CASE REPORT

# Subacute combined degeneration of the spinal cord following recreational nitrous oxide use

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## SUMMARY

We describe a case of a young woman who developed myelopathy and peripheral neuropathy following 1 year of recreational nitrous oxide ($N_2O$) use. She presented with uncomfortable tingling sensation in her feet and poor balance. Physical examination revealed mild weakness and hyper-reflexia in the lower limbs. Proprioception and vibration were absent in the lower limbs. Pinprick and light touch sensations were reduced below the sixth thoracic dermatome. A broad-based gait and a positive Romberg sign were noted. The level of vitamin $B_{12}$ was low (76 pmol/l). T2-weighted MRI scans showed hyperintensity changes at the posterior column from the second to the fifth cervical vertebrae. She made a full recovery following injections of vitamin $B_{12}$ and physiotherapy. This case discusses subacute combined degeneration of the spinal cord on a background of $N_2O$ abuse.

## BACKGROUND

Subacute combined degeneration of the spinal cord is a well-documented complication of vitamin $B_{12}$ deficiency. However, nitrous oxide ($N_2O$) toxicity as an aetiology of the condition is not well known. Recreational $N_2O$ use is prevalent among young people. This case highlights a potential rare complication of $N_2O$ toxicity and the importance of the consideration of $N_2O$ toxicity-induced subacute combined degeneration of the spinal cord as a possible diagnosis of a young patient with undifferentiated neurological symptoms.

## CASE PRESENTATION

A 22-year-old woman with no significant medical history presented with a gradual worsening of uncomfortable tingling sensation in her feet over 8 weeks and a 3-day history of poor balance. Upon further questioning, her social history was remarkable for recreational $N_2O$ bulb use. These are available at supermarkets for use in a dispenser for making whipped cream. First exposure was 1 year ago and since then she has been abusing $N_2O$ intermittently until approximately 2 months ago when she regularly used $N_2O$ approximately three times weekly with 60 bulbs per session. The patient reports good dietary intake and social alcohol use of no more than two standard drinks a day on average. There was no history of illicit drug use.

Upon examination, the patient was alert and oriented. Repeated voluntary movements of lower limbs were noted which patient reported improved paraesthesia. Cranial nerve and upper-limb neurological examinations were unremarkable. Lower-limb neurological examination revealed mild weakness (4-/5) and hyper-reflexia. Proprioception and vibration sensations were absent over the lower limbs. Pinprick and light touch sensations were reduced from below the sixth thoracic dermatome. A broad-based gait, positive Romberg and Lhermitte's signs were noted. Funduscopy revealed no optic atrophy.

## INVESTIGATIONS

Blood tests show a low serum vitamin $B_{12}$ level of 76 pmol/l (140–770 pmol/l). Anaemia was not detected and mean corpuscular volume was within the normal range. Methylmalonic acid level was raised at 0.92 (<0.35 μmol/l). Blood sugar level, thyroid function test, serum folate, copper and ceruloplasmin levels were normal. Antibodies to syphilis, Epstein-Barr virus, cytomegalovirus and HIV were negative. Intrinsic factor and parietal cell autoantibodies were absent. Swabs taken for gonorrhoea and chlamydia were all negative. T2-weighted MRI scans of the spinal cord showed subtle hyperintensity changes at the posterior column from the second to the fourth cervical vertebrae.

Cerebrospinal fluid analysis was not performed in this case because of the subacute presentation and a lack of risk factors for infectious causes.

## DIFFERENTIAL DIAGNOSIS

The clinical presentation is of symmetric subacute parasethesia, loss of propioception and progressive ataxic weakness that indicates posterior and lateral columns' involvement. Differential diagnoses such as infectious (HIV-1 associated myelopathy, neurosyphilis), autoimmune (autoimmune myelopathy, Guillain-Barré syndrome), demyelinating (multiple sclerosis), nutritional (vitamin $B_{12}$, copper deficiency) and neoplastic (paraneoplastic syndrome) disorders should be considered.

With investigations showing vitamin $B_{12}$ deficiency and posterior column changes on MRI, subacute combined degeneration of the spinal cord was most likely. Common causes of vitamin $B_{12}$ deficiency including pernicious anaemia, acquired malabsorption and malnutrition were ruled out with patient history and blood tests. The diagnosis of subacute combined degeneration of the spinal cord as a complication of $N_2O$ toxicity was made.

## TREATMENT

The patient was admitted to the hospital under neurology for daily vitamin $B_{12}$ injections (1000 μg/day) and physiotherapy.

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## OUTCOME AND FOLLOW-UP

She gradually improved and was discharged on day 13 with weekly injections of vitamin $B_{12}$ (1000 μg/week) for 4 weeks. She was lost to follow-up postdischarge and repeat MRI could not be performed. She was reviewed incidentally at 18 months postdischarge and noted to be well and free of any disabling neurological symptoms.

## DISCUSSION

$N_2O$ is an inhalational anaesthetic agent commonly used in dentistry. Industrial applications include its uses as a food aerosol propellant and an engine accelerant.

$N_2O$ exerts its harmful effects by irreversibly oxidising the cobalt ion of cobalamin (vitamin $B_{12}$). Oxidation of the cobalt ion by $N_2O$ inhibits methylcobalamin as a cofactor of methionine synthase in the production of methionine and subsequently *S*-adenosylmethionine, which is necessary for methylation of myelin sheath phospholipids.[1 2] The result is demyelination of the nervous system involving the spinal cord and sometimes peripheral neuropathy and optic atrophy.[3] Thus, $N_2O$ induces subacute combined degeneration through inactivation of the vitamin $B_{12}$ metabolism. Pathological changes occur initially in the lower cervical and upper thoracic segments of the spinal cord which appear as high-signal lesions on T2-weighted MRI scans because of increased water content secondary to oedema.[4 5] Clinically, patients with subacute combined degeneration may present with a subacute onset of paraparesis and impaired sensation and proprioception. The clinical diagnosis could be confirmed by an abnormal signal on MRI of the spinal cord, low-serum vitamin $B_{12}$ levels and slowing of motor conduction velocities in peripheral nerve conduction studies. However, the findings of these tests could sometimes be normal.[6] Measurement of methylmalonic acid levels can be employed to make the diagnosis in the presence of normal or low-normal vitamin $B_{12}$ level.[7]

Abuse of $N_2O$ has been previously reported in the literature among healthcare workers, such as dentists, as well as young adults who use the drug more frequently.[4 5] Despite its purportedly high-rate of usage, serious side-effects as a result of its abuse remain uncommon, with less than 20 cases reported in the literature.[8–18] $N_2O$ use occurs among the younger population, with men more likely to have experimented with the drug and also more likely to present with neurological symptoms.[15] The usual amount of $N_2O$ bulbs inhaled in a session is usually <5, but the average of bulbs inhaled among reported cases ranges from 10–20 to >100.[8–18] This suggests that $N_2O$ use alone is unlikely to result in serious neurology among most young, healthy adults, but when used in excess of 10 bulbs/day, the risk of permanent neurological deficits, including ataxic paraplegia, increases exponentially. Among the reported cases, there appears to be a correlation between the amount of use and extent of symptoms although significant symptoms can occur with moderate use.[8–18]

Removal of the offending agent and vitamin $B_{12}$ replacement appear to be an effective treatment. Whether the patient makes a partial or full recovery depends on the degree of the neuropathological damage to the spinal cord.[18] The absence of sensory deficits and Romberg and Babinski signs were associated with a higher full recovery rate.[18] In cases where symptoms persist methionine treatment has been successful where vitamin $B_{12}$ treatment alone has failed.[1 2]

The incidence of $N_2O$-induced neurotoxicity is underestimated and should be recognised as an important cause of subacute combined degeneration of the spinal cord especially in young patients presenting with undifferentiated neurological symptoms considering serious complications such as irreversible paralysis and cardiac arrest can occur, if not detected early.[11]

### Learning points

- Nitrous oxide ($N_2O$) abuse is not uncommon among young people.
- $N_2O$ toxicity-induced subacute combined degeneration of the spinal cord should be considered as a possible diagnosis in a young patient with undifferentiated neurological symptoms.
- Usage of more than 10 $N_2O$ bulbs/day has a potential to result in significant neurological complications.
- Measurement of methylmalonic acid levels can be employed to make the diagnosis in the presence of normal or low-normal vitamin $B_{12}$ level.

**Competing interests** None.

**Patient consent** Obtained.

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