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CASE REPORT

# Nitrous Oxide induced neuropathy correlated with MRI imaging

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The neurotoxic effects of Nitrous Oxide ($N_2O$), a recreational drug also known as laughing gas, are well known. Despite its declining use in medical settings due to side effects, $N_2O$ abuse is on the rise, particularly among young people. Amongst the most serious side effects is neurotoxicity, caused by a reduction in the bioavailability of vitamin B12.

We report the case of a 27-year-old male who, after heavy recreational use of $N_2O$, presented to the emergency department, complaining of bilateral paraesthesia in his arms and legs, leading to their hospitalisation. A blood test was performed, finding decreased vitamin B12 levels. An electromyography found a decreased conduction speed of the left sural nerve and an MRI revealed hyperintense zones in the dorsal column of the cervical spinal cord, compatible with $N_2O$ toxicity. The patient's vitamin B12 deficiency was corrected, and they received physical therapy as an inpatient, before continuing to receive outpatient treatment once they were able to use a walking frame.

The neurotoxicity of $N_2O$ is linked to the induction of vitamin B12 deficiency, which can lead to demyelination. This diagnosis can be made despite the presence of normal serum vitamin B12 levels, probably due to a reduction in cellular bioavailability. Homocysteine levels may be elevated in $N_2O$ toxicity, providing a crucial diagnostic clue. Treatment is based on reversing the vitamin B12 deficiency, but no consistent regimen has been established. The prognosis varies but may be improved by prompt treatment with vitamin B12.

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Nitrous oxide ($N_2O$) gas, commonly known as laughing gas, has long been used as an anaesthetic in medical settings.[1–3] However, its use is declining due to its known side effects which include neurotoxicity resulting from reduced vitamin B12 bioavailability in cases of abuse.[1,2] Recently, there has been a reported rise, particularly amongst young people, in the abuse of this substance with the lifetime prevalence in the UK being around 38.6%, being the thirteenth most used recreational drug according to the Global Drug survey of 2021.[4–6] When inhaled, $N_2O$ creates a sense of euphoria, but can also cause dizziness, slurred speech, drowsiness and can even cause loss of consciousness in some cases.[2,7] Although most use the drug infrequently, with little harm ensuing, there appears to a subset of users that use it significantly more often and may develop dependency.[5] Symptoms of nitrous oxide abuse have been reported as mainly neurological, with subacute combined spinal cord degeneration, likely linked to the decrease in bioavailable vitamin B12.[8]

## CASE REPORT

A twenty-seven-year-old male presented to the emergency department complaining of bilateral paraesthesia in their arms and legs which had been developing over the past two weeks, without any history of recent trauma. The patient's daily treatment was 20mg of methylphenidate and two 500mg pills of diosmin (450mg) and hesperidin (50mg). The neurological exam showed decreased tactile and pain sensitivity in the legs and feet, with the patient being unable to stand. The patient exhibited dysmetria when asked to perform a finger-to-nose test, attributed to a lack of strength. The rest of the physical exam was normal. The physician requested a cervical spine CT-exam to exclude a disc hernia. The patient was then seen by a neurologist, to whom he admitted having heavy recreational use of $N_2O$, having consumed multiple balloons, filled with $N_2O$ from small canisters, two weeks prior. A blood test was performed, revealing vitamin B12 < 150ng/L, a slightly increased white blood cell count (11 000/ $mm^3$), increased fibrinogen (472mg/dl), increased direct bilirubin (0,3 mg/dl) and GPT (44 U/L) and a slightly increased CRP (12.8mg/L) The rest of the blood test was normal. The patient promptly hospitalised and seen by a neurologist, whom, suspecting $N_2O$ toxicity, requested a CSF analysis, an electromyography and an MRI.

The electromyography exam revealed a decreased conduction speed of the left sural nerve. The CFS analysis was normal.

The patient was treated with 1mg of vitamin B12 per day via intramuscular injection (IM) on the 3rd day after admission. This regiment continued for one week, followed by 1mg IM per week thereafter.

The MRI revealed hyperintense zones in the dorsal column of the cervical spinal cord from C2 to C6 in T2-weighted sequences (Figure 1 and Figure 2).

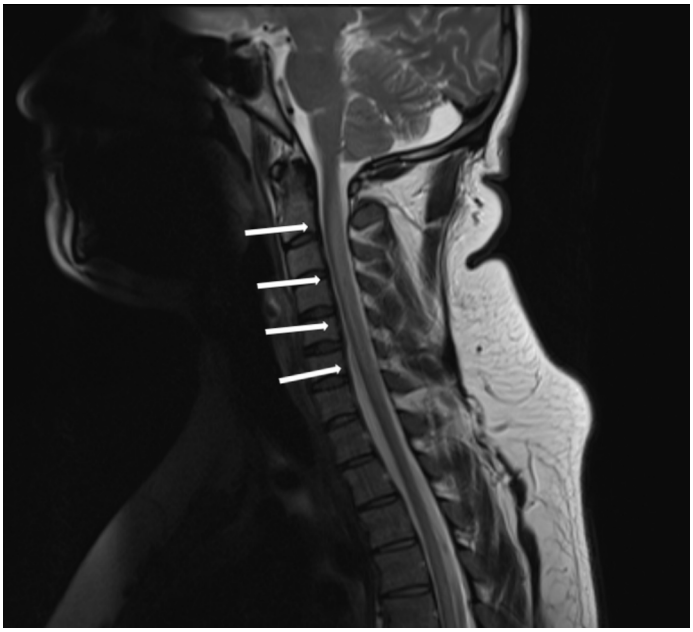

**Figure 1** *Sagittal T2-weighted image of the cervical spine showing a hyperintense signal from C2 to C6 within the spinal cord (arrows)*

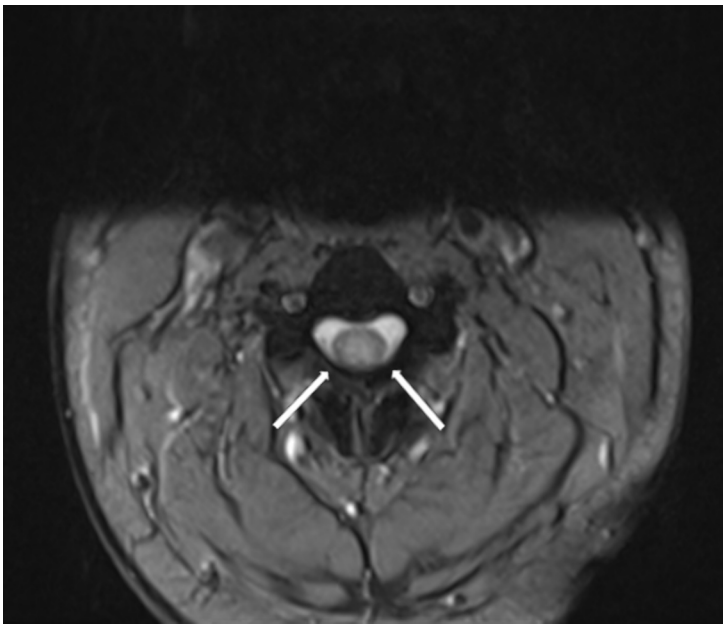

**Figure 2** *Axial T2-weighted image of the cervical spine showing a hyperintense signal (arrows) within the dorsal column of the spinal cord*

Further T1-weighted imaging, with and without gadolinium, did not show any anomalies or enhancement (Figure 3 and Figure 4). This exam was deemed compatible with $N_2O$ toxicity.

The patient's clinical evolution was positive; quickly regaining some of his strength. A follow up blood test performed 8 days later showed vitamin B12 levels above the norm due to the treatment. Following this, the patient underwent 2 months of intensive physical therapy as an inpatient. During this time, he regained much of his strength, being able to walk without support between parallel bars, though requiring a walking frame to move around. However, he continued to exhibit limited ataxia and required help to get up if he fell. He was discharged after 2 months to an outpatient clinic to continue his treatment once he was able to move using a walking frame. After 4 months he regained of the ability to walk at a pace of 5km/h for 20 minutes and use a stationary bicycle for the equivalent distance of 10km. He showed marked strength improvement, however he remained ataxic and had difficulty maintaining balance. At six months the patient continued to have difficulty maintaining balance and had not yet regained the ability to run.

## DISCUSSION

Nitrous oxide abuse is a growing problem, with an increased prevalence amongst teenagers and young adults.[9] The gas is often inhaled from the balloons.[9] Other methods of administration include direct inhalation from the canister, connecting the canister to a face mask or releasing it into a bag which is then placed over the head of the user.[9]

Nitrous oxide toxicity can result in subacute combined degeneration of the dorsal and lateral spinal columns as well as the spinocerebellar tract.[2,10] The symptoms include paraesthesia, which our patient presented with, and sensory ataxia which can be associated with loss of proprioception.[2,7,10] Symptoms can progress to spasticity, clonus, muscle weakness, paraplegia, and faecal and urinary incontinence.[7,10] Further features of the disease can be peripheral axonal degeneration as well as central nervous symptoms such as Lhermitte phenomenon.[7,10]

The MRI features of this condition are T2-signal hyperintensity of the posterior, and sometimes lateral column, of the spinal cord.[8,10] Cases of mild contrast-enhancement of the lesions have also been described.[8] However, some cases exist where there are no visible MRI abnormalities.[8]

There are many purported mechanisms for the neurotoxicity of $N_2O$ involving the induction of vitamin B12 deficiency, classically defined as a serum level under 200pg/ml.[2] One theory is the $N_2O$ affects vitamin-B12 by permanently oxidising cobalt ions and making the vitamin non-functional without decreasing the concentration itself.[2,8] Vitamin B12 is an essential co-factor in turning homocysteine into methionine, which is necessary for the methylation of myelin, and methylmalonic acid.[2,8] In this way, $N_2O$ toxicity can result in demyelination.[8] One should note that due to

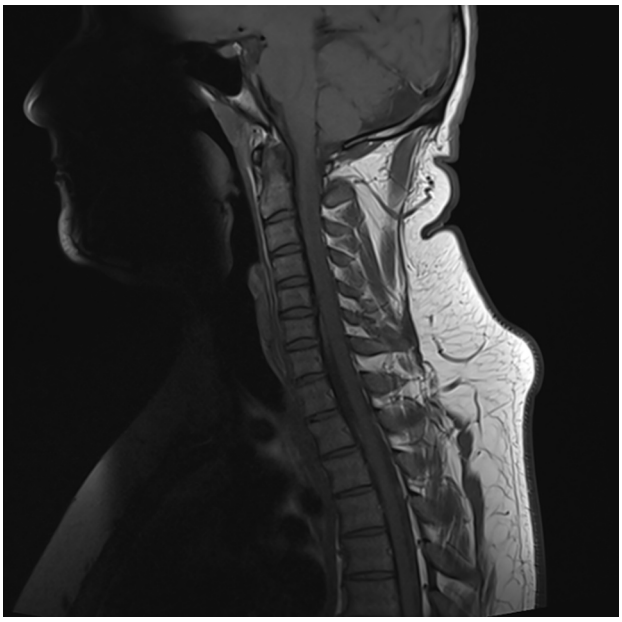

**Figure 3** *SSagittal T1-weighted image of the cervical spine showing no hyper or hypointense areas within the spinal cord*

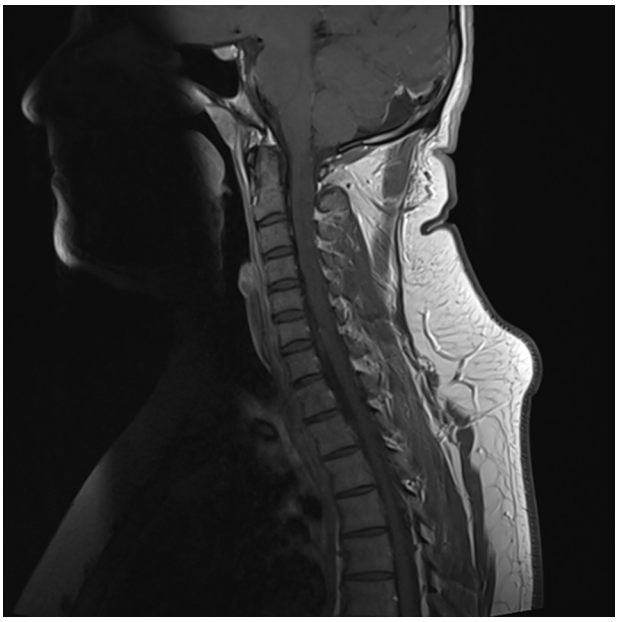

**Figure 4** *Sagittal T1-weighted contrast-enhanced image of the cervical spine showing no zones of focal enhancement*

the method of action of $N_2O$, vitamin B12 levels may appear normal, which could be due a disruption of vitamin B12 availability at the cellular level.[2,8] For this reason, one should also test homocysteine levels, as these may be elevated in $N_2O$ toxicity and provide an essential clue for the diagnosis.[8]

The treatment of nitrous oxide toxicity is based on reversing the vitamin B12 deficiency, with no consistent treatment regimen being apparent amongst the various case reports.[8] The prognosis is variable, but seems to depend upon prompt treatment, with intramuscular vitamin B12 seeming to be associated with better outcomes than oral supplementation.[8] Importantly, this treatment must be accompanied by folate supplementation to avoid the methyl folate trap[11]. To our knowledge, no guidelines exist for the required length of the treatment.

## CONCLUSION

Nitrous oxide is a commonly used recreational drug which can occasionally present with severe neurological side effects. Patients presenting with bizarre neurological symptoms that are clinically compatible with $N_2O$ toxicity, abuse of the substance should be suspected.

MRI features typically include spinal cord T2 hyperintensities centred on the posterior and lateral columns, though these may be absent in some cases. Patients should undergo a blood test for vitamin B12 levels, which may also be normal, and homocysteine levels, which should be increased in cases of $N_2O$ toxicity.

Once the diagnosis of $N_2O$ toxicity is established, prompt vitamin B12 administration, alongside folate supplementation, is required. However, even with rapid diagnosis and treatment, a positive prognosis for the patient is not guaranteed.

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