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Title:

Nitrous Oxide-Induced Neurological Disorders – an increasing public health concern

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Nitrous Oxide-Induced Neurological Disorders – an increasing public health concern

Abstract

Background:

Neurologic presentations resulting from nitrous oxide (N_2O) abuse are increasing in Australia and worldwide. Despite known neuropsychiatric sequelae nitrous oxide canisters remain readily available and its use unregulated.

Aims:

To examine the demographics, clinical and electrophysiological findings of patients presenting with neurological complications of N_2O abuse, and thus inform clinicians and public health decision makers of the significant public health concerns of this increasing practice.

Methods:

Consecutive patients presenting to a tertiary referral, metropolitan hospital were included in this series. Patients were identified by a search of discharge summaries of patients admitted with acute or subacute neuropathy or myelopathy and a history of N_2O abuse, and from the electrophysiology database.

Results:

Thirteen patients were identified, most presenting with subacute paraesthesia, sensory ataxia and lower limb weakness. Eleven had low serum vitamin B_{12}. Spinal magnetic resonance imaging was consistent with subacute combined degeneration (SACD) in 8. Nerve conduction studies revealed a motor or sensorimotor axonal neuropathy (3 with motor predominance). There was a bimodal demographic distribution consisting of socially isolated, international university students and local residents with a history of mental illness and polydrug abuse.

Conclusions:

Recreational N_2O use is an emerging health problem in Australia. International university students and patients with pre-existing mental illness or polydrug use appear to be at increased risk. A severe motor neuropathy may emerge following Vitamin B_{12} replacement. Public health measures are required to limit the availability of N_2O and to educate adolescents and young adults about the potential for significant harm.

Nitrous Oxide-Induced Neurological Disorders – an increasing public health concern

Introduction

Nitrous oxide (N_2O) is a colourless, non-flammable gas that has long been used as a dissociative anaesthetic agent[1]. Since its discovery, there have been reports of recreational use (colloquially referred to as “nagging” or “nanging”) due to the brief dissociative, euphoric and hallucinogenic effects[1-7]. There has been a notable rise in use of N_2O recreationally in recent years. The Global Drug Survey (n≥110 000) listed N_2O as the 14th most commonly used drug worldwide in 2020[8]. Recreational use is also increasing in Australia[9-12]. The Ecstasy and Related Drug Markets Survey 2019 found within their sample (n=797 self-reporting when interviewed) that use of N_2O in the past six months had increased from 26% in 2003 to 53% in 2019[10]. With the perceived benefits of low cost, legal status and easy accessibility, N_2O abuse has become a common problem in diverse parts of the world[7] including the UK[2,13], Saudi Arabia[14], China[15-17], and Australia[9-12]. Despite its widespread abuse, the risks associated with N_2O exposure are not sufficiently recognised by either consumers or healthcare providers. This is of significant concern given early recognition of N_2O misuse and reduction in exposure may reduce the risk of permanent neurological sequelae.

Here we report 13 cases of recreational N_2O abuse presenting with myeloneuropathy to a single metropolitan tertiary referral hospital in Australia from 2017-2021, to highlight the

public health risk of this increasing phenomenon and advocate for greater regulation of this drug throughout Australia

Patients and Methods

Thirteen patients diagnosed with N_2O-induced neurological disorders were retrospectively identified at our hospital between 2017 and 2021. All patients had developed neurological symptoms such as acute ascending paraesthesia and symmetrical limb weakness after exposure to N_2O. All patients had undergone clinically guided investigations, including complete blood count, vitamin B_{12}, folate and for the majority, nerve conduction studies and spine magnetic resonance imaging (MRI). Investigations to exclude alternate causes of acute neuropathy and myelopathy were performed as clinically required.

Results

Patient Characteristics:

The demographic data, clinical manifestations and investigation results of the patient cohort are outlined in Table 1. The mean patient age was 23.8 ± 1.18. Eight patients were female. The median N_2O exposure period was 6 months. Five patients were of Chinese heritage, 6 Caucasian and 2 Somalian. Of the patients of Chinese heritage, 4 were international university students and 1 was a high school student. All were living in Australia alone without family members and reported feeling socially isolated and under considerable stress related to their studies. Two Chinese patients also used marijuana. Of the 6 Caucasian

patients, all had pre-existing mental illness and five had a history of associated marijuana and alcohol abuse.

Clinical Manifestations:

The majority of patients presented with subacute sensory symptoms, lower limb weakness and sensory ataxia. Three patients had associated confusion and three had urinary retention at presentation. Two patients presented acutely and were initially investigated for Guillain Barré Syndrome prior to elucidation of the history of N_2O abuse.

Laboratory Data:

Eleven patients had low serum vitamin B_{12} levels. Plasma homocysteine levels were performed in 4 patients and were markedly elevated. The mean corpuscular volume (MCV) was increased in 2 patients.

Electrophysiologic Characteristics:

All patients had nerve conduction studies (NCS) performed, although in one patient this was only performed at the time of readmission with the same problem. Nine NCS revealed a sensorimotor axonal neuropathy (2 motor predominant), 3 revealed a motor axonal neuropathy/neuronopathy, and 1 study was normal.

MRI findings:

Eleven patients underwent spinal MRI scans of which 8 were abnormal. All abnormal studies demonstrated T2 hyperintense signal in the dorsal columns ("inverted V" sign), most commonly extending for 3-4 cervical segments but in 3 cases involving the entire cord. Cord expansion was present in 4 cases.

Discussion

Although N_2O has been used for decades as an anaesthetic and to relieve pain and anxiety during dental and medical procedures, recreational N_2O abuse is a relatively modern phenomenon. Sustained or excessive use of nitrous oxide results in toxicity due to dose-dependent inactivation of vitamin $B_{12,}$. The pathophysiological mechanisms of neurological damage due to B_{12} deficiency are well-established [5, 6, 18,19], however it is important to note that due to the inactivation of B_{12} by N_2O (and thus development of a "functional" B_{12} deficiency with normal serum levels in some patients), self-administration of oral B_{12} supplementation to prevent the harmful sequelae of prolonged N_2O abuse is usually ineffective[16,19,20].

There are several unifying features amongst the patients presenting with neurological manifestations of N_2O abuse in our case series. The reported heavy nitrous use of between 20-900 canisters per session over a period of weeks to months is in keeping with the established dose-dependent relationship of developing neurotoxicity[21]. Serum vitamin B_{12} levels were in the range of low to low-normal for all patients in our series, although in another series of 33 patients with neurologic complications, serum B_{12} was normal in 72%[16], in keeping with a functional vitamin B_{12} deficiency [4, 16, 18, 19, 22]. Interestingly, only 2 patients in

our series had haematologic abnormalities with macrocytosis, one of whom also had anaemia with elongated and tear drop cells and mild polychromasia. Clinical manifestations of N_2O neurotoxicity characterised by myelopathy and/or symmetrical, length-dependent sensory or sensorimotor large fibre peripheral neuropathy are well represented in our patient cohort, in keeping with the established literature[1-3, 6, 10, 16-19, 22, 23].

Notably however three of the patients in this case series (patients 1,5,11) developed a pure motor neuropathy/neuronopathy with no electrophysiological evidence of large fibre sensory involvement. Another two patients (2 and 13) had a motor predominant axonal neuropathy with only mild sensory involvement. These findings are not typical of neuropathy due to vitamin B_{12} deficiency. This is a significant finding in our cohort, adding to emerging reports of a severe motor neuropathy as a manifestation of N_2O toxicity[19 22]. Of particular concern is that this motor neuropathy has been observed to develop after B_{12} administration and following clinical recovery from an initial, sensory predominant myeloneuropathy, when functional measures of B_{12} deficiency have normalised and no effective treatment is available. We also observed clinical deterioration after administration and normalisation of B_{12} in Patients 1 and 5 of our series, with a predominant motor phenotype also being present in Patients 2, 11 and 13. The precise cause of this motor predominant neuropathy is not yet known; a recent study investigated pathophysiologic differences between the neuropathy caused by N_2O toxicity and that caused by vitamin B_{12} deficiency using motor and sensory nerve excitability tests.[24] N_2O abuse patients showed prominent motor superexcitability changes and less prominent sensory superexcitability changes suggesting a unique pathological process affecting the paranodal region[24]. This phenomenon suggests that N_2O toxicity on motor nerve may be independent of vitamin B_{12}

dependent metabolic pathways[19] . Recognition of this B_{12}-independent component of N_2O neurotoxicity is important as there is no current effective treatment other than B_{12} repletion, further highlighting the significant individual and public health risk posed by N_2O abuse.

The breadth of neurological complications of N_2O abuse are thus well-illustrated in this case series, with resultant significant impacts on morbidity and quality of life. Whilst the majority of cases improve with B_{12} supplementation and abstinence from N_2O use, the symptoms can be slow to resolve, and patients are not guaranteed complete recovery following treatment and rehabilitation[5, 9].

The public health significance of this issue is further demonstrated by the demographics of this patient cohort, with certain groups in the community appearing particularly at risk of N_2O abuse and its complications. Five patients in the series were international students with no significant past medical history (patients 1, 5, 6, 9, 11). Since the first case report of neurological disorders associated with recreational use of N_2O in mainland China in 2016, the number of related papers published, and patient numbers from both mainland China and Taiwan has been rapidly increasing each year[15-17,25]. International students are a major market for “nang” retailers, with some using services such as WeChat to target Chinese students. It has been suggested that these students are targeted as they do not have parental supervision and often have disposable income. The students in our series all reported social isolation, lack of family support, and high levels of stress and anxiety related to their studies. They perceived the use of N_2O to be both safe and legal. The remainder of these patients were Australian residents all with a prior history of mental illness and substance abuse. As all the patients in our cohort are young adults, the potential long-term

impact on function and quality of life as a result of neurotoxicity raises significant concern. Three of our patients were modified Rankin Score (mRS) 4 at discharge and three were mRS 3, representing significant disability. As the majority of reported case series are relatively recent without focus on long term prognosis, there is limited data on the long-term effects and burden of disease with disability affected life years.

Whilst no recreational drug use is ever considered completely "safe", N_2O has historically not been considered a drug of dependence[5, 18] and its sale is not regulated despite emerging evidence of psychological dependence, significant health impacts from neurotoxicity as described by this case series and the risk of death[18]. Under Australian Consumer Law, nitrous oxide canisters can be legally and cheaply purchased online and in store for use as a propellant in food preparation apparatus, such as whipping cream, however we have observed services clearly targeting recreational use (for example delivery services are available offering very rapid delivery of N_2O canisters 24-hours a day). Possession and recreational use is not restricted by legislation[11]. In South Australia, New South Wales and Victoria there are laws that state it is an offence to supply or sell nitrous oxide for non-medical human consumption, however it appears that enforcing these laws is challenging as the substance crosses a number of legislative boundaries.

As of April 1st 2020, the Government of South Australia updated the Controlled Substances Act to impose new penalties for the sale of N_2O in stores and online. These changes now make it an offence in that state to sell or supply N_2O to people under the age of 18 (and require notice of this on the premises), sell between 10pm and 5am, and to have N_2O visible or accessible to the public in retail stores. In addition, penalties for breaches in these regulations are now harsher.[26]

This case series illustrates contemporaneous experience with N_2O abuse in Australia, highlights particular groups at risk, and provides clear evidence of the urgent need for public health measures to protect the community from harm. We propose that better regulation of N_2O is required in all regions, in line with aforementioned changes made in South Australia. In addition, a targeted education campaign to warn about the risks is required to change the behaviour of young people frequently utilising this readily available and unregulated drug. Overall it is clear that a targeted, government-driven harm minimisation strategy is required to reduce the recreational use of nitrous oxide.

Conclusion

The neurological sequelae of N_2O toxicity have long been established, however recreational use is increasing. The breadth of neurological complications presenting to our tertiary referral hospital in Melbourne are in line with those described in current literature. We further illustrate the emerging, poorly understood, phenomenon of a pure motor neuropathy occurring independent of vitamin B_{12} inactivation by N_2O. The individual and public health implications of N_2O abuse require further recognition and public action to prevent significant harm in Australia.

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Table 1- Demographics, clinical and investigation findings in patient cohort

Patient	**Age**	**Sex**	**Clinical Presentation**	**Serum B12 (pmol/L)‡**	**Nerve Conduction Studies**	**Canister use Number/duration**	**MRI† spine** High T2 signal in dorsal columns	**MCV (fL)§**
1	19	F	Dysesthesia, ataxia, urinary retention, weakness, confusion	<92 ↓ HC¶ ↑	Motor axonal neuropathy/ neuronopathy LL>UL	††n/r / >3months	Yes	106 ↑
2	29	M	Paraesthesia, sensory ataxia	296	Length-dependent motor predominant axonal neuropathy	900 twice per week / 6 months	n/p#	84
3	29	M	Paraesthesia	112 ↓	Sensory > motor axonal neuropathy	400 daily / 3 months	Normal	97
4	24	F	Paraesthesia, ascending numbness, sensory ataxia	116 ↓ HC↑	Length-dependent sensorimotor axonal neuropathy	200-300 daily / 10 months	Yes	96
5	19	F	Behavioural change, confusion, Lower limb weakness, difficulty walking	<92 ↓	Length-dependent motor axonal neuropathy/ neuronopathy	100 daily / >3 months	Yes	97
6	18	F	Ataxic gait, lower limb weakness, paraesthesia	128 ↓	Length-dependent sensorimotor axonal neuropathy	300 per month / 6 months	Yes	88

7	24	F	Paraesthesia, numbness, ataxia	104 ↓	Normal	30-40 daily / years	Yes	95
8	28	F	Lower limb weakness, paraesthesia	39 ↓ HC ↑	Sensory > motor axonal neuropathy	600 daily / years	n/p	94
9	26	M	Confusion, lower limb weakness	<92 ↓	Length-dependent sensorimotor axonal neuropathy	100 daily / 1 month	Normal	94
10	20	M	Lower limb weakness, numbness	133 ↓	n/p on initial admission Length-dependent sensorimotor axonal neuropathy on 2nd admission	50-100 daily / 2 years	Yes	90
11	30	F	Lower limb weakness, ataxia, numbness, urinary retention	153 HC↑	Reduced LL motor amplitudes No sensory neuropathy	250 thrice per week / 18 months	Yes	99
12	22	M	Lower limb weakness, paraesthesia, ataxia	114 ↓	Length-dependent sensorimotor neuropathy	20-30 daily / 3 months	Normal	97
13	22	F	Subacute lower>upper limb paraesthesia, sensory ataxia, Lhermitte's sign	128↓	Length-dependent motor>>sensory axonal neuropathy	100 daily / >3 months	Yes	103 ↑

†MRI = magnetic resonance imaging. ‡B_{12} Reference range (140-650pmol/L). §MCV reference range (80-99 fL).
¶HC = plasma homocysteine. #n/p = not performed. ††n/r = not reported.

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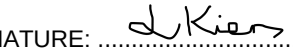
NAME: A/Prof Lynette Kiers ..... SIGNATURE: 

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Nitrous Oxide-Induced Neurological Disorders – an increasing public health concern

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1) Research project: A. Conception, B. Organization, C. Execution;

2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

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