Case report

Myeloneuropathy caused by nitrous oxide toxicity

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Introduction

Nitrous oxide (N_2O) is a nonflammable gas with a sweet taste and odor which was first synthesized by English natural philosopher and chemist Joseph Priestley in 1772. It is used as an inhaled anesthetic and analgesic agent in medicine and dentistry. It is also used as a propellant in food industry (eg. in the whipped cream dispensers), nitrating agent for alkali metals and as a component in rocket fuel[1]. Abuse of nitrous oxide might cause significant neurological disability. The mechanism of N_2O neurotoxicity is the interference with vitamin B_{12} bioavailability and the resulting neurological syndromes are indistinguishable from vitamin B_{12} deficiency due to malabsorption or low dietary intake. We present a case of a young male who presented to a tertiary care center in London, United Kingdom with clinical, radiological and biochemical features of N_2O abuse.

Case report

A 26-year-old Afro Caribbean male presented with two week history of paraesthesiae – 'pins and needles' affecting both his lower limbs. He had been previously well without any medical comorbidities and paraesthesia started from soles of both legs two weeks prior to the admission which gradually progressed to up to knees. Two days before the admission his hands got involved. There were no pain, weakness or bladder / bowel involvement. Interestingly he was experiencing electric shock like sensation travelling through his limbs on bending of the neck for uncertain duration. Symptoms such as visual loss, double vision, vertigo, slurred speech or difficulty in swallowing were absent. Apart from that there were no joint pain, swelling, rashes or photosensitivity. He did not recall any recent chest infection or diarrhoeal illness. Family members were free of any neurological disorders. He worked as a customer care officer in a private establishment and had been using alcohol infrequently. He denied any substance or recreational drug abuse.

Neurological examination revealed normal mental state, speech and cranial nerves. Muscle power in limbs were normal. On sensory examination pain, joint position and vibration position was absent upto ankle joint. He had global hyporeflexia and plantar responses were flexor. However Romberg's test was negative. He was able to walk unaided but the gait was unsteady.

Initial haematological and biochemical parameters were within normal range including full blood count (FBC), inflammatory markers, random blood sugar, HbA1c, renal profile, liver profile and thyroid profile. However his vitamin B_{12} was marginally low (167 ng / L (180 – 1100)) with raised methylmalonic acid – 3800 nmol / L (0 – 280 nmol / L) and homocysteine -26.4 mic.mol / L (< 15 mic.mol /L). Magnetic resonance imaging (MRI) of spine demonstrated T2 signal hyperintensity extending from C1 to T2 vertebral segments (Figure 1). They were more prominent on posterior part of the cord on axial views (Figure 2). There was no cord swelling or enhancement with gadolinium. MRI brain was normal. Lumbar puncture had normal manometry and cerebrospinal fluid (CSF) analysis showed normal proteins, glucose and no cellular reaction. Nerve conduction studies (NCS) demonstrated moderately severe axonal type sensory neuropathy without any significant motor axon loss. He had a normal serum copper, negative autoantibodies (Anti-Nuclear Antibodies (ANA), Anti Neutrophil Cytoplasmic Antibodies (ANCA), antibodies to Extractable Nuclear Antigens (ENA), Anti Parietal Cell Antibodies, Anti Tissue Transglutaminase Antibodies and was negative for HIV, syphilis and hepatitis serology.

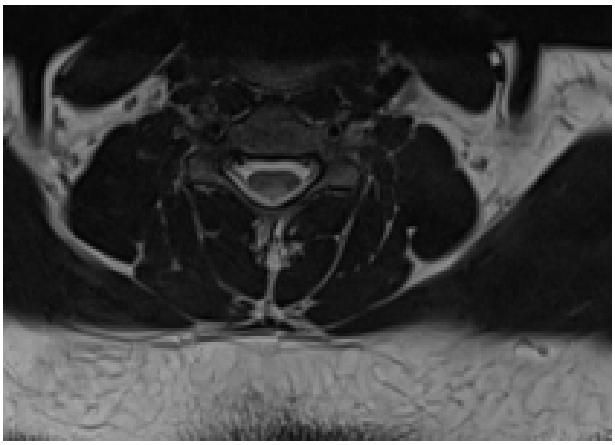

Figure 1. MRI Spine (Sagittal section). T2 hyperintensities extending from C1 to T2 vertebral segments.

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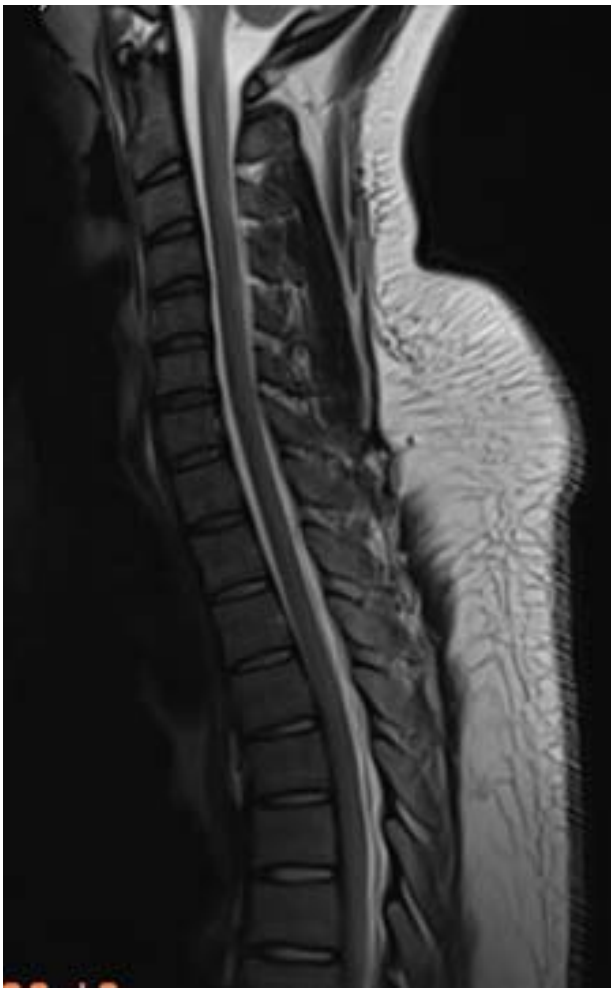

Figure 2. MRI Spine (Axial section). T2 hyperintensities mostly affecting posterior columns of spinal cord.

During hospital stay his symptoms progressed with numbness extending upto buttocks and inguinal region, loss of vibration upto knee and development of faecal incontinence and urinary urgency. Once the vitamin B_{12} deficiency was confirmed, he was started on intramuscular vitamin B_{12} replacement. At this stage he revealed the fact that he had been abusing nitrous oxide (N_2O) every weekend for 2 years. This varied from 2 to 200 canisters per weekend. Finally the diagnosis of myeloneuropathy secondary to nitrous oxide toxicity was made.

Discussion

Nitrous oxide (N_2O) is also known as "laughing gas" due to the euphoric effects of inhaling it, a property that has led to its recreational use as a dissociative anaesthetic since 1800s. Even though N_2O abuse is uncommon in Sri Lanka, it is not the case in western countries. Its misuse was previously largely restricted to and widespread among medical professionals (a survey in 1979 reported that 20% of medical and dental students used it recreationally). However for the last two to three decades it has gained popularity in clubs, parties and music festivals. The 2012 Global Drug Survey – an international online survey of drug use in mainly young adults with over 22000 respondents – reported that almost half of UK respondents had used nitrous oxide recreationally at some point. This is in large part due to its free availability in nightclubs and low cost in the form of 'whippits' (aerosol chamber used in canisters of whipped cream). As reported by Advisory Council on the Misuse of Drugs (ACMD) in the UK, the most common method of inhalation among 2014 users was from a balloon (94%), followed by whipped cream dispensers (5%)[2].

The toxic effects of nitrous oxide are mediated through oxidation of cobalt ions in vitamin B_{12} making it inactive – impaired vitamin B_{12} bioavailability[3]. This inhibits the conversion of homocysteine to methionine, which is needed for methylation of myelin proteins, causing demyelination of central and peripheral nervous system. This reaction is necessary for the production of tetrahydrofolate (which is essential for DNA synthesis) as well. Apart from that vitamin B_{12} is necessary for the conversion of methylmalonyl CoA to succinyl CoA. Because of these two vitamin B_{12} dependent pathways, impaired metabolism of that causes elevation of methylmalonic acid and homocysteine. Resulting neurological syndromes (subacute combined degeneration of cord, peripheral neuropathy, cognitive decline, optic atrophy and psychiatric manifestations such as depression and anxiety) are indistinguishable from B_{12} deficiency caused by malabsorption or low dietary intake[3]. Diagnosing nitrous oxide induced neurological disease may be difficult if the patient does not disclose inhalational activity or the examiner fails to inquire about it. Elevated serum concentrations of Methylmalonic Acid (MMA) or Homocysteine may be the only clues as vitamin B_{12} can be normal. There is no correlation between haematological (megaloblastic anaemia, elevated mean corpuscular volume (MCV)) and neurological features.

Our patient presented with clinical features compatible with subacute peripheral neuropathy (glove and stocking type sensory symptoms and signs, hyporeflexia). Apart from that he had evidence of myelopathy – positive Lhermitte's and sphincter disturbance. This was confirmed by nerve conduction studies (NCS) and MRI of spine which demonstrated axonal type sensory neuropathy and T2 high signal intensities extending throughout the cervical cord (features compatible with subacute combined

degeneration of cord) respectively. Vitamin B_{12} levels were reduced and the homocysteine and methylmalonic acid levels were raised pointing towards abnormality in vitamin B_{12} metabolism. Initially he didn't disclose his inhalational activity which made some delays in definitive diagnosis.

In the literature there are numerous case reports of myeloneuropathy caused by N_2O abuse or occupational exposure (as that is used as anaesthetic agent and analgesic in medicine and dentistry). One of the first cases was of a patient inhaling whipped cream propellant although the authors did not associate N_2O toxicity with disturbed vitamin B_{12} metabolism[4]. Treatment of nitrous oxide induced neurotoxicity is abstaining from the exposure and high dose vitamin B_{12} replacement. There is limited evidence that replacing methionine also helps[2,5]. Methylmalonic acid and homocysteine levels return to normal after starting vitamin B_{12} replacement. Recovery may be slow and incomplete – depending on the extent of damage. This case highlights an important cause of potentially avoidable cause of neurological disability.

Competing Interests

The authors declare that they have no competing interests.

References

1. Van Amsterdam J, Nabben T, van den Brink W. Recreational nitrous oxide: Prevalence and risks. *Regulatory Toxicology and Pharmacology* 2015. http://dx.doi.org/10.1016/j.yrtph.2015.10.017
2. Thompson AG, Leite MI, Lunn MP, Bennett DL. Whippits, nitrous oxide and the dangers of legal highs. *Practical Neurology* 2015; **15**: 207-9.
3. Waclawik AJ, Luzzio CC, Juhasz-Pocsine K, Hamilton V. Myeloneuropathy from nitrous oxide abuse: Unusually high methylmalonic acid and homocysteine levels. *Wisconsin Medical Journal* 2003; **102**: 43-5.
4. Sahenk Z, Mendell JR, Gouri D, Nachtman J. Polyneuropathy from inhalation of N_2O cartridges through a whipped cream dispenser. *Neurology* 1978; **28**: 485-7.
5. Pema PJ, Horak HA, Wyatt RH. Myelopathy caused by nitrous oxide toxicity. *Am J Neuroradiol* 1998; **19**: 894-6.