Nitrous Oxide misuse and Vitamin B12 deficiency

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Summary

A 36-year-old male presented to hospital with a five-week history of ascending limb paraesthesiae and balance difficulties. There was no past medical history of note, no recent foreign travel but admitted habitual nitrous oxide (N_2O) 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 imaging 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 nitrous oxide 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 as a recreational drug, and to highlight use of this drug as a potential cause for a myeloneuropathy. The consequences of repeated nitrous oxide inhalation are increasingly being seen during acute medical admissions, and recognising its potential neurological sequelae are important in obtaining a relevant history and reaching a clinical diagnosis. Nitrous oxide also impacts homocysteine metabolism (Figure 1), increasing haematological coagulability and potentially increasingly the risk of venous thrombosis. This too is important to recognise, ensuring that all patients receive adequate anticoagulant prophylactic therapy.

Case Presentation

A 36-year-old male was hospitalised after becoming unable to stand after five weeks of ascending limb paraesthesiae and progressive balance difficulties. His past medical history

was unremarkable. He denied recent foreign travel or alcohol ingestion but admitted to habitual nitrous oxide (N_20) inhalation from 'whippits'. 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.

Investigation

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 (MCV 100 fl). Subsequent investigations revealed raised serum homocysteine concentration (188.3 µmol/l; normal range <16 µmol/l) but negative anti-intrinsic factor, anti-parietal cell, and anti-TTG antibodies. Cerebrospinal fluid was acellular with normal constituents. Neurophysiological studies identified a mixed demyelinating and axonal sensorimotor neuropathy. T2-weighted MR images of the spinal cord are shown (Figures 2 and 3).

Differential Diagnosis

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

Treatment

He was treated with intramuscular B12 replacement (6 x 1 mg over two weeks, then maintenance) and intensive physiotherapy, and advised to stop inhaling nitrous oxide.

Outcome and Follow-up

On discharge at four weeks he was mobilising short distances using a zimmer frame; at twelve weeks he was mobilising independently. Repeat cord MRI at this time demonstrated significant improvement (Figures 4 and 5).

Discussion

Nitrous oxide 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 nitrous oxide used in whipped cream dispensers; Figure 6). Despite public perception, nitrous oxide 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), 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 nitrous oxide 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]

Learning Points

- Importance of spinal MRI imaging in patients with new onset sensory ataxia
- To include metabolic disturbance (e.g. vitamin B12, copper and vitamin E deficiencies) as potential causes of a spinal 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

References

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Figure Legend

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

Figures 2 and 3: T2-weighted MRI images of cervical and thoracic cord pre-treatment demonstrating increased signal extending C1 to T11 (more marked in the cervical region), in keeping with a longitudinal myelitis.

Figures 4 and 5: T2-weighted MRI images of cervical and thoracic spine post-treatment. These demonstrate an improvement to the cervical cord with a reduction in overall diameter, although some signal increase persists.

Figure 6: Photographic example of used ‘whippit’ canisters.