows signal change in the posterior cord (arrow). (B) T2-weighted axial images of the cervical spine show cord signal change isolated to the dorsal columns.

SECTION 3

In this case, B₁₂ deficiency and neurosyphilis were the treatment team's top differential diagnoses. However, during his evaluation in the ED, the patient endorsed a recent history of N₂O abuse. Six weeks prior to presentation, the patient underwent a dental procedure with N₂O. The following day, he and a friend bought a case containing 24 cans of "whippets" (cansisters of N₂O used in refillable whipped cream containers, commonly used recreationally for the "high" that results from inhalation of N₂O). They inhaled 1 to 2 cans daily for about 10 days, after which, he stopped. His symptoms developed approximately 2 weeks later.

Although the patient had a low B₁₂ level, in the context of this subsequent history it is most likely that N₂O toxicity was the main contributing factor to his symptoms. His evaluation for pernicious anemia excluded B₁₂ malabsorption. When asked about his diet, he denied being a vegan or vegetarian, and ingested B₁₂-containing foods on a regular basis. It is unclear why his B₁₂ concentration was low. Perhaps he had an underlying mild B₁₂ deficiency, which was exacerbated by N₂O exposure even at a lower dose compared to other reported cases.^{1,2} Another possibil-

ity is that a premorbid B₁₂ deficiency may have increased his risk of neurologic injury in the setting of N₂O exposure.

Under normal conditions, methionine synthase is required to catalyze the conversion of homocysteine to methionine and methyltetrahydrofolate to tetrahydrofolate (THF). Methionine then gets converted to S-adenosylmethionine (SAM) and THF becomes 10-Formyl-THF. SAM is a one-carbon donor in methylation reactions and 10-Formyl-THF promotes DNA synthesis. B₁₂ is a cofactor for methionine synthase. N₂O oxidizes the cobalt moiety of B₁₂, inactivating it. As a result, methionine synthase becomes irreversibly inhibited, yielding an elevated homocysteine concentration and a depressed concentration of methionine. Thus, DNA production and myelin formation are inhibited.^{3,4} This places N₂O abusers at risk for bone marrow abnormalities (including macrocytic anemia and leukopenia) as well as myelopathies, neuropathies, and encephalopathies.

Questions for consideration:

1. How should this patient be managed?
2. What is the patient's prognosis?

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SECTION 4

The most important step in the management of patients with N₂O-induced toxicity is advising its discontinuation. With cessation of N₂O use, some patients experience full recovery. In contrast, continued use often leads to progression of symptoms and decreased mobility.^{1,2} In addition, B₁₂ supplementation may help alleviate symptoms, especially in B₁₂ deficiency or short-term N₂O exposure. In addition to B₁₂ supplementation, a methionine-rich diet may be beneficial.⁵

The patient was admitted to the neurology service for continued management and evaluation by physical therapy. He was educated about the possible association between N₂O exposure and his symptoms, as well as the importance of avoiding future N₂O exposure. He received intramuscular B₁₂ supplementation and was started on a methionine-rich diet. The physical therapists recommended a walker for the patient, and he was discharged on hospital day 3 with B₁₂ supplementation, 1,000 µg weekly.

One week following discharge, the patient showed considerable improvement. Vibratory loss was only clearly detectable in his feet and ankles, although he had persistent weakness in great toe extension and was still using a walker. Three weeks after discharge, his B₁₂ and homocysteine concentrations were 863 pg/mL and 12.9 µmol/L, respectively. Six weeks following discharge, he showed continued functional improvement, only using a cane occasionally to walk, although his sensory and motor examination was similar to the week after discharge.

DISCUSSION N₂O is an inhaled anesthetic that has been used since the 1800s. It continues to be popular for dental procedures and is used as a propellant for whipped cream, rockets, and racing automobiles. N₂O is lipophilic, crosses the blood–brain barrier, and produces a euphoric effect. This N₂O-induced euphoria leads some to use it recreationally. Because of their easy accessibility to N₂O, dentists appear to be at increased risk of N₂O abuse and toxicity.^{6–8}

In the case presented here, sensory abnormalities and gait disturbance emerged as a consequence of B₁₂ deficiency in combination with N₂O exposure. According to a systematic review, low-normal or low B₁₂ concentrations are common in symptomatic patients with N₂O abuse.⁹ Repeated N₂O exposure is associated with myeloneuropathy, subacute combined degeneration of the spinal cord, peripheral neuropathy/polyneuropathy, and myelopathy. According to this systematic review, the N₂O dose and duration of exposure associated with toxicity varied greatly. The diagnosis of N₂O toxicity can be established by measuring homocysteine and methylmethionine concentrations in

the urine. In lieu of prevention, cessation of N₂O exposure is the most important step in quelling N₂O toxicity.

We have presented the case of a 27-year-old man with gait disturbance, sensory abnormalities, and lower extremity weakness with MRI evidence of dorsal column involvement of the cervical spine, found to be due to N₂O toxicity in the setting of B₁₂ deficiency. Clinicians should remain vigilant of this diagnosis, and should inquire about repeated N₂O exposure especially when symptoms are reported after dental procedures.

AUTHOR CONTRIBUTIONS

Denise Fernández, MD: wrote original draft of the manuscript and was consult toxicology fellow involved in this patient's care and edited the video content. Michael G. Fara, MD: critical revision of the manuscript for important intellectual concept, was the neurology consult resident on the case, and obtained MRI. Rana Biary, MD: critical revision of the manuscript for important intellectual concept, was supervising toxicology attending on the case, and recorded the video content. Robert S. Hoffman, MD: critical revision of the manuscript for important intellectual concept and assisted with the patient's management. Susi Vasallo, MD: critical revision of the manuscript for important intellectual concept and was the patient's ED attending who consulted the neurology and toxicology teams. Laura Balcer, MD: critical revision of the manuscript for important intellectual concept and was the neurology admitting attending. Daniel Torres, MD: critical revision of the manuscript for important intellectual concept, is the patient's neurologist who referred him to the ED.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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