CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 15-2023: A 33-Year-Old Man with Paresthesia of the Arms and Legs

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PRESENTATION OF CASE

Dr. Priyanka Pullarkat (Medicine): A 33-year-old man was evaluated in the emergency department of this hospital because of progressively worsening paresthesia.

The patient had been in his usual state of health until 8 weeks before the current evaluation, when he began to have an abnormal tingling sensation in the toes that he described as "pins and needles." Over the course of several days, the paresthesia extended to the feet.

Six weeks before the current presentation, episodes of headache that lasted approximately 5 minutes and affected the left periorbital region began to occur on a daily basis. The headaches became less severe after the patient took acetaminophen. He had no associated nausea, vomiting, or neck pain.

Two weeks before the current presentation, paresthesia developed in the fingertips and, over the course of several days, extended to the hands and then the forearms. One week before the current presentation, the patient was evaluated by his primary care physician. The temporal temperature was 36.9°C, the blood pressure 134/82 mm Hg, the heart rate 92 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 100% while he was breathing ambient air. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 25.9. He had no rash. Sensation to light touch and pinprick was absent from the toes to the midfoot.

Screening tests for human immunodeficiency virus (HIV), hepatitis B and C viruses, and Lyme disease were negative. The blood level of folate was greater than 20 ng per milliliter (45 nmol per liter; reference value, >4.6 ng per milliliter [>10 nmol per liter]), the vitamin B_1 (thiamine) level 149.1 nmol per liter (reference range, 66.5 to 200), and the vitamin B_{12} (cobalamin) level 235 pg per milliliter (173 pmol per liter; reference range, 232 to 1245 pg per milliliter [171 to 919 pmol per liter]). Testing for anti–myelin-associated glycoprotein antibodies was negative. Imaging studies were obtained.

Dr. Saurabh Rohatgi: Magnetic resonance imaging (MRI) of the head (Fig. 1) was performed. T2-weighted and fluid-attenuated inversion recovery images, obtained before the administration of intravenous contrast material, showed mild, nonspe-

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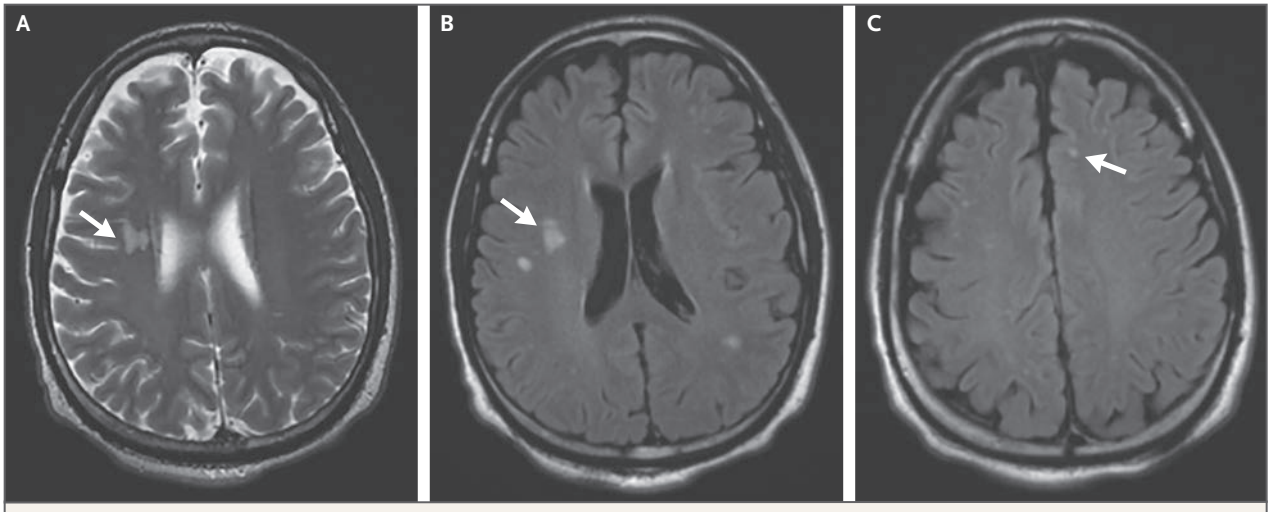

Figure 1. MRI of the Head.

MRI of the head was performed 5 days before the current presentation. An axial T2-weighted image (Panel A) and fluid-attenuated inversion recovery (FLAIR) images (Panels B and C) show mild, nonspecific, scattered foci of hyperintensity involving the supratentorial white matter (Panel C, arrow), with a dominant lesion in the right frontal centrum semiovale and corona radiata (Panels A and B, arrows). There was no associated abnormal enhancement.

cific, scattered foci of hyperintensity involving the supratentorial white matter; the dominant lesion, which was located in the right frontal centrum semiovale and corona radiata, measured 1.4 cm in diameter. No associated abnormal enhancement was seen on images obtained after the administration of contrast material.

Dr. Pullarkat: The patient was referred to a neurology clinic. One week later, while the patient was awaiting an appointment in the neurology clinic, paresthesia extended into the thighs and torso. The patient was advised by his primary care physician to present to the emergency department of this hospital for further evaluation.

In the emergency department, the patient reported worsening paresthesia and loss of dexterity in his hands. He was no longer able to play guitar. He had no motor weakness, bowel or bladder incontinence, or double vision. There was no change in sensation in his face or in articulation of his speech, and he had no dysphonia, dysphagia, or shortness of breath.

Other medical history included depression and chronic knee and ankle pain after trauma. Medications included bupropion and mirtazapine. There were no known allergies. The patient was a graduate student and lived with several roommates. He was sexually active with women. He had smoked one pack of cigarettes per day for 11 years before quitting 4 years before the current presentation. He had consumed three alcoholic drinks daily for many years, but 1 month before the current presentation, he had reduced consumption to two drinks one or two times per week. He used intranasal cocaine three or four times per week and inhaled nitrous oxide once per week. He had last used lysergic acid diethylamide and ketamine 10 weeks before the current presentation during a camping trip in rural New England; there were ticks in the area where he had camped, but he had not found any ticks on his body. The patient had a normal diet with no dietary restrictions, and there was no history of diarrhea or unintentional weight loss. His maternal grandfather had diabetes, and his paternal grandfather had gastric cancer.

The patient was alert and interactive and followed commands. The temporal temperature was 36.5°C, the blood pressure 131/82 mm Hg, the heart rate 88 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen saturation 96% while he was breathing ambient air. He had a flat affect but was oriented to time, place, and person. Speech was fluent with intact naming, repetition, and comprehension. Cranial nerve examination was normal. Muscle tone and strength were normal. In the legs, there was reduced sensation to pinprick and to tempera-

ture that extended from the toes to the hips and flanks, with sparing of the anterior trunk and the back. In the arms, there was reduced sensation to pinprick and to temperature that extended from the fingers to the shoulders. The reduced sensation was most pronounced in the fingers and toes. Vibratory sensation and proprioception were decreased below the shins. The reflexes were 2+ in the arms but were absent in the legs. The patient was able to touch the tip of his nose with his index finger when his eyes were open but was unable to do so when his eyes were closed. His gait was unsteady, and the Romberg test was positive.

A diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. William P. Schmitt: This 33-year-old graduate student — who had a history of use of alcohol, cocaine, nitrous oxide, lysergic acid diethylamide, and ketamine — presented with progressively worsening, painless, symmetric sensory deficits that had begun 8 weeks earlier, with eventual gait and hand ataxia. Because the patient's presentation is most consistent with a neurologic process, I will begin by localizing the lesion before considering the possible causes of his illness.

LOCALIZATION

Although imaging of the head in this patient showed a 1.4-cm lesion in the right frontal centrum ovale and corona radiata, his symptoms and examination findings are not consistent with a process involving the central nervous system. He appeared to have a pure sensory deficit that started in the toes and progressed proximally to the legs and eventually to the hands and arms; strength was fully preserved, and there were no signs of cranial nerve involvement.

The symmetric, progressive nature of the patient's sensory deficit is suggestive of a process involving the peripheral nerves, the spinal cord, or both. Paresthesia of the arms in conjunction with normal reflexes in the arms may indicate a myelopathic process rather than neuropathy. The patient's normal results on the strength examination are consistent with a process that is selectively affecting the posterior columns of the spinal cord; weakness would be expected if there was involvement of the lateral columns of the spinal cord. However, the absence of reflexes in the legs suggests involvement of the peripheral nerves as well. He appeared to have a subacute, progressively worsening myeloneuropathy involving both the posterior columns of the spinal cord and the peripheral nerves of the legs.[1] What could cause this?

INFECTION

Tickborne illness is a consideration in this case, owing to the patient's recent camping trip. The most common neurologic manifestations of Lyme disease are cranial neuropathies and meningoencephalitis; patients with Lyme disease can also have polyradiculopathies and, very rarely, transverse myelitis. However, this patient had no prodromal symptoms, such as rash or fever, and serologic tests for Lyme disease were negative. Other tickborne illnesses are unlikely in the absence of systemic symptoms, and myelopathy would be unusual with these illnesses.

Poliovirus and enteroviruses can cause transverse myelitis. However, patients with viral myelitis typically present with weakness that progresses over a period of 2 weeks. The absence of weakness during this patient's steady progression of symptoms over the course of 8 weeks makes viral myelitis very unlikely.[1] Infection with varicella–zoster virus (VZV), herpes simplex virus (HSV), or HIV can cause myelopathy. However, this patient did not have evidence of either acute VZV or HSV infection or reactivation of VZV or HSV replication, and the slow pace of illness is not consistent with these infections. HIV infection is unlikely, given the negative screening test. Syphilis should also be considered in any patient with suspected disease in the posterior columns of the spinal cord. However, classic tabes dorsalis (the form of neurosyphilis in which nerves of the posterior columns of the spinal cord degenerate) usually occurs 10 to 20 years after initial untreated infection with *Treponema pallidum*. Although tabes dorsalis is unlikely in this relatively young patient, I would still recommend testing for syphilis.

MECHANICAL DISRUPTION

Mechanical disruption of the cervical spinal cord by a mass, cervical stenosis, or cervical disk disease can produce myelopathic features. However, it would be unusual for a mechanical process to affect only the posterior columns of the spinal cord, and I would expect the leg reflexes

to be brisk as opposed to absent. This patient's steady progression of symptoms also makes a mass, cervical stenosis, or cervical disk disease unlikely. However, imaging would be necessary to rule out a mechanical process that disrupts the cervical spinal cord.

INFLAMMATORY DEMYELINATING POLYNEUROPATHIES

Acute inflammatory demyelinating polyneuropathy (AIDP) and chronic inflammatory demyelinating polyneuropathy (CIDP) can both cause sensory symptoms such as those seen in this patient. However, the course of illness in patients with AIDP usually peaks within 2 to 4 weeks after the onset of symptoms. Although the time course of this patient's presentation could be consistent with CIDP, both AIDP and CIDP usually affect the motor nerves, which results in weakness. Uncommon variants of CIDP that cause purely sensory effects have been reported; however, the symptoms tend to progress more slowly than those seen in this patient, and loss of reflexes in the arms would be expected.[2] In contrast, this patient had paresthesia involving the arms but had normal reflexes in the arms. The negative test for anti–myelin-associated glycoprotein antibodies also argues against a sensory-predominant variant of CIDP.[3]

Patients with Sjögren's syndrome can present with peripheral neuropathy, but myelopathy is rare. Patients with Behçet's disease can have myelitis, although the presence of myelitis in such patients is usually associated with other central nervous system findings. This patient did not have dry mouth, dry eyes, or enlargement of the salivary glands — features that would suggest Sjögren's syndrome — nor did he have features that would be consistent with Behçet's disease, such as oral or urogenital lesions. Sarcoidosis can also cause neuropathy and myelitis, which develop over a period of hours to days until a maximum level of myelopathy symptoms is present; the pace of this patient's illness and the absence of pulmonary symptoms make sarcoidosis an unlikely diagnosis.[4]

MULTIPLE SCLEROSIS AND OTHER AUTOIMMUNE DISEASES

The first manifestation of multiple sclerosis commonly includes sensory symptoms that range from mild paresthesia to loss of sensation. Multiple sclerosis can cause myeloneuropathy, although the pace of this patient's progression is atypical for either the relapsing–remitting or primary progressive form of multiple sclerosis. The relapsing–remitting form of multiple sclerosis, which is the most common form, is characterized by symptoms that occur acutely, over a period of days, before remitting; the pace of this process is too fast to have been present in this case. The primary progressive form of multiple sclerosis progresses slowly in a linear fashion over a period of years, and motor symptoms predominate; the pace of this process is too slow to have been present in this case.[5] In addition, patients with multiple sclerosis typically have asymmetric sensory loss, which reflects the patchy distribution of neurologic lesions. This patient had no cranial nerve abnormalities, eye-movement abnormalities, or spasticity that would support the diagnosis of multiple sclerosis, and the absence of distal leg reflexes would be atypical. Other forms of autoimmune transverse myelitis, such as systemic lupus erythematosus and systemic sclerosis, can also cause symmetric sensory changes; however, such changes are almost always accompanied by motor findings, and the pace of evolution is often much faster than that seen in this patient.[6-8]

CANCER

Patients with paraneoplastic subacute sensory neuronopathy can present with neuropathy that precedes the diagnosis of cancer.[9] However, such neuropathy is usually painful, and this patient's relatively young age and modest smoking history make this diagnosis unlikely.

TOXIC METABOLIC PROCESS

This patient had several toxic exposures, including the frequent use of alcohol, cocaine, and nitrous oxide. Alcohol use can lead to peripheral neuropathy, although this outcome is more typical in patients who consume larger amounts of alcohol than this patient described. Also, the progression of symptoms in this patient is more rapid than would be expected for peripheral neuropathy associated with alcohol use. The use of cocaine can cause strokes and nerve infarcts, and a stroke could explain the brain lesion seen on MRI, but cocaine use is not commonly associated with myelopathy or neuropathy.

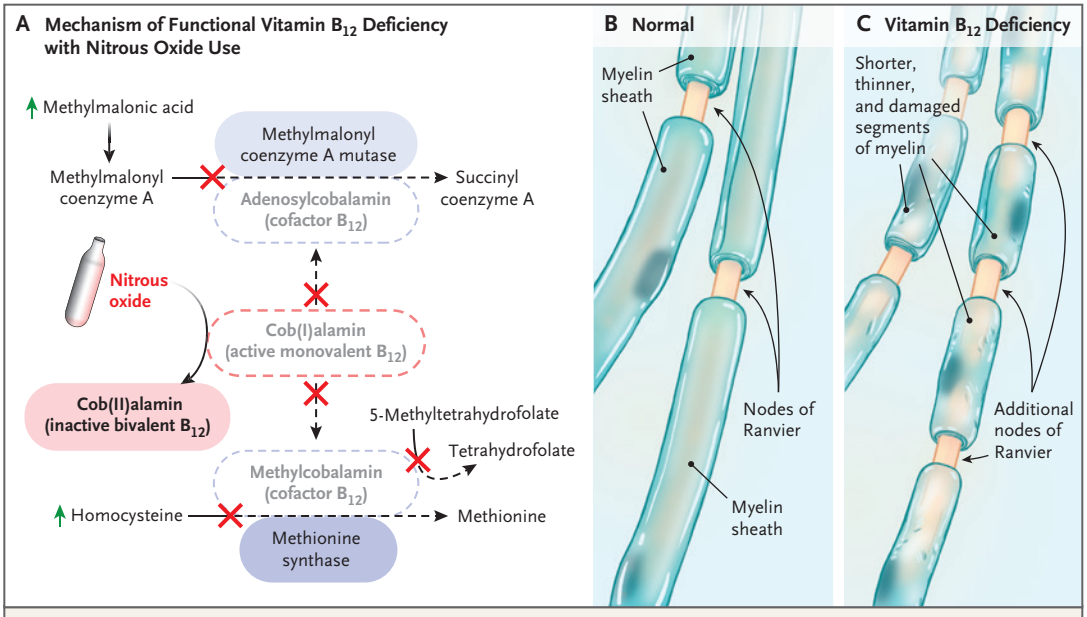

Figure 2. Mechanism of Functional Vitamin B_{12} Deficiency with Nitrous Oxide Use.

Panel A shows the mechanism of functional vitamin B_{12} deficiency in a patient with nitrous oxide use. Nitrous oxide irreversibly inhibits the catalytic functions of vitamin B_{12} by transforming it from the active monovalent form to the inactive bivalent form through the oxidation of the cobalt portion of methylcobalamin. Vitamin B_{12} acts as a critical enzyme that converts methylmalonic acid to succinyl coenzyme A and converts homocysteine to methionine (with folate as a cofactor). Increased levels methylmalonic acid can be neurotoxic. Decreased levels of methionine impair the production and maintenance of the myelin sheaths of sensory neurons. The red X indicates a blocked pathway, and the green arrow an increased concentration. Panels B and C show the features of a normal axon and an axon in a patient with vitamin B_{12} deficiency, respectively.

Patients with vitamin B_{12} deficiency can have myeloneuropathy that is caused by dysfunction in the posterior columns of the spinal cord that leads to progressive symmetric loss of sensation in the legs, accompanied by ataxia.[10] The condition can progress to involve the arms and, if left untreated, can result in distal neuropathy. Vitamin B_{12} acts as a critical enzyme that converts homocysteine to methionine (with folate as a cofactor) and converts methylmalonic acid to succinyl coenzyme A. Functional vitamin B_{12} deficiency causes decreased levels of methionine, which in turn impair the production and maintenance of the myelin sheaths of sensory neurons. In addition, functional vitamin B_{12} deficiency results in an increase in the level of methylmalonic acid, which can be neurotoxic. Patients with copper deficiency can have a similar presentation.[11] Although this patient did not have typical risk factors for copper deficiency, such as previous bariatric surgery, malnutrition, or overuse of zinc-containing denture cream, I would still measure the blood level of copper.

This patient's clinical picture is most consistent with vitamin B_{12} deficiency, even though his vitamin B_{12} level was normal. Risk factors for vitamin B_{12} deficiency include poor nutrition, impaired absorption of vitamin B_{12} (e.g., due to pernicious anemia or previous bariatric surgery), or inactivation of vitamin B_{12} as a result of interference with its catalytic activity. This patient's frequent use of nitrous oxide (also known as "laughing gas" or "whippets") may provide the explanation for his presentation. Nitrous oxide irreversibly inhibits the catalytic functions of vitamin B_{12} by transforming it from the active monovalent form to the inactive bivalent form (Fig. 2).[12] Despite the presence of a normal blood level of vitamin B_{12} in this patient, the vitamin may not have been in a functional form and therefore may have caused the same pathological process as that which occurs in patients who are deficient in vitamin B_{12}.

To establish the diagnosis of functional vitamin B_{12} deficiency in the context of nitrous oxide use, I would obtain an MRI of the spine to look

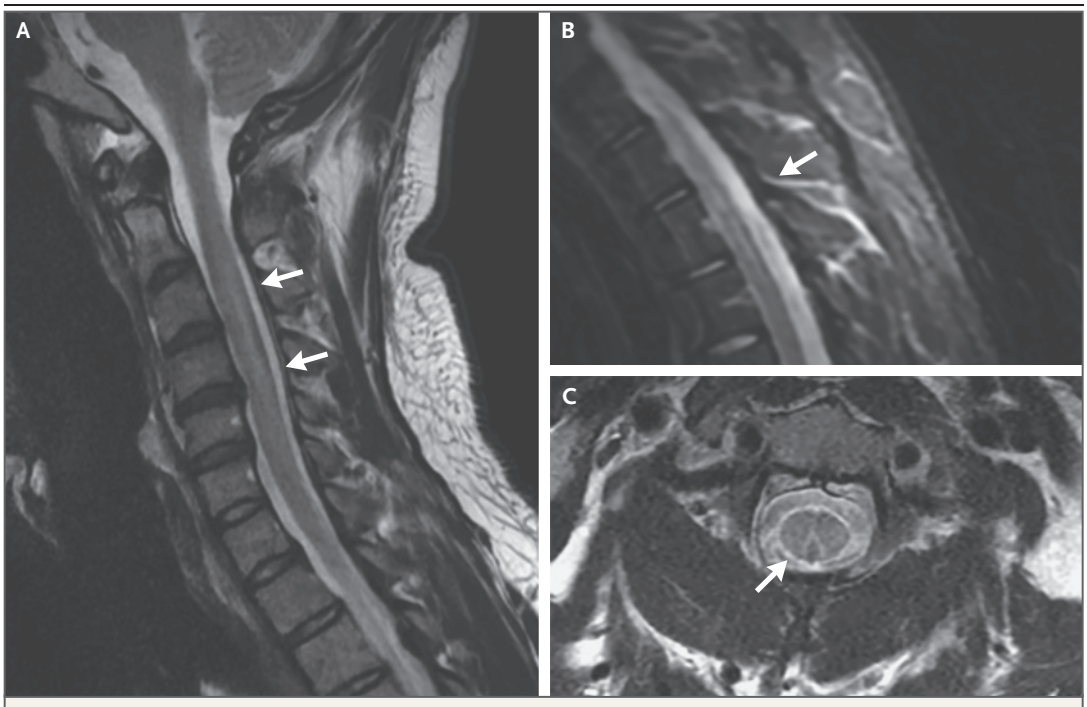

Figure 3. MRI of the Spine.

MRI of the cervical and thoracic spine was performed after admission. A sagittal T2-weighted image of the cervical spine (Panel A) and a short-tau inversion recovery (STIR) image of the thoracic spine (Panel B) show a long segment of hyperintensity involving the cervical and thoracic spine (at C2–C6 and T1–T5) (Panels A and B, arrows). There was no associated abnormal enhancement. An axial T2-weighted image of the cervical spine (Panel C) shows hyperintensity involving the posterior columns of the cervical spine in an inverted-V pattern (arrow).

for enhancement of the posterior columns of the cervical and thoracic spinal cord, a finding that would be highly suggestive of vitamin B_{12} deficiency or copper deficiency. I would expect the blood levels of methylmalonic acid and homocysteine to be elevated.

DR. WILLIAM P. SCHMITT'S DIAGNOSIS

Functional vitamin B_{12} deficiency from use of nitrous oxide.

CLINICAL IMPRESSION

Dr. Marcelo Matiello: This patient's progression of symptoms fit the clinical presentation of subacute combined degeneration of the spinal cord. His symptoms were related to degeneration of the posterior columns of the spinal cord, including paresthesia (observed in the form of tingling and burning) followed by impaired proprioception and vibratory sensation (leading to ataxia). No signs of impairment of the lateral columns (e.g., muscle weakness, diffuse hyperreflexia, or spasticity) were present at the time of diagnosis.[13]

The patient's subacute course over a period of weeks to months and his history of substance use strongly pointed to a metabolic process or a direct effect of drugs or toxins. His history of nitrous oxide use made a functional vitamin B_{12} deficiency most likely.

CLINICAL DIAGNOSIS

Functional vitamin B_{12} deficiency from use of nitrous oxide.

IMAGING STUDIES

Dr. Rohatgi: MRI of the cervical and thoracic spine was performed (Fig. 3). T2-weighted and short-tau inversion recovery images showed a long segment of hyperintensity involving the cervical and thoracic spine (at C2–C6 and T1–T5) with no

associated enhancement. An axial T2-weighted image showed hyperintensity involving the posterior columns of the cervical spine in an inverted-V pattern. The differential diagnosis of signal change within the cord is broad. After a compressive myelopathy or cancer is ruled out, the differential diagnosis can be further narrowed on the basis of the pattern of cord involvement (Fig. 4).[14-16] In this patient, the posterior columns of the spinal cord were involved; this pattern is commonly seen in patients with deficiencies of vitamin B_{12} or copper, in patients with toxic effects from excess ingestion of zinc or from the use of nitrous oxide, or in patients with tertiary syphilis.

LABORATORY TESTING

Dr. Matiello: The blood levels of copper and zinc were normal, and a screening test for *T. pallidum* IgG and IgM was negative. The blood methylmalonic acid level was 6.41 nmol per milliliter (reference value, <0.40) and the blood homocysteine level 63.9 μmol per liter (reference range, 0 to 14.2). Taken together with the patient's history of nitrous oxide use and the findings on MRI of the spine, a diagnosis of functional vitamin B_{12} deficiency from the use of nitrous oxide was made.

IMAGING AND LABORATORY DIAGNOSIS

Functional vitamin B_{12} deficiency from use of nitrous oxide.

DISCUSSION OF NEUROLOGY MANAGEMENT

Dr. Matiello: Recreational exposure to nitrous oxide causes irreversible inactivation of vitamin B_{12} through the oxidation of the cobalt portion of methylcobalamin. Inactivation of vitamin B_{12} leads to the impairment of myelin production and maintenance.[17,18] Moreover, inactivation of vitamin B_{12} results in elevated levels of methylmalonic acid, which can be neurotoxic and can cause further damage.

Two main treatment steps are simple yet efficacious in stopping further nervous system damage. The first step is cessation of the use of nitrous oxide. Education regarding the toxic effects of nitrous oxide was provided to this patient, and his cessation efforts were further supported by consultation with the addiction medicine service. The second step is supplementation with vitamin B_{12}, which in this patient was achieved by the administration of intramuscular injections of cyanocobalamin once daily for 5 days. In patients with normal absorption,

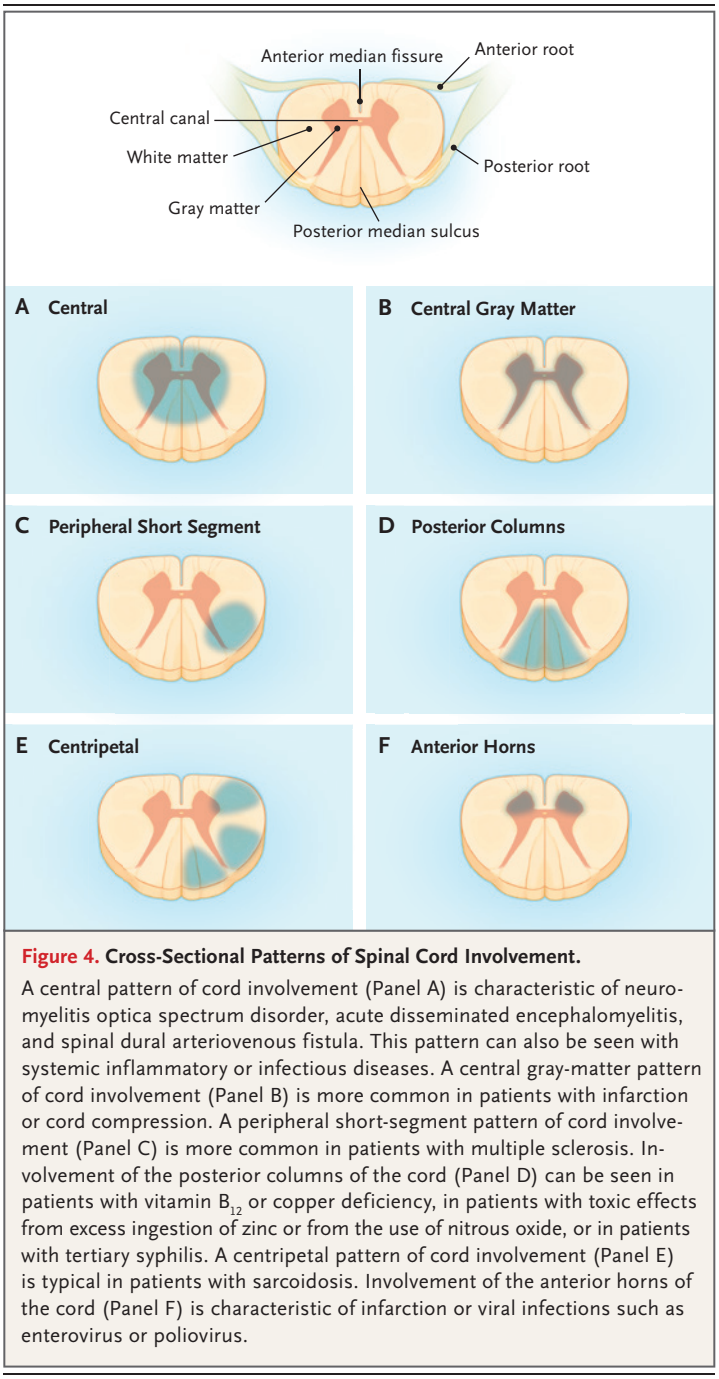

Figure 4. Cross-Sectional Patterns of Spinal Cord Involvement.
A central pattern of cord involvement (Panel A) is characteristic of neuromyelitis optica spectrum disorder, acute disseminated encephalomyelitis, and spinal dural arteriovenous fistula. This pattern can also be seen with systemic inflammatory or infectious diseases. A central gray-matter pattern of cord involvement (Panel B) is more common in patients with infarction or cord compression. A peripheral short-segment pattern of cord involvement (Panel C) is more common in patients with multiple sclerosis. Involvement of the posterior columns of the cord (Panel D) can be seen in patients with vitamin B_{12} or copper deficiency, in patients with toxic effects from excess ingestion of zinc or from the use of nitrous oxide, or in patients with tertiary syphilis. A centripetal pattern of cord involvement (Panel E) is typical in patients with sarcoidosis. Involvement of the anterior horns of the cord (Panel F) is characteristic of infarction or viral infections such as enterovirus or poliovirus.

oral and intramuscular cyanocobalamin treatments result in similar serum vitamin B_{12} levels; therefore, oral supplementation with cyanocobalamin once daily can be used after initial parenteral replacement. Although the most important management step is the cessation of nitrous oxide use, oral cyanocobalamin supplementation is planned to be continued indefinitely, given that this patient also had low-normal vitamin B_{12} levels.[19]

Vitamin B_{12} deficiency can lead to many neuropsychiatric manifestations, including apathy, decreased memory, personality changes, emotional lability, and, in more severe cases, psychosis and auditory and visual hallucinations.[20] Later in this patient's hospitalization, he began to have severe symptoms, including depression, suicidal ideation, and signs of catatonia. He was transferred to the psychiatry floor, and treatment included electroconvulsive therapy.

On follow-up, 3 months after the diagnosis, the patient had mild improvement in the dexterity of his hands, although he continued to have difficulty with fine movements including playing guitar. He continued to have numbness and tingling in the fingertips and feet, along with gait instability. There was no recurrence of suicidal ideation, and he had stopped using nitrous oxide.

FINAL DIAGNOSIS

Functional vitamin B_{12} deficiency from use of nitrous oxide.

This case was presented at the Medicine Case Conference.

Disclosure forms provided by the authors are available with the full text of the article at NEJM.org.

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