Nitrous oxide myelopathy: a case series
Shilpan G Patel, Tony Zhang, Bernard Liem, Frederick Sundram, Richard H Roxburgh, P Alan Barber

ABSTRACT

AIMS: To describe the clinical features and outcomes of patients with myelopathy and neuropathy due to recreationally inhaled nitrous oxide.

METHODS: We identified patients presenting with nitrous oxide-associated myelopathy from an electronic database of all discharges in a large tertiary hospital between 2016 and 2023. Demographics, clinical features and the results of investigations were recorded. The primary outcome was modified Rankin Scale score (mRS) at least 3 months after hospital discharge where available.

RESULTS: There were 12 patients identified, six women, mean (SD) age 27.5 (5.1) years, range 19–47 years. The most common symptoms were numbness, weakness and mental state changes. Four patients used large amounts of inhaled nitrous oxide and also took over-the-counter vitamin B12 supplements. The median (range) hospital length of stay was 8.5 (2–56) days. Functional independence at last assessment (median [range] of 3 [1–34] months after discharge) was achieved in nine of the patients, with three requiring ongoing support for activities of daily living (mRS ≥3).

CONCLUSION: Nitrous oxide abuse and its neurological complications are an important public health issue. Clinicians should be aware that some patients who use large amounts of nitrous oxide may self-supplement vitamin B12.

The use of nitrous oxide (N₂O) for anaesthesia has been established for over 100 years. It is also sold as a dairy-cream whipping agent in 8g canisters which, for recreational purposes, are dispensed into balloons that are then inhaled. The consequent feelings of euphoria have led to it becoming a drug of abuse. Lifetime prevalence of recreational N₂O has been reported as high as 38% in the United Kingdom and 29% in the United States, with 17% of young people admitting to using it in the 2014–2016 Global Survey. There are concerns that the prevalence of N₂O abuse has been increasing. N₂O use has been associated with adverse effects, including neuropathy and myelopathy. In the Global Survey, 3% of regular users reported permanent sensory symptoms. The proposed mechanism of neurological damage is N₂O inactivation of vitamin B12 resulting in a functional deficiency of vitamin B12. This affects cellular structures such as myelin, which are dependent on B12-mediated cellular pathways. Low serum vitamin B12 indicates that a patient may be at risk for this deficiency. Importantly, it is the elevated serum methylmalonic acid (MMA) level that confirms the diagnosis of a functional B12 deficiency. MMA accumulates in the body when vitamin B12 is inactivated and unable to facilitate the conversion of methylmalonyl-CoA to succinyl-CoA in the Krebs cycle.

We present a case series of patients admitted to a tertiary hospital with N₂O-associated myelopathy. We aim to describe the demographic and clinical features of these patients and outcome on follow-up.

Methods

Patients admitted to our institution with N₂O myelopathy from 2016 to 2023 were identified from an electronic hospital discharge database. Our hospital provides neurology care for a regional population of 1.7 million people. Clinical data, investigation results and outcome data from community physiotherapy and occupational therapy assessments were extracted retrospectively. The dose of N₂O was determined from the self-reported number of cannisters inhaled, with the highest number of cannisters used in a single day in the month prior to presentation defined as the peak daily use. Patients were contacted either by telephone or seen in person after discharge and had a structured interview to assess ongoing symptoms and dependence using the modified Rankin Scale (mRS). The mRS is a 7-point scale, with 0 normal and 6 dead, with the primary outcome measure of functional independence defined as mRS 0, 1 or 2. An attempt was made to follow-up patients for at least 3 months or until asymptomatic; one patient was lost to follow-up before 3 months. We present the results
### Table 1: Summary of cases.

<table>
<thead>
<tr>
<th>#</th>
<th>Patient details and age range</th>
<th>Clinical presentation</th>
<th>Serum B12 (N: 170–800pmol/L)</th>
<th>MRI spine location of T2/FLAIR hyperintense lesions</th>
<th>Peak daily N₂O canister use in month prior to presentation</th>
<th>Length of hospital stay (days)</th>
<th>Follow-up duration (months)</th>
<th>Modified Rankin Scale at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26–30y Alcoholic gastritis.</td>
<td>LL weakness and paraesthesia</td>
<td>B₁₂ = 125 M₃₃A = 1.14</td>
<td>Cervical cord</td>
<td>10</td>
<td>7</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>31–35y</td>
<td>Cognitive impairment, auditory hallucinations, sensory ataxia</td>
<td>B₁₂ = 115 M₃₃A not done</td>
<td>Entire spinal cord</td>
<td>50</td>
<td>20</td>
<td>12</td>
<td>0</td>
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<tr>
<td>3</td>
<td>46–50y</td>
<td>Paraesthesia and sensory ataxia</td>
<td>B₁₂ = 247 M₃₃A = 0.93</td>
<td>Not done</td>
<td>Regular use, quantity not disclosed</td>
<td>3</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>21–25y PCOS on metformin</td>
<td>Apathy, sensory ataxia, quadriplegia, urinary retention</td>
<td>B₁₂ = 117 M₃₃A = 1.14</td>
<td>Cervical cord</td>
<td>Single session of 200 canisters</td>
<td>56</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>21–25y</td>
<td>Sensory ataxia</td>
<td>B₁₂ = 91 M₃₃A = 7.30</td>
<td>Cervical and thoracic cord</td>
<td>40</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>41–45y Taking oral B₁₂ replacement Alcohol dependence</td>
<td>Low mood, sensory ataxia</td>
<td>B₁₂ = 115 M₃₃A not done</td>
<td>Cervical cord</td>
<td>100</td>
<td>15</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 1 (continued): Summary of cases.

<table>
<thead>
<tr>
<th>#</th>
<th>Patient details and age range</th>
<th>Clinical presentation</th>
<th>Serum B12 (N: 170–800pmol/L) MMA (N: &lt;0.4umol/L)</th>
<th>MRI spine location of T2/FLAIR hyperintense lesions</th>
<th>Peak daily N₂O canister use in month prior to presentation</th>
<th>Length of hospital stay (days)</th>
<th>Follow-up duration (months)</th>
<th>Modified Rankin Scale at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>26–30y</td>
<td>Paraesthesias, Lhermitte’s and gait impairment</td>
<td>B12 = 98 MMA not done</td>
<td>Cervical and thoracic cord</td>
<td>Regular use, quantity not disclosed</td>
<td>10</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>16–20y</td>
<td>Gait impairment, numbness, paraesthesia and sensory ataxia</td>
<td>B12 = 168 MMA = 3.26</td>
<td>Cervical cord</td>
<td>200</td>
<td>4</td>
<td>3</td>
<td>2</td>
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<tr>
<td>9</td>
<td>21–25y</td>
<td>Poor concentration, LL numbness and weakness</td>
<td>B12 = 142 MMA = 2.75</td>
<td>Not done</td>
<td>100</td>
<td>7</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>21–25y</td>
<td>LL weakness, sensory ataxia, distal numbness and low mood</td>
<td>B12 &gt;1,470 MMA = 1.69</td>
<td>Cervical and lumbar cord</td>
<td>720</td>
<td>26</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>16–20y</td>
<td>LL weakness, sensory ataxia, distal numbness and low mood</td>
<td>B12 = 379 MMA = 0.47</td>
<td>Entire spinal cord</td>
<td>360</td>
<td>19</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>26–30y</td>
<td>UL parasthesiae</td>
<td>B12 = 234 MMA = 1.16</td>
<td>Entire spinal cord</td>
<td>100</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

LL = lower limb; UL = upper limb; MMA = methylmalonic acid; PCOS = polycystic ovarian syndrome.
of the last assessment for each patient.

The study had approval from a regional ethics committee (Ref AH26091). Patient 8 provided informed written consent for their MRI images to be published.

Patients were involved in the conduct of this research. They were asked during follow-up which measures of function were most important to them, and this helped to inform our outcome measures.

Results

There were 12 patients (six women, mean [SD] age 27.5 [5.1] years, range 19–47 years) with N₂O-induced myelopathy identified (Table 1). Of the 12 patients, five had Chinese, four European and three Polynesian ethnic backgrounds. All 12 patients presented with spinal posterior column involvement (impaired light touch, vibration and joint position sensation in the lower limbs), and 11 patients had a sensory ataxia. Pain and temperature sensation was impaired in three patients. Numbness conformed to a glove-and-stocking distribution. Five patients reported lower limb weakness, one of whom also had upper limb weakness. Five patients reported changes in mental state, including three with poor concentration, one with impaired cognition confirmed on cognitive testing and one who presented with psychosis. The median (range) hospital length of stay was 8.5 (2–56) days. The most severely affected person (patient 4) presented with quadriparesis, had risk factors for a vitamin B12 deficiency and had used 200 canisters of N₂O in a single day for the first time in their lifetime.

All patients had laboratory evidence of low serum vitamin B12 or elevated MMA. Four patients had been self-supplementing vitamin B12 prior to presentation. Ten patients had MRI of the spine, and all had T2 FLAIR hyperintense lesions in the dorsal columns of the cervical cord. Two also had involvement of the thoracic cord, one the cervical and lumbar cord, and three had involvement of the whole spinal cord (Figure 1).

Use of N₂O varied between patients with the median (range) use of 100 (10–720) N₂O canisters per day in the month prior to presentation. We were unable to determine a relationship between N₂O peak usage and severity of clinical presentation, which was complicated by two factors. Firstly, four patients had been self-supplementing vitamin B12. Secondly, two patients had other risk factors for vitamin B12 deficiency; one with alcoholic gastritis, and another with polycystic ovarian syndrome being treated with metformin and a calorie-restricted diet.

All patients were offered counselling support and ceased N₂O use. All were treated with at least 2 weeks of vitamin B12 at a dose of 1mg intra-muscularly on alternate days, and rehabilitation where this was required.

Eleven patients were followed-up after discharge for at least 3 months (median [range],

Figure 1: Magnetic resonance imaging (1.5T) of the cervical spine: A) sagittal T2 demonstrating signal hyperintensities predominantly in the upper cervical cord; B) corresponding axial T2 demonstrating signal hyperintensities affecting the dorsal columns.
3 [1–34] months). Functional independence (mRS <3) was achieved at last assessment in nine of the patients, with three requiring ongoing support for activities of daily living at last follow-up (however, one of these three patients was lost to follow-up at 1 month after discharge). Mental state changes resolved rapidly within 1 to 2 weeks following treatment. Weakness resolved within the first 2 to 4 weeks following treatment. Sensory ataxia often improved within the first 3 to 6 months following treatment.

Discussion

This case series highlights the dangers of inhaled N\textsubscript{2}O, with patients presenting with cognitive, psychiatric and neurological impairment. Most patients were using large quantities of N\textsubscript{2}O on a regular basis; the two patients who had used smaller quantities had risk factors for vitamin B12 deficiency. All of the patients had clinical and imaging involvement of the spinal dorsal columns consistent with previous reports,\textsuperscript{7–9} and three had imaging changes extending down the whole spinal cord. Seven of the patients continued to have symptoms at their last follow-up assessment and three required ongoing support for activities of daily living. The prevalent recreational use of N\textsubscript{2}O underscores the need to improve education and restrict access to this drug.

Knowledge about the risks of N\textsubscript{2}O use has been reported as being poor among the general population.\textsuperscript{4} However, four of our cohort who were using large quantities of N\textsubscript{2}O with a peak daily use of more than 100 canisters per day were aware of the potential dangers and were taking over-the-counter vitamin B12. It suggests that patients who self-supplement vitamin B12 may tolerate very large quantities of N\textsubscript{2}O before experiencing symptoms. We have not seen this described previously. Importantly, such supplementation was not sufficient to prevent their developing myelopathy and may falsely reassure patients and clinicians. These patients require a harm reduction approach to management with addiction counselling and psychological support. In patients who continue to use N\textsubscript{2}O, vitamin B12 supplementation may be indicated as part of a harm reduction strategy.

There are limited reports on recovery following treatment of N\textsubscript{2}O myelopathy, with assessments limited to 2 months or less.\textsuperscript{4,7,10–12} Our patients were followed for a median of 3 months after hospital discharge. Mental state changes, weakness and sensory symptoms improved within the first 6 months of follow-up.

Where possible, we recommend public health interventions to discourage people from using N\textsubscript{2}O recreationally. However, N\textsubscript{2}O remains accessible to the general public, where large quantities can be purchased legally online. Restricting sales from commercial vendors, including limiting the number of cannisters sold to only those required for non-recreational day-to-day use, and the provision of education about the potential adverse effects of N\textsubscript{2}O may help reduce harm.

This report has a number of limitations. This is a single-centre report and there are likely other presentations to hospitals outside of our district that have not been captured. Additionally, some patients may not have had their condition accurately documented in their electronic clinical record. We were not able to identify patients with milder symptoms who did not present to hospital.

Recreational nitrous oxide abuse can cause a myelopathy and cognitive changes, leading to young people presenting with significant psychiatric and neurological disturbance with incomplete recovery. This case series highlights the importance of early identification, prompt treatment and support from addiction and psychological services to discontinue N\textsubscript{2}O use to improve long-term outcomes. Clinicians should be aware that some young people may self-supplement vitamin B12; however, this did not prevent presentation with myelopathy.
COMPETING INTERESTS
The authors have no conflicts of interest to declare.

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