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CLINICAL

An unusual cause of falls in a young woman

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ABSTRACT Nitrous oxide is commonly used as an analgesic and anaesthetic agent. Nitrous oxide is also in use in industry as an aerosol propellant and is now recognised as a recreational drug whose use is growing, especially among the young. Nitrous oxide from whipped cream canisters is inhaled to produce a dissociative, intoxicated state. Nitrous oxide is known to inactivate vitamin B12 via oxidation, which can precipitate a demyelinating myelopathy akin to the classical B12 deficiency syndrome, subacute combined degeneration of the spinal cord. This case describes a young woman with chronic pain and a poor nutritional state who took regular nitrous oxide as an opiate-sparing agent. She developed a progressive subacute myelopathy with a sensory level, profoundly impaired joint position sense, extensor plantars and required a wheelchair. Once diagnosed, she responded well to a regime of nitrous oxide withdrawal, high-dose B12 replacement and physiotherapy. The case illustrates the need for clinical teams to be able to identify a nitrous oxide-precipitated myelopathy as its use as a drug of abuse increases; particularly in the case of malnourished patients who receive nitrous oxide surgically or obstetrically.

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INTRODUCTION

Entonox (also known as 'gas and air') is an equal mix of nitrous oxide and oxygen, commonly used as a means of emergency and obstetric analgesia. Humphrey Davy was the first to record its euphoric and analgesic properties in 1800.[1] It has been abused by medical and dental professionals for as long as it has been in clinical use; one survey revealed that 8.5–20% of medical and dental students had taken nitrous oxide recreationally.[2]

Nitrous oxide is now a commonly used recreational drug in the general population, with 6.1% of 16–24 year olds admitting to having taken it in the previous year.[3] It is most often obtained as aerosol containers used to whip cream (hence the street name for the drug is 'whippits') or inflate balloons, the contents of which can then be inhaled.

CASE HISTORY

A 29-year-old woman attended the emergency neurology clinic in a wheelchair with a two month history of increasing falls and urinary frequency. She described bilateral leg numbness below the knee, pins and needles from the level of the hips distally and altered sensation over the palms of both hands. Her past medical history included 20 years of intermittent abdominal pain following a ruptured appendix. She had undergone multiple laparotomies, which revealed adhesions and a right-sided ovarian cyst. She was still in severe pain and took regular long and short-acting morphine preparations, hyoscine butylbromide, paracetamol and ondansetron. As her GP decreased her opioid dose, she made increasingly frequent ambulance trips to A&E for pain relief and at the time of referral was attending twice a day. She had recently given up her job as a shop assistant due to falls. She smoked ten cigarettes a day and was teetotal. Her abdominal pain led to erratic eating habits.

On examination, upper limbs, cranial nerves, speech, and cognition were all normal. Tone was difficult to assess but there was no clonus. Lower limb strength was grade 4 out of 5 bilaterally. Ankle reflexes were normal, knee reflexes were brisk and both plantar responses were extensor. Joint position was impaired at the toes and pain perception was impaired below the level of the T6 dermatome.

Full blood count, thyroid stimulating hormone, copper and caeruloplasmin were all normal. Vitamin B12 was low at 162 pg/ml; (normal range = 145–569 pg/ml). She underwent magnetic resonance imaging (MRI) scan of her spinal cord, which revealed hyper-intensity of the posterior cord from C2–T5 (Figure 1). The combination of myelopathy, peripheral neuropathy and typical MRI changes suggested subacute combined degeneration of the spinal cord. The most common cause of this presentation is vitamin B12 deficiency; however, her

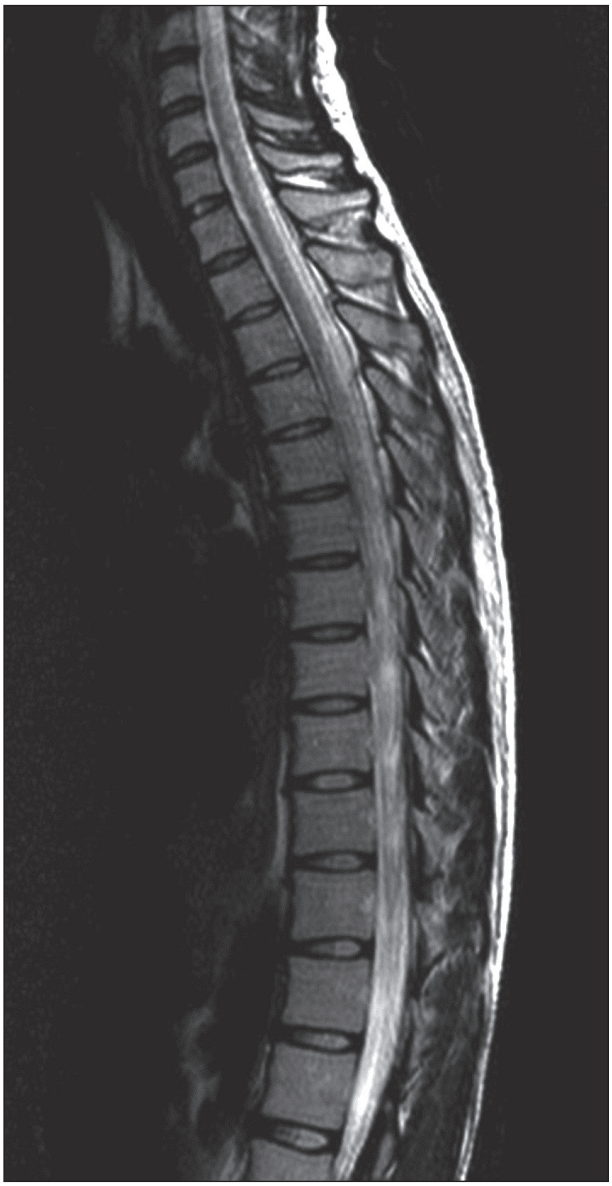

FIGURE 1 T2-weighted image of the patient's spinal cord at presentation

levels were not low enough to account for her symptoms. She had been receiving inhaled nitrous oxide in A&E as an opioid-sparing agent and, coupled with poor nutritional status, this had precipitated subacute combined degeneration of the spinal cord ('nitrous oxide myelopathy').

Nitrous oxide analgesia was withdrawn and she received vitamin B12 injections and intensive physiotherapy. Two years later, she was able to walk with the aid of crutches and was continuing to improve, though she was still liable to falls when walking outside and unable to work.

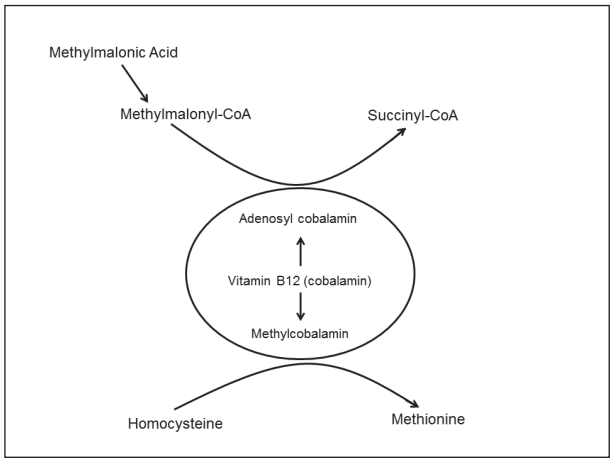

FIGURE 2 Vitamin B12 is a co-factor in the reaction which converts methylmalonyl coenzyme A to succinyl coenzyme A and homocysteine to methionine, based on Thompson et al.[14]

DISCUSSION

Nitrous oxide toxicity causes demyelination of the posterior and lateral columns of the spinal cord, and degeneration of large myelinated peripheral nerves. In our case, the patient's lower limb weakness with extensor plantar responses and urinary symptoms were caused by damage to the corticospinal tract. The combination of extensor plantar responses with normal tone was due to the admixture of corticospinal tract involvement and peripheral neuropathy. The impaired joint position sense was due to damage to the posterior columns, which relay vibration and proprioceptive signals. The loss of sensation in her hands and legs could have been due to peripheral neuropathy or demyelinating myelopathy of the spinothalamic tracts. In retrospect, an electromyelogram would have been useful to clarify this; however, as the diagnosis of nitrous oxide myelopathy was secure this was not performed. Other signs of this condition include Lhermitte's sign (an electric shock-like phenomena on flexing the neck), ataxia and broad-based gait due to posterior column involvement, spasticity, hyperreflexia, and clonus due to corticospinal tract involvement.

In nitrous oxide myelopathy, the cobalt ion of cobalamin (vitamin B12) is oxidised and irreversibly inactivated. Thus, it cannot act as a coenzyme to convert methylmalonyl coenzyme A to succinyl coenzyme A and homocysteine to methionine (Figure 2). As a consequence, methylation of the myelin sheath fails, leading to loss of fibre tracts,[4] polyneuropathy and spinal cord degeneration.[5]

T2-weighted MRI images of the spinal cords of patients with chronic nitrous oxide-induced myelopathy reveal posterior column hyper-intensity, with the inverted 'V' sign on axial images.[6,7] This classically starts in the thoracic cord and affects the cervical cord later.

In the 1950s, nitrous oxide, used to ease tetanus spasms, was found to cause severe bone marrow suppression due to vitamin B12 inactivation.[8] The first cases of nitrous oxide neuropathy among healthcare professionals were described in the mid-1970s.[9] It has been suggested that 80 g (10 cylinders/day) would be a risk factor for neurological sequelae,[10] though illicit use makes this difficult to quantify. Most nitrous oxide abusers develop myelopathy over months; however, recent case studies suggest inhaling large amounts (e.g. 240 canisters/day) can lead to symptoms within weeks.[11]

Even in healthy subjects, inhaling nitrous oxide during a 12 hour operation can lead to transient megaloblastic bone marrow changes.[4] In patients with marginally low vitamin B12 or macrocytic anaemia, peri-operative nitrous oxide use can lead to neurological sequelae two days to six weeks postoperatively. A pre-operative vitamin B12 screen should be considered in malnourished patients. Vitamin B12 should be replaced if borderline, or an alternative considered if surgery is required at short notice.

The most important step in treatment is ensuring that the patient completely abstains from nitrous oxide use. Intramuscular vitamin B12 injections can aid recovery, even if serum vitamin B12 levels are normal, as the measured circulating B12 is the oxidised, inactivated form produced by the effect of nitrous oxide.[4] The treatment regime varies but five days of 1000 µg/day vitamin B12, followed by an additional two month treatment at a dose of 1000 µg/week has been used successfully in a number of cases. Physiotherapy appears to allow patients to regain mobility and reduce the risk of falls, although there is little empirical evidence for its efficacy.

There is currently no clear evidence to guide prognosis in a patient with nitrous oxide myelopathy. Case reports suggest that improvement is often slow and most patients still have symptoms and functional impairment for months following their initial presentation and vitamin B12 replacement.[12] Case reports suggest that the degree of impairment on presentation and the length of the abnormality on spinal MRI are associated with prognosis. The outcomes of patients with subacute combined degeneration of the spinal cord caused by vitamin B12 deficiency suggest that younger age, shorter MRI lesions and absence of Romberg and Babinski signs are associated with a better prognosis,[13] and it may prove that the prognostic factors are similar for nitrous oxide myelopathy.

KEY POINTS

- Nitrous oxide is the second most common recreational drug in England
- Neurotoxicity occurs when vitamin B12 is inactivated, leading to demyelination
- Even brief exposure, e.g. during anaesthesia, can cause symptoms in patients with subclinical vitamin B12 deficiency
- At risk patients should be screened for vitamin B12 deficiency prior to nitrous oxide administration if practical
- Diagnosis relies upon a history of nitrous oxide inhalation, high homocysteine, low or low/normal vitamin B12 and thoracic /cervical posterior column hyper-intensity on an MRI scan
- Treatment involves withdrawal of nitrous oxide, vitamin B12 injections and physiotherapy

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