

Iatrogenic B12-deficient peripheral neuropathy following nitrous oxide administration for functional tonic leg spasm: a case report.

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Keywords: functional leg spasm, B12, cobalamin, neuropathy, nitrous oxide;

Highlights:

1. N₂O-induced B12-deficient neuropathy can be entirely iatrogenic in nature
2. Long-term use of N₂O, even in controlled clinical environments, should be avoided.
3. Severe prolonged and painful spasms are suggestive of a functional origin.

Introduction

Vitamin B12 (Cobalamin) deficiency is a well-known cause of central and peripheral nervous system dysfunction, including sensorimotor peripheral neuropathy [1]. In individuals with normal renal function, a normal or low serum B12 level, high plasma methylmalonic acid (MMA) and homocysteine (Hcy) levels indicates a *functional* B12 deficiency, where there is failure of intracellular transport of B12 by transcobalamin-2.

Nitrous oxide (N₂O) is an increasingly recognised cause of Vitamin B12 deficiency [2] and subsequent neuropathy, mostly occurring in the context of long-term N₂O overuse, or short term N₂O exposure in patients with coexisting B12 deficiency [3]. We present a case of peripheral neuropathy secondary to N₂O-induced functional B12 deficiency in a 27-year-old male presumably without prior B12 deficiency who received N₂O exclusively under controlled clinical administration.

Case report

A 27-year-old right-handed man had suffered recurrent patellar dislocations resulting in multiple bilateral knee operations from the age of 15yrs. He was admitted for investigation of a 5-year history of severely painful abrupt onset right paroxysmal leg spasms (Video 1). He required manipulation under anaesthesia (MUA) to abort the spasm and straighten the leg. These events were preceded by a prodrome of anxiety followed by a severe ascending pain from the toes to the hip. This pattern recurred on >50 occasions over a period of 5 years. During these exacerbations he would typically be administered Entonox, a 50:50 mixture of N₂O and Oxygen (Video 1) in the emergency department. Spasms would resolve over 5-45min, but not necessarily related to N₂O administration. He was prescribed baclofen, clonazepam, and pregabalin, all with variable results.

Incidentally, he complained of bilateral paraesthesia of the soles, and numbness of the feet. The neurological examination was normal apart from absent ankle jerks bilaterally and a distal sensory loss over his feet bilaterally to both pain and vibration, extending to the ankles.

The patient did not drink alcohol, was not vegan, and had no gastrointestinal conditions. He was not taking any regular or over-the-counter medications.

MRI of the brain and spine performed as a work-up for the leg spasms were normal. Nerve conduction studies showed a mild large fibre, length-dependent axonal sensorimotor polyneuropathy. Haemoglobin and mean cell volume were normal, as was a full autoimmune, vasculitis, infectious, metabolic and paraneoplastic blood test screen. His B12 and associated laboratory results are shown in Table 1.

He was diagnosed with a functional (psychogenic) left leg spasm, and a sensorimotor neuropathy secondary to a functional (organic) B12 deficiency, related to controlled N₂O administration. He was advised complete cessation of N₂O and commenced B12 replacement. Two months after intramuscular hydroxycobalamin injections, his sensory symptoms had improved, laboratory tests of B12 were normal (Table 1), but the reflexes remained absent and the neurophysiological findings unchanged (Table 2). He continued to experience frequent leg spasms and significant psychological distress, and was referred for psychological support and in-patient treatment of the functional disorder as part of a multidisciplinary team setting.

Discussion and conclusions

To date, neurological complications from N₂O mostly occur either through uncontrolled long-term use or during single/short term use in the presence of undiagnosed B12 deficiency. More commonly, myelopathy or neuropathy are reported in long term uncontrolled recreational exposure to N₂O, such as with N₂O abuse, which has rapidly increased amongst young people in the last 5 years [2]. We were unable to estimate the exact number of N₂O doses that the patient received over the 5-year period as he presented to different emergency departments across the country, though the patient estimated that this was given on >30 occasions. We nevertheless hypothesise that the cumulative exposure to N₂O gave rise to this clinical picture. Similar findings were reported in 3 individuals with sickle cell disease who developed peripheral sensorimotor neuropathy after recurrent admissions to the emergency department for painful crises that required treatment with N₂O[4]. Unlike our patient, all of these individuals had B12 levels below the normal range.

The painful nature of the patient's functional (psychogenic) leg spasm was a precursor to the recurrent use of N₂O. Functional tonic spasms frequently affect the lower more than the upper limbs, have an

abrupt onset, with early fixed postures, paroxysmal symptoms and complete remissions [5]. Severe painful spasms lasting hours to days, with normal function between episodes, are suggestive of a functional origin [5]. Despite increasing recognition of functional neurological symptoms in the acute setting, awareness of the poor prognosis, and degree of disability such disorders may engender, is still lacking.

This case report highlights that delayed diagnosis of functional leg spasm can lead to long-term complications, and that nitrous oxide administration in the acute setting, even under controlled administration, should be used with caution.

Abbreviations Hcy= homocysteine; MMA= methylmalonate; MUA= manipulation under anaesthesia; N₂O= nitrous oxide.

Declarations

Ethics approval and consent to participate: Not applicable

Consent to publish: Consent for publication has been obtained in writing.

Availability of materials and data: Not applicable

Competing interests: The authors declare that they have no competing interests.

Funding: Not applicable

Authors contributions: DK obtained the clinical history, performed the clinical examination, obtained consent for publication, prepared the manuscript and figures, and edited the video. PK obtained clinical data, and prepared the manuscript. EM provided biochemical expertise and reviewed the finished manuscript. TTW performed the clinical examination, reviewed clinical data, and approved the final version of the manuscript.

Acknowledgements: We are grateful to the patient for consenting to this publication, sharing his personal experience, and reviewing the manuscript for factual errors and inconsistencies.

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Video legend

The video shows a typical tonic right leg spasm, captured approximately 3 minutes into the event. The patient is shown to be in extreme distress and severe pain, requiring inhaled Entonox. The spasm

involves the hamstring, with flexion of the knee, and foot, with flexion of the toes (particularly the first metatarsophalangeal joint).

Table 1. Vitamin B12, methylmalonate, and homocysteine levels before and after vitamin B12 replacement.

Test	Pre-treatment	3 months post treatment	Reference interval
Vitamin B12 (pg/mL)	263	>2000	197-771
Plasma Methylmalonate (umol/L)	9.96	0.13	0-0.28
Plasma Total Homocysteine (umol/L)	101	8	5-12

Table 2. Results of the nerve conduction studies pre-treatment and 3 months after B12 replacement. Needle electromyography of the right tibialis anterior and gastrocnemius was normal (not shown). For sensory studies, amplitudes are peak-to-peak values, conduction velocities are to onset. For motor studies, amplitudes are baseline to negative peak values. Laboratory reference values appear in brackets.

Pre-treatment			3 months post treatment			
<i>Sensory nerve conduction study</i>						
	Amplitude (μV)	Velocity (m/s)	Distance (mm)	Amplitude (μV)	Velocity (m/s)	Distance (mm)
Median (D3-wrist)	11 (>6)	51 (>40)	150	-	-	-
Left sural (calf-ankle)	6 (>6)	35 (>40)	110	4 (>6)	42 (>40)	110
<i>Motor Nerve conduction studies</i>						
Left median nerve	7.4 (>6)	52 (>40)	80	-	-	-
F-wave (wrist)	-	54 (>40)	-	-	-	-
Left common peroneal nerve	1.5 (>4)	37 (>40)	80	1.6 (>4)	38 (>40)	80
Left tibial nerve	2.1 (>4)	37 (>40)	80	1.5 (>4)	39 (>40)	80
F-wave (ankle)		absent			absent	