Nitrous oxide induced motor axonal peripheral neuropathy: a phenotype distinct from vitamin B12 deficiency

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LETTER TO THE EDITOR

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LETTER TO THE EDITOR

Dear Editor,

Recreational abuse of nitrous oxide (N_2O) is widely prevalent and on the rise internationally. [1,2] Unsurprisingly, the incidence of associated neurological complications is also reported to be increasing. [3] Clinicians accordingly need to be aware of the full spectrum of N_2O-related neurological manifestations.

N_2O inactivates vitamin B12 at the biochemical level through deleterious effects on various pathways, but principally through irreversible oxidation of its coenzyme form (methylcobalamin) required for conversion of homocysteine to methionine via methionine synthase. [4] These pathophysiological mechanisms and the similar myeloneuropathic appearances of N_2O toxicity and vitamin B12 deficiency have led to the commonly held view that neurological features arise through its effects on vitamin B12 metabolism. [5]

We report three patients, in the context of N_2O use, presenting to our neuromuscular clinic with a peripheral neuropathy phenotype that is less typical of vitamin B12 deficiency. Each patient demonstrated a subacute, length-dependent and predominantly motor axonal peripheral neuropathy. The striking disparity between sensory and motor nerve involvement is evident from results of nerve conduction studies, shown in **Table 1**. Needle EMG (not depicted) in all three patients revealed a length-dependent pattern of active denervation involving the lower limbs.

Patient 1 is a 21-year-old Afro-Caribbean man without prior co-morbidities. He presented with a 10 day history of gradually worsening numbness of his feet, distal lower limb weakness and gait unsteadiness (worse in the dark). He regularly inhaled recreational N_2O, averaging 25-75 canisters (each 8 grams N_2O) a week, for the last 2 years. Significant

examination findings were lower limb hypotonia, bilateral weakness of ankle dorsiflexion [3/5] and plantarflexion [4/5], pathologically brisk knee reflexes, absent ankle reflexes, absent joint position sense to ankle, impaired vibration sense to costal margin, a high-steppage gait and positive Romberg's sign. His haemoglobin was normal but MCV was raised (106 fL; range 80-97). Serum vitamin B12 was in the lower end of the normal range (226 ng/L; range 197-771) and homocysteine was elevated (33.5 µmol/L; range 5-15). Serum methylmalonate was not measured due to a laboratory error. CSF analysis was unremarkable. MRI spine revealed longitudinally extensive dorsal column signal hyperintensity typical of subacute combined degeneration of the spinal cord, likely accounting for his proprioceptive deficits. His NCS are shown in Table 1. He completely stopped his N_2O use, received intensive intramuscular vitamin B12 therapy and at 6 months follow-up his clinical neurological deficits had all resolved apart from residual lower limb proprioceptive deficits.

Patient 2 is a 22-year-old South Asian lady with a history of obesity, anxiety and depression. She presented with a 4 week history of gradually worsening numbness of her feet and distal lower limb weakness. She regularly inhaled recreational N_2O over the last 6 months, but declined to disclose the amount. Significant examination findings were bilateral weakness of ankle dorsiflexion [3/5] and plantarflexion [3/5], absent ankle reflexes and absent joint position sense to ankles. Her haemoglobin and MCV were within normal range but her vitamin B12 was low (101 ng/L; range 197-771). Serum homocysteine and methylmalonate were not initially measured and she had already been started on intensive intramuscular B12 therapy in the 2 weeks prior to being seen in our neuromuscular clinic. CSF analysis and MRI whole spine were normal. Her NCS are shown in Table 1. She completely stopped her N_2O use and on follow up at 18 months her clinical neurological deficits had resolved.

Patient 3 is a 19-year-old Caucasian lady with a congenital structural abnormality of her right patella predisposing her to recurrent painful patellar dislocations. This led to numerous presentations to our emergency department over the prior 2 years - on each occasion receiving analgesia in the form of inhaled N_2O. She presented with gradually worsening numbness of her feet and distal lower limb weakness over 2 weeks. Significant examination findings were bilateral weakness of ankle dorsiflexion [3/5] and plantarflexion [4/5], absent ankle reflexes, knee reflexes that could only be obtained with reinforcement and a normal

lower limb sensory examination. Her haemoglobin was normal but MCV was elevated (107 fL; range 80-97). Serum vitamin B12 was low (124 ng/L; range 197-771) and there was marked elevation of her serum homocysteine (131 µmol/L; range 5-15) and methylmalonate (2553 nmol/L; range 0-280). CSF analysis and MRI whole spine were normal. She received intensive intramuscular B12 therapy and alternative analgesia was advised. Although her clinical neurological deficits improved, there is still objectively residual distal lower limb weakness and subjective numbness of feet on follow-up 2 years post-symptom onset.

The peripheral neuropathy in our three patients is clearly predominantly motor. However the sensory symptoms, particularly in patients 2 and 3 (without radiological evidence of myelopathy), also indicate peripheral sensory involvement. Standard electrophysiological studies have several limitations in this setting. Whilst sensory nerve action potential (SNAP) amplitudes were within normal *absolute* limits, it may be that pre-morbid SNAPs were significantly higher in these young adults. Additionally, small fibre dysfunction (not assessed with standard SNAP measurement), is recognised to occur in vitamin B12 deficiency [6], and is very likely to be contributing to sensory symptoms and signs in our patients.

N_2O toxicity and vitamin B12 deficiency are both classically recognised to cause a pure sensory or sensorimotor (but predominantly sensory) neuropathy. [6,7] Predominant involvement of peripheral motor nerves, as seen in our 3 patients, is not typical of isolated B12 deficiency. However reports of electrophysiologically predominant distal peripheral motor nerve involvement with N_2O abuse can be found in the literature as early as 40 years ago, [8] and more recently [9]. In addition to its above-described effects on vitamin B12 metabolism, N_2O has been proposed to directly exert neural toxicity via various mechanisms including NMDA receptor inhibition and stimulation of noradrenergic descending neuronal pathways. [10] Similarly, recent work examining sensorimotor excitability profiles points to more significant peripheral motor axonal dysfunction in patients with N_2O toxicity compared to isolated vitamin B12 deficiency [11]. The N_2O group displayed more prominent superexcitability changes in motor as compared to sensory nerves, a pattern not seen in isolated vitamin B12 deficiency patients, suggesting pathophysiological differences. [11]

In summary, clinicians should be aware that N_2O abuse can present with a subacute, length-dependent and motor-predominant axonal peripheral neuropathy. This aetiology should be considered in the differential diagnosis of such presentations, and such patients should be specifically questioned about N_2O abuse. It can, as in our first patient, present in association with a myelopathy. The mechanism for this particular peripheral neuropathy phenotype may possibly be related to N_2O direct neural toxicity that is distinct, or in addition to, its well-recognised effects on B12 metabolism.

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