

Lessons of the month: Nitrous oxide-induced functional vitamin B₁₂ deficiency causing subacute combined degeneration of the spinal cord

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ABSTRACT

We discuss the case of a 22-year-old man who presented with paraesthesia, reduced sensation and weakness in his limbs. Examination was in keeping with a myeloneuropathy. Initial investigations including vitamin B₁₂ were unremarkable but magnetic resonance imaging of the spinal cord showed subacute combined degeneration. The patient reported heavy recreational use of nitrous oxide, which can cause functional deficiency of vitamin B₁₂ with neurological sequelae. A diagnosis of functional vitamin B₁₂ deficiency was made and confirmed by an elevated methylmalonic acid level. The patient received intramuscular hydroxocobalamin and made a good recovery following rehabilitation. Nitrous oxide use is prevalent and can have significant health effects. Many adverse effects are mediated through inactivation of vitamin B₁₂ and can be detected by elevated homocysteine and methylmalonic acid levels. Early identification and prompt treatment are important to support neurological recovery.

KEYWORDS: Nitrous oxide, functional vitamin B₁₂ deficiency, subacute combined degeneration, myelopathy, myeloneuropathy

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Case presentation

A 22-year-old man was referred by his general practitioner to the acute medical take due to a subacute history of neurological symptoms. He reported a 3-week history of paraesthesia affecting the extremities of his left upper and lower limbs. He subsequently developed weakness and reduced sensation in his left lower limb.

The patient had no past medical history of note. He was a non-smoker and rarely drank alcohol but reported substance misuse, namely nitrous oxide on a weekly basis, cocaine on alternate weeks, ketamine and various unidentified pills (presumed

amphetamine derivatives). He described a 3-year history of nitrous oxide use, which increased over the preceding 3 months, from approximately 120 to 288 canisters weekly.

On initial neurological examination by the admitting medical team, power was reduced in the left foot on both dorsiflexion and plantar flexion (4/5 as per Medical Research Council (MRC) grading). Sensation was intact.

Initial blood results showed normal haemoglobin, white cell count and mean corpuscular volume. Basic biochemistry, including urea and electrolytes, adjusted calcium, magnesium and phosphate, was unremarkable. Vitamin B₁₂ levels were 222 ng/L (normal range 180–910), with folate and thyroid-stimulating hormone also within the normal range.

The initial differential diagnosis was of a possible side effect of heavy nitrous oxide use but it was determined that a demyelinating process such as multiple sclerosis needed to be excluded. The acute medical team requested magnetic resonance imaging (MRI) of the brain and referred to neurology for inpatient review.

MRI of the brain was unremarkable. On day 3 of admission, the patient was transferred to a general medical ward, where the differential diagnosis was broadened to include transverse myelitis and mononeuritis multiplex. There was suspicion of functional vitamin B₁₂ deficiency caused by nitrous oxide use, so methylmalonic acid (MMA) and homocysteine levels were checked. HIV and syphilis serology were also tested; these came back negative.

Repeat neurological examination identified a slight spastic catch on supination of the right upper limb but otherwise normal tone. Limb power was normal (MRC 5/5) other than bilateral reduced power of ankle dorsiflexion, left (3/5) more than right (4/5). Reflexes were brisk in both upper limbs with Hoffmann's jerks. Lower limb reflexes were reduced and only manifested with reinforcement. Vibration and proprioception were absent distal to the ankle bilaterally. Romberg's sign was positive and gait was unsteady. The findings were in keeping with myeloneuropathy with possible subacute combined degeneration of the cord (SACD); the likeliest aetiology was functional vitamin B₁₂ deficiency caused by nitrous oxide use.

MRI of the whole spine (Fig 1) showed increased signal in the cervical dorsal columns, consistent with SACD. The patient was treated with intramuscular hydroxocobalamin injections to raise levels of active vitamin B₁₂.

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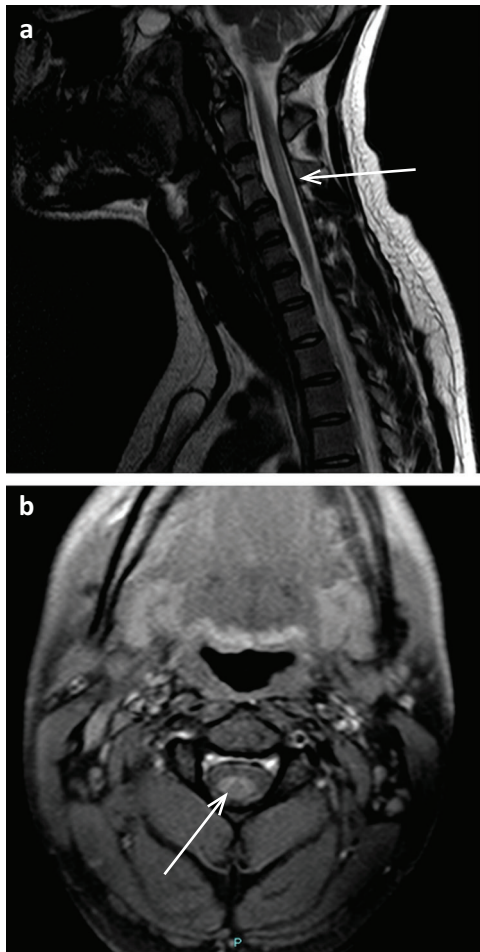


Fig 1. Magnetic resonance imaging of the spine demonstrating abnormal signal in the dorsal columns of the cervical spinal cord in keeping with subacute combined degeneration of the spinal cord.
a) T2-weighted sagittal view. b) T1-weighted fat-saturated axial view.

Over the next 5 days, the patient's neurological function recovered partially (5/5 power in lower limb flexors, 4/5 in lower limb extensors and reduced hand grip strength). He improved enough that he was successfully discharged home with ongoing rehabilitation in the community and neurology follow-up. He left hospital a week after admission and received monthly intramuscular hydroxocobalamin injections.

Following discharge, MMA levels returned significantly elevated at 3,003 nmol/L (reference range 0–280), confirming functional vitamin B₁₂ deficiency. Vitamin E and copper levels were normal. Homocysteine levels were requested but not performed due to laboratory error; they were not repeated as they were unlikely to alter patient management.

The patient was reviewed in the clinic 8 weeks following the original admission. Other than an intermittent abnormal buzzing sensation in his spine, his symptoms had resolved and he was regularly attending the gym. Proprioception was reduced in the right foot yet preserved at the ankle. Neurological examination was otherwise unremarkable. Intramuscular hydroxocobalamin injections were continued on a 3-monthly basis. The patient had followed advice to abstain from nitrous oxide use.

Discussion

Nitrous oxide (N₂O), colloquially called 'laughing gas', is an inhalant used medically for short-lasting procedural analgesia.¹ It acts as an N-methyl-D-aspartate antagonist with additional opioid receptor activity, leading to analgesic and euphoric effects; it has therefore been used recreationally for over 200 years.^{1–3} Aluminium N₂O canisters, the commonest recreational source, are colloquially known as 'whippits' from their intended use as a propellant in whipped cream.²

The sale or purchase of nitrous oxide for recreational use is illegal in the UK under the Psychoactive Substances Act 2016. The UK Home Office estimates prevalence of nitrous oxide use at 2.3% in England and Wales, with the highest prevalence (8.8%) in the 16–24 years age group.⁴ It has been estimated that 38.6% of people in the UK will use nitrous oxide in their lifetime.⁵ In the decade 2008–2017, nitrous oxide played a role in 28 deaths in England and Wales, though these were likely asphyxia-related.^{2,6}

Nitrous oxide causes adverse neurological effects such as neuropathy, myelopathy or SADC.^{1–3} These may present with paraesthesia, gait disturbance, unsteadiness or weakness.^{1,7} Heavy users are more prone to neurological sequelae.²

Nitrous oxide neurotoxicity is mediated through nitrous oxide binding to and inactivating cobalamin. This reduces cobalamin's effect as a cofactor in the conversion of homocysteine to methionine.³ The methionine metabolite S-adenosylmethionine is required for myelin synthesis and maintenance, so depletion causes neuropathy and myelopathy.⁷ In a separate metabolic pathway, B₁₂ is a cofactor in converting MMA to succinyl CoA; deficiency of active cobalamin leads to MMA accumulation and subsequent demyelination.^{3,7}

Most patients with nitrous oxide-induced neurological symptoms have low measured vitamin B₁₂ but 29.3% will have normal levels.¹ High levels of MMA and homocysteine can be used as a marker for functional B₁₂ deficiency if suspected, even when B₁₂ levels are normal.^{1,7}

Treatment consists of abstinence from nitrous oxide and replacement of vitamin B₁₂.^{2,7} Methionine supplementation has evidence of efficacy but use is hampered by limited supply.⁸ Despite treatment, neurological symptoms can take months to resolve and many patients report residual symptoms.^{2,5,7,8}

Summary

Nitrous oxide is commonly used by UK adults and can cause neurological complications. Patients may develop clinical features of vitamin B₁₂ deficiency with normal serum levels; elevated homocysteine and MMA levels can indicate functional vitamin B₁₂ deficiency. ■

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