CASE REPORT

Nitrous oxide misuse and vitamin B₁₂ deficiencyThomas H Massey,¹ Trevor T Pickersgill,² Kathryn J Peall¹

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SUMMARY

A 36-year-old man presented to hospital with a 5-week history of ascending limb paraesthesiae and balance difficulties. He had no medical or travel history of note, but admitted habitual nitrous oxide (N₂O) inhalation. Neurological examination revealed a sensory ataxia with pseudoathetosis in the upper limbs and reduced vibration sensation to the hips bilaterally. Significant investigation results included a low serum vitamin B₁₂ concentration, mild macrocytosis and raised serum homocysteine concentration. T2 MRI of the spinal cord demonstrated increased signal extending from C1 to T11 in keeping with a longitudinal myelitis. The patient was diagnosed with a myeloneuropathy secondary to vitamin B₁₂ deficiency, resulting from heavy N₂O inhalation. He was treated with intramuscular vitamin B₁₂ injections and received regular physiotherapy. At discharge, he was able to mobilise short distances with the aid of a zimmer frame, and was independently mobile 8 weeks later.

BACKGROUND

The principal drivers for the writing up of this case were the increasing use and ready access of inhaled nitrous oxide (N₂O) as a recreational drug, to highlight use of this drug as a cause of myeloneuropathy. The consequences of repeated N₂O inhalation are increasingly being seen during acute medical admissions, and recognising its potential neurological sequelae is important when obtaining a relevant history and reaching a clinical diagnosis. N₂O also impacts homocysteine metabolism (figure 1), increasing haematological coagulability and potentially increasing the risk of venous thrombosis. This too is important to recognise, ensuring that all patients receive adequate thrombo prophylactic therapy.

CASE PRESENTATION

A 36-year-old man was hospitalised after becoming unable to stand after 5 weeks of ascending limb paraesthesiae and progressive balance difficulties.

His medical history was unremarkable. He denied recent foreign travel or alcohol ingestion but admitted to habitual N₂O inhalation from 'whippits' (figure 6). Neurological examination revealed pseudoathetosis in the upper limbs, brisk but symmetrical reflexes throughout, flexor plantars, reduced vibration sensation to the hips bilaterally and an inability to stand unaided due to sensory ataxia. The remainder of the general and neurological examination was normal.

INVESTIGATIONS

Routine blood tests were within normal limits, apart from low serum vitamin B₁₂ concentration (92 ng/L; normal range 130–900 ng/L) and mild macrocytosis (mean corpuscular volume 100 fL). Subsequent investigations revealed raised serum homocysteine concentration (188.3 µmol/L; normal range <16 µmol/L) but negative anti-intrinsic factor, antiparietal cell and anti-TTG antibodies. Cerebrospinal fluid was acellular with normal constituents. Neurophysiological studies identified a mixed demyelinating and axonal sensorimotor neuropathy. T2-weighted MRI of the spinal cord is shown (figures 2 and 3).

DIFFERENTIAL DIAGNOSIS

The patient was diagnosed with a myeloneuropathy. Differential diagnoses included copper deficiency, vitamin E deficiency and vitamin B₁₂ deficiency causing a subacute combined degeneration of the cord. Causes of vitamin B₁₂ deficiency would include poor dietary intake, malabsorption, pernicious anaemia due to lack of intrinsic factor or, as in this case, heavy N₂O use (300 'whippits' per day).

TREATMENT

He was treated with intramuscular B₁₂ replacement (6 × 1 mg over 2 weeks, then maintenance) and intensive physiotherapy, and advised to stop inhaling N₂O.

Figure 1 Schematic representation of the role of vitamin B₁₂ in homocysteine metabolism and the point at which nitrous oxide exerts its effect. N₂O, nitrous oxide.

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Figures 2 T2-weighted MRI of cervical and thoracic cord (pre-treatment) demonstrating increased signal extending C1–T11 (more marked in the cervical region), in keeping with a longitudinal myelitis.

OUTCOME AND FOLLOW-UP

On discharge at 4 weeks, he was mobilising short distances using a zimmer frame; at 12 weeks, he was mobilising independently. Repeat cord MRI at this time demonstrated significant improvement ([figures 4 and 5](#)).

Figure 3 T2-weighted MRI of cervical and thoracic cord (pre-treatment) demonstrating increased signal extending C1–T11 (more marked in the cervical region), in keeping with a longitudinal myelitis.

Figures 4 T2-weighted MRI of cervical and thoracic spine (post-treatment). This demonstrates an improvement to the cervical cord with a reduction in overall diameter, although some signal increase persists.

DISCUSSION

N₂O gas, long used as an anaesthetic agent, is becoming increasingly popular as a recreational drug due to its euphoric properties and easy availability as a so-called ‘legal high’. It is usually inhaled from balloons filled from ‘whippits’ (small, pressurised canisters of N₂O used in whipped cream dispensers; [figure 6](#)). Despite public

Figure 5 T2-weighted MRI of cervical and thoracic spine post-treatment. This demonstrates an improvement to the cervical cord with a reduction in overall diameter, although some signal increase persists.

Figure 6 Photograph of used 'whippit' canisters.

perception, N₂O is not a safe drug. It irreversibly binds, oxidises, inactivates and eventually depletes vitamin B₁₂. Given that B₁₂ is an essential cofactor for cellular methionine synthase, its inactivation leads to depletion of methionine and accumulation of homocysteine (figure 1). The former reduces levels of downstream s-adenosylmethionine (required for myelin production and maintenance), while the latter increases the risk of venous thromboembolism and atherosclerosis.¹ Neurologically, B₁₂ depletion causes demyelination and subsequent gliosis within the central

nervous system (particularly the dorsal cord) and, less commonly, peripheral nerves. Occasionally, it can cause cognitive impairment and optic atrophy.²

A review of 18 published cases of N₂O toxicity identified the most common neurological presentations as paraesthesiae and gait disturbance, improving over weeks to months with high-dose B₁₂ replacement (although only 25% of cases regained their original level of function).³ Positive prognostic markers at presentation include negative Romberg's sign, flexor plantar responses, age <50 years, absence of significant sensory deficit and MRI changes involving ≤7 segments of the spinal cord.⁴ With prompt treatment, resolution of cord signal changes can occur without atrophy and may precede clinical improvement by several months.⁵

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Competing interests None declared.

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Learning points

- Importance of spinal MRI in patients with new onset sensory ataxia.
- Include metabolic disturbances (eg, vitamin B₁₂, copper and vitamin E deficiencies) as potential causes of a myeloneuropathy.
- Consideration of nitrous oxide inhalation as a potential cause of vitamin B₁₂ deficiency.
- Prompt measurement of homocysteine levels and vitamin B₁₂ replacement in the event of reduced serum vitamin B₁₂ levels. Ensure appropriate thromboprophylaxis.

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