Paralysis caused by "nagging"

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A woman in her 20s presented to the emergency department, malnourished and dehydrated, and with acute paralysis of the lower limbs. Over the previous 10 days, she had inhaled nitrous oxide from "whipped-cream bulbs" (10–20 per day) for pain caused by a sprained ankle. She had a history of intravenous drug use and was on a methadone program. The nitrous oxide misuse combined with the malnutrition, with low vitamin B_{12} levels, apparently resulted in subacute combined degeneration of the spinal cord — a rare complication of nitrous oxide misuse. ***(MJA 2007; 187: 366-367)***

Clinical record

A young woman in her 20s presented to the emergency department with a history of increasing difficulty in mobilising over the previous week. For the 3 days before presentation, she had been confined to the back seat of a car (from which she was extricated with difficulty on arrival at the emergency department). An estimated 60 empty "whipped-cream bulbs" were found on the floor of the car.

She had a history of intravenous drug use and was on a methadone program, but there was no other significant medical history. She had sprained her ankle 10 days before presentation, and had been inhaling nitrous oxide from whipped-cream bulbs for the pain (10–20 per day). Further immobility and boredom had increased her usage.

On examination, she was pleasant, but dishevelled and malnourished, with evidence of needle track marks from intravenous drug use on her extremities. She had a Glasgow Coma Scale score of 14/15 (best eye response, 4; best verbal response, 4; best motor response, 6); her respiratory rate was 20 breaths/min; heart rate, 95 beats/min; blood pressure, 95/63 mmHg; temperature, 35.6°C; and oxygen saturation in room air was 94%.

She had a 1/5 flaccid proximal weakness of the lower limbs (Medical Research Council [United Kingdom] scale), with a flicker of power preserved distally, but absent plantar and knee-jerk reflexes. She had a patchy sensory level to T10, and absent vibration sense to her anterior superior iliac spines bilaterally. There was a proprioception deficit to her feet, knees and hips bilaterally. She was in urinary retention, and 1800 mL was drained through an indwelling urinary catheter. Rectal examination showed atony of the anal sphincter.

There were mild pressure areas on the dorsal surfaces of her legs and buttocks, with diffuse oedema of the lower limbs. The rest of the examination was unremarkable.

Investigations

Differential diagnoses included a space-occupying lesion of the spinal cord, transverse myelitis, HIV myelopathy, Guillain–Barré syndrome, and multiple sclerosis. We were concerned about the presence of a neurological toxin in the whipped-cream bulbs, given the history of neurological deterioration coinciding with the patient's excessive use of the bulbs. Our diagnosis was initially delayed, as we were unable to ascertain the exact constituents of a whipped-cream bulb. Magnetic resonance imaging (MRI) of the whole spine and brain was performed and was initially reported as showing no abnormality.

Initial laboratory investigations showed: a raised serum creatine kinase level of 9000 U/L (reference range [RR], < 150 U/L); acute renal failure, with a creatinine level of 490 μmol/L (RR, 80–140 μmol/L) and a urea level of 41 mmol/L (RR, 2.5–7.5 mmol/L); a troponin leak of 0.7 μg/L (RR, < 0.05 μg/L); and a normocytic anaemia, with a haemoglobin level of 83 g/L (RR, 120–140 g/L) and a mean cell volume of 95 fL. Vitamin B_{12} levels were 124 pmol/L (RR, > 210 pmol/L).

A lumbar puncture was attempted but, on sitting the patient upright, she had a bradycardiac arrest and required cardiopulmonary resuscitation (CPR) for 30 s, resulting in spontaneous return to circulation and heart rate. Her arrested circulation was most likely the result of her being dehydrated (as evidenced by prerenal renal failure). Given her clinically demonstrated neuropathy, it is possible that a combination of autonomic neuropathy and reduced intravascular volume from dehydration, together with orthostatic stress on positioning, resulted in the precipitous fall in blood pressure, bradycardia, and arrest. This would explain the rapid return to cardiac output on return to a supine position, with only transient CPR.

A Doppler ultrasound scan of the lower limbs showed bilateral deep venous thrombosis (DVT) to the level of the common femoral arteries. Indirect evidence of pulmonary embolus (PE) included a large alveolar–arterial gradient of > 100 mmHg (RR, 10–25 mmHg) and electrocardiogram changes — tachycardia and a right bundle branch block. It was decided not to perform a computed tomography pulmonary angiography, given the strongly supportive evidence for PE, and an intravenous contrast load was contraindicated given her acute renal failure. A further PE on upright positioning may also have contributed to her cardiac arrest; however, her rapid return to baseline clinical status on returning to a supine position does not support this.

Clinical course

The patient was resuscitated in the emergency department, with fluid loading for prerenal renal failure and as therapy for rhabdomyolysis. She was then transferred to the intensive care unit (ICU) for observation, and given vitamin B_{12} replacement therapy and methionine. Her acute prerenal failure resolved with rehydration, and she was given an intravenous heparin infusion as anticoagulation therapy for bilateral proximal DVT, and subsequently given warfarin for a target international normalised ratio of 2.0–3.0. Further imaging, such as a ventilation–perfusion scan for the presence of PE, was not performed as it would not have contributed to her management.

After 2 days in the ICU, she was transferred to a general medical unit. An MRI scan on review 2 weeks after her admission showed an increased T2 signal within the posterior columns of the spinal cord. She slowly regained partial motor function of her limbs and normal sensory levels over the following 5 months.

She was discharged after 7 months of rehabilitation and inpatient care. She was able to walk short distances, with the aid of a walking frame, but had residual neurological deficits affecting the distal lower-limb muscle groups.

Discussion

Nitrous oxide is a colourless, odourless gas with a weak anaesthetic but useful analgesic action.[1] It is used during short, painful procedures. Because of its ability to elevate mood, nitrous oxide is colloquially known as "laughing gas", and is a common drug of misuse. "Nagging" or "nanging" are terms used to describe the recreational use of nitrous oxide, derived from the repetitive sound distortions experienced by nitrous oxide users.[2,3] In a New Zealand survey of first-year university students, 57% were aware of its recreational use and 12% used it regularly.[2] Nitrous oxide is readily available from most supermarkets and online, as it is used as the aerator and propellant for whipped-cream dispensers. The average bulb used for aerating whipped cream contains 8 g of nitrous oxide.

Pathophysiology and diagnosis

Subacute combined degeneration of the spinal cord is a recognised complication of vitamin B_{12} deficiency or of nitrous oxide exposure (with or without pre-existing normal vitamin B_{12} levels). This complication is well documented in anaesthesia literature in relation to frequent nitrous oxide exposure in anaesthesia, such as during multiple operations, or analgesic use for repeated dressing changes for burns patients.[4,5] Patients with long-term nitrous oxide recreational use are reported to have neurological symptoms ranging from paraesthesias to incoordination and autonomic dysfunction.[6-9]

There is no known neurological toxicity threshold for nitrous oxide exposure. Toxicity is related not to the frequency or level of nitrous oxide exposure, but to the patient's levels of vitamin B_{12}. Spinal cord degeneration resulting from a single short exposure to nitrous oxide anaesthesia, in association with vitamin B_{12} deficiency, has been reported.[10,11]

The neuropathological changes observed in the affected spinal cord include initial swelling and irregularity of the myelin sheath surrounding the nerve cell axons (reversible), followed by frank demyelination and loss of axons (irreversible).[12] This occurs in the central regions of the posterior columns and, to a lesser extent, in the posterolateral regions of the spinal cord. The changes manifest as high-signal lesions on MRI T2-weighted scans caused by increased water content secondary to oedema.[10,11]

Nitrous oxide inhibits the active form of vitamin B_{12}, rendering it unavailable to form the myelin sheath proteins, resulting in axonal swelling and eventual axonal loss. The mechanism of action is the inactivation of vitamin B_{12} (cobalamin) from its monovalent, active cobalt form (Co^{+}) to the inactive, bivalent cobalt form (Co^{2+}). The irreversibly inactivated vitamin B_{12} (Co^{2+}) results in failure of methylation of proteins in the myelin sheaths[4] and a loss of nerve cell axon integrity.[12]

Another contributing factor to the toxicity of nitrous oxide is the role of vitamin B_{12} as a cofactor of the methionine synthase reaction. The enzyme catalyses the reaction in which homocysteine is converted to methionine; tetrahydrofolate is also formed, which is a cofactor in the metabolism of nucleic acids (eg, DNA).[9] Thus, nitrous oxide has a direct effect on DNA synthesis, as well as nerve axon integrity.

Other postulated mechanisms of action for central nervous system toxicity of nitrous oxide include inhibitory effects on *N*-methyl-D-aspartate receptors, stimulatory effects on dopamine neurones, stimulation of descending noradrenergic neuronal pathways, provoked release of noradrenaline in dorsal horn neurones, and sympathetic action via α-1-adrenergic stimulation.[8,9]

A diagnosis of subacute combined degeneration of the spinal cord can be confirmed by MRI, in association with low serum vitamin B_{12} levels, but in some cases MRI scans show no abnormality.[11] The differential diagnoses include demyelination, neoplasms, infections (eg, with *Listeria* spp., or HIV), myelopathy, and syringomyelia.

Treatment and prognosis

Treatment involves ceasing nitrous oxide use and giving vitamin B_{12} replacement therapy. Administration of methionine may also be required as an adjunct, given the direct effects of nitrous oxide on methionine synthase. Exogenous methionine would provide a direct substrate for methionine synthase, while the body slowly replaces the inactive vitamin B_{12} and commences repletion of endogenous methionine. Two patients receiving vitamin B_{12} replacement therapy experienced a worsening of their neurological symptoms until the addition of oral methionine, which halted the neurological decline and accelerated their recovery.[9]

Reported recovery periods vary from 1 week to 1 year. Partial versus full recovery will depend on the extent of the neuropathological damage to the spinal cord; spinal cord oedema and myelin sheath loss will resolve, but axon loss is permanent.

Competing interests

None identified.

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