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Case Report

CASE REPORT

Recurrent paraparesis and death of a patient with 'whippet' abuse

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Abstract

Nitrous oxide is increasingly used as a recreational drug that is easily and legally available worldwide. Occasional nitrous oxide use has been considered relatively safe without the development of addiction or major adverse effects. However, heavy long-term nitrous oxide abuse can be associated with severe neurological complications, and even deaths have been described. The characteristic presentation is myeloneuropathy with dorsal column degeneration and demyelinating sensory polyneuropathy related to vitamin B12 deficiency. Described is a 23-year-old male who developed recurrent paraparesis related to nitrous oxide abuse. A second, more severe, episode of paraparesis was associated with predominantly lower motor neuron damage. A partial recovery was achieved by discontinuation of nitrous oxide use and initiation of vitamin B12 supplementation. However, the patient relapsed and ultimately died while being intoxicated with several abusive substances. The case adds to the cumulative literature about the clinical phenomenology and dangers of nitrous oxide abuse.

INTRODUCTION

Nitrous oxide (N_2O, 'laughing gas') is used as an anaesthetic, for example, during small dental procedures and labour. However, it is also widely available for non-medical use, such as for making of whipped cream. The inhalation of nitrous oxide reduces anxiety and induces euphoria, and is thus used as a recreational drug. However, long-term nitrous oxide can have serious adverse consequences, including toxicity to the nervous system [1].

Here, we describe a patient who extensively used nitrous oxide inhalations using gas from whipped cream dispensers (referred to as a 'whippet'), as a substitute for illicit drugs he previously abused. As a consequence, he developed two separate episodes of paraparesis: first with symptoms of myelopathy and second with symptoms of severe motor neuropathy (resembling Guillain–Barré syndrome) accompanied with mild myelopathy. Ultimately, the patient died while being intoxicated with several abusive substances.

CASE REPORT

A 23-year-old male was referred to the emergency unit because of rapidly progressive gait difficulties with subacute onset.

The patient had a history of depression and substance use disorders (alcohol and amphetamine). He was treated as an outpatient at the department of psychiatry. Current medications included citalopram 40 mg, hydroxyzine 25 mg and quetiapine

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50–100 mg per day, and oxazepam 15 mg as needed. A year before presentation, the patient had a transient episode of mild gait difficulties with unclear aetiology that had resolved spontaneously. At that time, he had gait ataxia with signs of upper motor neuron damage in all extremities. Brain and cervical spinal cord MRI were unremarkable, except for mild atrophy of the cerebellar vermis and frontal cortex, which were interpreted to be related to the long-term alcohol abuse.

The patient presented at the university hospital emergency care unit (ECU) with a 2–3-week history of progressive, painless gait difficulty associated with numbness in the hands. The patient had been abstinent from alcohol and amphetamine at least for the past 6 months, which was confirmed by regular laboratory investigations. However, the patient reported having replaced these substances with excessive daily 'whippet' abuse. He had discontinued 'whippet' use and started oral vitamin B12 substitution based on the information he found on the Internet a couple of weeks before presenting to the ECU. At the time of presentation, the gait difficulty had progressed to a state that he was unable to walk unaided.

In the ECU, the patient showed bilateral lower extremity weakness that was the most prominent in distal lower limb muscles. In addition, there were minor distal paraesthesias in all extremities. Vibration sense was absent up to the knee level, but all other sensory modalities were intact on clinical examination. Deep tendon reflexes were 2+ in the upper limbs but absent in the lower limbs. Plantar reflexes were evaluated as extensions in the ECU, but as flexions later in the neurological ward. Gait was ataxic, and there was ataxia in the lower limbs, but not in the upper limbs. There were no signs of cerebellar involvement. Mental status and cranial nerves were intact. Vital signs, general medical examination and laboratory examinations were unremarkable.

In the neurological ward, laboratory examinations revealed markedly elevated plasma homocysteine levels (110 umol/l, normal range 5–15 umol/l), indicating vitamin B12 deficiency despite normal B12 levels (plasma B12 176 pmol/l and serum active B12 116 pmol/l). Electrophysiological examination was consistent with subacute axonal motor polyneuropathy affecting mainly the lower extremities. In addition, there was also mild demyelinating polyneuropathy in all extremities (Tables 1 and 2). The patient was treated with intramuscular vitamin B12 injections 1 mg per day for 2 weeks, followed by oral supplementation. At the ward, the clinical condition remained unchanged, and the patient was transferred to a rehabilitation unit 8 days later.

Three months later, the patient was re-evaluated as a neurology outpatient. The patient had remained abstinent from nitrous oxide and showed marked improvement. He experienced only weakness (muscle strength 4/5) in the distal lower limb muscles. Vibration sense had normalized, and tendon reflexes were normal throughout with plantar flexions. There was no muscular atrophy present, and he was able to walk unaided.

Approximately 1 ½ years following the symptom onset, the patient was found from his home lifeless in a 'lotus' position, face towards the floor. The patient was surrounded by empty nitrous oxide cylinders, and altogether there were thousands of nitrous oxide cylinders in the apartment. At the medicolegal examination, the main cause of death was determined as acute amphetamine intoxication. Furthermore, in the toxicological analysis of post mortal femoral blood, hydroxyzine (0.35 mg/l) and alprazolam (0.060 mg/l) concentrations exceeded the therapeutic levels. In the qualitative drug analysis of urine, also methamphetamine, phenylpropanolamine and fentanyl were found. There were no alcohols, volatile substances nor nitrous oxide detected in the samples, but the investigation was limited by the long interval between death and medicolegal examination.

Table 1: Nerve conduction studies

	Side	Distal latency (ms)	Amplitude (mV)	NCV (m/s)	F wave (ms)
Motor nerves					
Median	R	**4.2**	5.7/5.3	42.0	27.7
Ulnar	L	**3.7**	8.2/7.7/7.5	57.5/55.9	n.a.
Peroneal	R	–	**0.0/–**	–	–
Peroneal	L	–	–	–	–
Tibial	R	5.1	**0.0/0.0**	**27.8**	–
Tibial	L	5.3	**0.1/0.0**	**30.0**	**50.8**
Sensory nerves					
Ulnar	R		17	**46.8**	
Ulnar	L		14	**40.9**	
Radial	L		7.7	**49.6**	
Peroneal	R		2.2	**32.7**	
Peroneal	L		2.7	**35.8**	

The measurements were conducted with a distance of 80 and 140 mm (±10 mm) between the stimulating and recording electrodes in motor and sensory nerves, respectively. NCV, nerve conduction velocity. Motor amplitudes are presented from all stimulation sides from distal to proximal. L, left; R, right; n.a., not assessed. '–' indicates that the response was missing completely. Values that are more than 2 SD below age, gender and height-corrected normal range are highlighted in bold.

Table 2: Needle electromyography

Muscle	Side	Fibr.	Amp	Dur	Poly	IP
I dorsal interosseus	R	**2/10**	norm.	norm.	**1+**	norm.
Ext digiti communis	R	norm.	norm.	norm.	norm.	norm.
Deltoid	R	norm.	norm.	norm.	**1+**	**1+**
Ext hallucis longus	L	**9/10**	norm.	norm.	**2+**	**3+**
Ext hallucis longus	R	**10/10**	–	–	–	–
Tibialis anterior	R	**9/10**	**1+**	norm.	**1+**	**3+**
Vastus lateralis	L	**1/10**	**1+**	**1+**	**1+**	**3+**
Vastus lateralis	R	**5/10**	**1+**	**1+**	**1+**	**2+**

Fibr, fibrillation potentials per 10 insertion sites; Amp, amplitude; Dur, duration; Poly, polyphasic motor unit action potentials; IP, interference pattern. The findings are rated from normal (norm.) to highly abnormal (3+). '–' indicates that the response was missing completely. L, left; R, right; n.a., not assessed.

DISCUSSION

Long-term nitrous oxide abuse can lead to severe neurological complications within the peripheral and/or central nervous system, such as polyneuropathy, myelopathy and neuropsychiatric manifestations [2]. The pathophysiological mechanism of nitrous oxide toxicity is considered to be caused by inactivation of the vitamin B12 (cobalamin)-mediated pathways that are critical for normal cell function [3]. The most common neurological presentation is demyelinating myeloneuropathy affecting predominantly the dorsal columns [1]. However, nitrous oxide also seems to have neuronal toxicity independent of vitamin B12 supplementation, and there are rare cases (such as our patient) presenting with predominant lower motor neuronal degeneration [4, 5].

Eventually, our patient died while being intoxicated with several substances of abuse. The main cause of death was amphetamine intoxication, but nitrous oxide might have been a

contributing factor. There are rare cases of deaths associated with nitrous oxide abuse [6, 7]. The mechanism of death remains to be elucidated, but the patients have shown signs of asphyxia, which has been hypothesized to be caused by the lack of brain reactivity to hypoxia and hypercapnia due to the nitrous oxide [6]. However, part of the fatal cases that have been reported were due to insuffocation caused, e.g., by an airtight mask that was used to inhale nitrous oxide [6].

Our case adds to the cumulative literature about the serious adverse effects of nitrous oxide abuse. The case provides further evidence that nitrous oxide abuse should also be considered as a diagnostic alternative in patients presenting with subacute paraparesis with predominantly lower motor neuron damage.

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CONFLICT OF INTEREST STATEMENT

J.J. has received a lecturer honorarium from Boehringer-Ingelheim, travel grants from Abbvie and a research grant from Lundbeck and Orion research foundation. J.K. has received a lecturer honorarium from Allergan, Boehringer-Ingelheim, Pfizer and Medtronic.

FUNDING

The study received no funding.

ETHICAL APPROVAL

The case has been presented based on hospital medical records and written by the physicians participating in the treatment of the patient. Therefore, no ethical committee approval was required.

CONSENT

An informed consent was obtained from the closest relative of the patient.

GUARANTOR

J.H. is nominated as the guarantor and has had full access to the data.

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