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Case Report

A case of unusual substance abuse causing myeloneuropathy

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Study design: Case report.
Objectives: Examine an unusual drug related case of myeloneuropathy as well as the pathophysiology of nitrous oxide induced subacute combined degeneration.
Setting: Major metropolitan teaching hospital – Princess Alexandra Hospital, Queensland, Australia.
Methods: Review case notes, investigations, relevant medical literature and epidemiological data.
Results: A 23-year-old female developed a myeloneuropathy and encephalopathy after an 8-month history of nitrous oxide abuse. Her presentation was complicated by acute renal failure, deep vein thrombosis (DVT) and pulmonary embolism (PE) as well as severe cognitive deficits. After eight months of multidisciplinary rehabilitation the patient is able to walk short distances with mobility aids and is able to manage self cares. However, she still requires a wheelchair for long distances and will have significant residual neurological deficits.
Conclusion: The abuse of nitrous oxide has potentially serious outcomes that require discussion of issues related to harm minimisation and health promotion.
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Keywords: myeloneuropathy; myelopathy; subacute combined degeneration; nitrous oxide toxicity; substance abuse; cobalamin antagonists & inhibitors; vitamin B12 deficiency, nitrous oxide bulbs

Introduction

Chronic exposure to nitrous oxide (N_2O) can lead to significant vitamin B_{12} (cobalamin) deficiency resulting in subacute combined degeneration (SCD) myeloneuropathy. N_2O is abused infrequently but has serious medical sequelae including encephalopathy, myelopathy, neuropathy and endovascular effects.

Case description

A 23-year-old female presented with a history of profound tetraparesis. She had an extensive history of intravenous drug abuse.

Approximately eight months prior to presentation, the patient began inhaling N_2O; a practice known as 'nanging'. Initial use was limited to 1 box of 10 whipped cream ('whippet') bulbs per day, but had escalated to 13 boxes per day for 6 weeks before presentation.

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The patient described progressive limb weakness for 3 weeks, evolving such that she remained paralysed for the 3 days prior to admission. She was found by her partner and he was unable to rouse her.

On presentation, examination revealed evidence of a flaccid tetraparesis. Patchy paraesthesia (pain and light touch) was noted in upper limbs and trunk. Absent pelvic reflexes and Glasgow Coma Scale of 14 were noted.

Routine investigations showed a raised creatinine and urea consistent with acute renal failure. Enzymology revealed raised creatinine kinase (9160 U/l ($<$160 U/l)) and the presence of high urinary myoglobins reflecting rhabdomyolysis.

Apart from a normocytic anaemia (haemoglobin 66 ($>$115)), routine haematology was unremarkable.

The patient required admission to an intensive care unit, which was complicated by bilateral femoral vein DVTs and a PE confirmed by duplex ultrasound and Computer Tomography Pulmonary Angiogram.

Magnetic resonance imaging (MRI) revealed increased symmetrical signal intensity on T2 weighted images in the cervico-thoracic spinal cord (Figure 1).

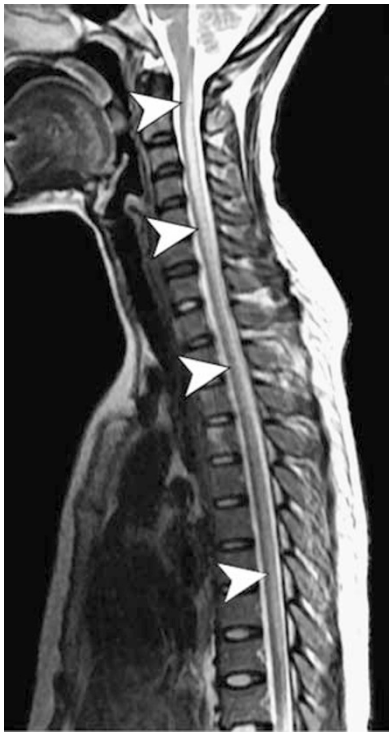

Figure 1 MRI imaging demonstrating diffuse dorsal hypersensitivity extending from C_1 to T_{12}. C_1 to C_5 show extensive involvement to include the central portion of the cord as indicated by the arrows

Clinical diagnosis

Further investigation included a toxicological screen, thyroid function tests, as well as cobalamin and folate levels. Nerve conduction studies showed peripheral axonal sensorimotor neuropathy. An electroencephalogram demonstrated a severe diffuse encephalopathy.

Cobalamin levels were found to be significantly depressed at 125 pmol/l (>210). Red cell folate was within normal limits.

A clinical diagnosis of toxic myeloneuropathy due to N_2O was made.

Discussion

Nitrous oxide

Joseph Priestley discovered N_2O in 1772. Since then its widespread applications have included use as a food aerosol propellant, inhalational anaesthetic and engine accelerant. Research is currently examining how N_2O can be used to deliver pure oxygen to astronauts' space suits.

N_2O is abused by direct inhalation when emitted from a dispenser or pre-inflated balloons. Whipped cream dispensers can be purchased for around $100 (AUD) from most home wares stores and a box of 10 N_2O bulbs costs around $10 (AUD).

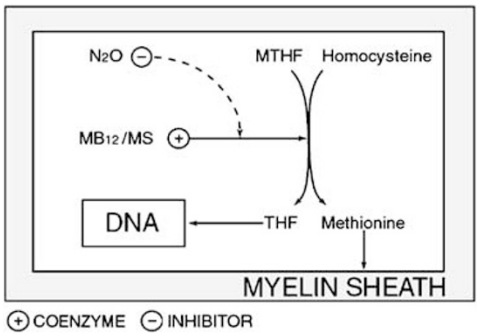

Figure 2 Cobalamin pathway in neuron inhibited by N_2O. N_2O acts to inhibit the methylated cobalamine (MB_{12})/methionine synthase (MS) complex which is a cofactor in the production of tetrahydrofalte (THF) and methionine (MS). Deficiencies of both THF and MS adversely affect the production of DNA and myelin, respectively[1]

Table 1 Interrelationship between cobalamin and IL-6, EGF and TNF-α[3]

	IL-6/EGF	*TNF-α*
Low cobalamin	↓	↑
Normal cobalamin	↔	↔

Low cobalamin causes decreased levels of neurothrophic IL-6/EGF and increased levels of potentially neurotoxic TNF-α

N_2O toxicity

N_2O inactivates cobalamin *in vivo* by irreversibly oxidising its cobalt ion. Methylated cobalamin (MB_{12}) acts as a coenzyme with methionine synthase (MS). Both MB_{12} and MS act to catalyse the conversion of homocysteine and methyltetrahydrofolate (MTHF) to methionine and 5-methyl-enetetrahydrofolate (THF), which are required for myelin sheath protein and DNA synthesis, respectively[1] (Figure 2). Chronic exposure of animal subjects to N_2O has been shown to progress to SCD myelopathy and axonal polyneuropathy.

Therefore underlying B_{12} deficiency from nutritional deficiency (vegetarianism[2]), pernicious anaemia or other absorption abnormality; compound the risk of neurotoxicity. At the time of presentation, the patient was not malnourished and subsequent investigation into concurrent causes of cobalamin deficiency failed to reveal any compounding factors.

Recent reports show that, apart from its coenzyme functions, cobalamin influences regulation of neurotrophic (interleukin 6 (IL-6), epidermal growth factor (EGF)) and potentially neurolytic (tumour necrosis factor alpha (TNF-α)) cytokines and growth factors. Decreased IL-6 and EGF and increased TNF-α have been noted in serum and central nervous system (CNS) samples from cobalamin deficient rats and human subjects. These anomalies normalise with B_{12} replacement[3] (Table 1).

Interestingly, TNF-α antagonists injected into the CNS of cobalamin deficient rats inhibited SCD.[4]

Radiographic appearance
SCD is only apparent on MRI. SCD appears most commonly in T2 weighted MRI as high symmetric signal intensities in the dorsal columns. SCD is thought to originate from the cervico-thoracic posterior columns,[5] and can extend to the anterior columns as well as longitudinally.[6]

Epidemiology
Illicit substance inhalation has gained increased prominence since the first published report of 'nanging' in 1978.[7] N_2O use tends to occur as one of many 'party drugs' among the younger population and those of higher socioeconomic status and education as well as being strongly associated with poverty and social isolation in chronic users.[8] In 2004, an estimated 400 000 Australians reported ever having used inhalants and 1 in 250 reported using in the previous 12 months.[9] Ng *et al*.[10] recently reported that 12% of students from engineering, law and health degrees at Auckland University inhaled N_2O for recreational purposes.

Treatment

Other than supplementation and supportive measures, N_2O induced myeloneuropathy currently has no readily available treatment. Reports have utilised between 1000 and 5000 μg of cobalamin daily for 5–14 days. One case reports the potential efficacy of additional oral methionine.[11] Our patient received 5000 μg of cobalamin daily for 12 days as well as supplementation with 3 g methionine daily.

Prognosis and recovery

Most cases of myelopathy or neuropathy due to cobalamin deficiency have a good prognosis; with up to 47% of patients in one series showing complete resolution of impairment.[12] It is prudent to note that duration of symptoms and absence of haematological changes prior to treatment are strongest predictors of residual impairment.[12]

Rehabilitation and progress

Initially the patient required substantial assistance with eating, grooming, bathing, toileting and mobility. She had reduced bladder and bowel function and required assistance with toileting. Her neuropathic bladder was initially managed with an indwelling catheter. She required daily oral aperients and suppositories for management of the neuropathic bowel. Therapy focussing on core stability, coordination and mobility were progressed as appropriate, as were fine motor drills to improve upper limb and hand function.

Multidisciplinary rehabilitation for 8 months improved lower limb function. She was able to walk independently with the use of assistive aids for short distances, but required a wheelchair for longer distances. She was independent with self cares and could maintain urinary and faecal continence.

Neuropsychometric testing revealed moderate to severe deficits in attention, speed of processing and executive function. This was thought to be due to toxic or hypoxic encephalopathy.

Despite the patient's gains, permanent neurological and functional deficits and reduced independence will persist. These deficits will translate to a large burden of care and ongoing financial costs on the patient's family and local community.

Conclusion

This case report serves to review the serious consequences of N_2O abuse in our community. Of the published cases, this patient's outcome appears to be one of the poorer reported, possibly correlating with the duration and severity of B_{12} deficiency and probable complicating hypoxic insult.

Ours is the fourth reported case of myelopathy caused by N_2O abuse originating from Australia.[2,13,14] This problem is under-reported and regrettably under-recognised. Further research and public discourse is required into preventative aspects of N_2O abuse.

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