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Original article

Recreational nitrous oxide abuse related subacute combined degeneration of the spinal cord in adolescents – A case series and literature review

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Abstract

Background: Nitrous oxide (N_2O) is a commonly used inhaled anesthetic in outpatient dental procedures. However, the increasing recreational use of N_2O may result in vitamin B_{12} deficiency-related neurologic and psychiatric symptoms. The aim of this study was to demonstrate the clinical features of chronic N_2O abuse in pediatric patients.

Methods: Patients under 20 years of age who were diagnosed with N_2O-induced subacute combined degeneration of the spinal cord from 2012 to 2018 were enrolled in this study. Clinical presentations, laboratory, imaging, ancillary studies, treatments and outcomes were analyzed.

Results: Nine patients were included, all of whom presented with symptoms of myeloneuropathy including limb numbness, limb weakness or unsteady gait. Six patients had low or low-normal vitamin B_{12} (cyanocobalamin) levels. Eight patients had evidence of subacute combined degeneration of the spinal cord via neuroimaging studies. All of the patients received vitamin B_{12} supplementation as treatment. All had full recovery of muscle power within 2 months. Five patients had persistent sensory deficits.

Conclusion: Chronic N_2O abuse can cause permanent neurological damage if not treated promptly. Clinical staff should be aware of the various presentations of neurotoxicity related to N_2O abuse.

Keywords: Nitrous oxide; Abuse; Vitamin B_{12} deficiency; Spinal cord

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1. Introduction

Nitrous oxide (N_2O), commonly known as laughing gas, has significant medical uses due to its anesthetic and analgesic effects, especially in dentistry. However, its recreational use is rapidly increasing, especially in the dance and festival scene. In the Netherlands, it is up to 44.6% of life time prevalence use according to the Global Drug Survey 2017 [1,2]. In addition, it has been reported to be the fourth most prevalent inhalant among adolescents in the USA [3] and the second most popular recreational drug after cannabis in the UK. Few studies have reported the prevalence among adolescents in Asia, however it has been reported to be the most commonly used illicit drug (1.3%) among juveniles on probation or parole in Taiwan [4].

Subacute combined degeneration of the spinal cord, an uncommon neuropsychiatric finding attributed to vitamin B_{12} deficiency, refers to degeneration of the posterior and lateral columns of the spinal cord. Initial neurological symptoms include paresthesia, diminished proprioception and vibration sensation, which can subsequently be followed by motor weakness. Sensory deficits usually begin in the feet and spread to the hands with varying degrees of ataxia [5]. Autonomic dysfunction may also be present, as well as intellectual or behavioral impairment [6]. The causes of vitamin B_{12} deficiency include impaired gastrointestinal absorption, pancreatic insufficiency, decreased intake, a congenital/inherited etiology, and drugs such as N_2O [7].

Subacute combined degeneration of the spinal cord was first described by Ludwig Lichtheim, a German physician in 1889, and it has been associated with a strict vegetarian diet without vitamin supplementation, nutritional deficiencies following gastrectomy, and N_2O anesthesia [6,8]. As the recreational use has increased, neurologic and psychiatric manifestations of N_2O abuse have been increasingly reported in adults [9]. Herein, we report nine juvenile patients with subacute combined degeneration of the spinal cord following chronic N_2O abuse, which, to the best of our knowledge, is the largest pediatric case series to date.

2. Methods

This retrospective hospital-based case series study was conducted at Chang Gung Children's Hospital, Taoyuan, Taiwan, a tertiary referral medical center, and Saint Paul's Hospital, Taoyuan, Taiwan, a secondary referral center from March 2012 to January 2018. Patients under 20 years of age who were diagnosed with N_2O-induced subacute combined degeneration of the spinal cord were enrolled. Clinical symptoms, onset and duration, laboratory data, nerve conductive velocities, somatosensory evoked potential and spinal magnetic resonance images of these patients were analyzed. The treatments and outcomes were compared.

Degeneration of the spinal cord was defined as increased signal intensity on T2-weighted magnetic resonance imaging (MRI) within the white matter of the spinal cord without contrast enhancement. It was considered to be related to N_2O if the patient had a history of N2O abuse during the period of 6 months before the onset of symptoms, and the degeneration was predominantly restricted to posterior and lateral columns. Detailed clinical history, diet behavior, physical and laboratory examinations were carefully obtained to exclude the other possible causative agents and etiologies. Ethical approval for this study was obtained from the Institutional Review Board of Chang Gung Memorial Hospital (IRB No. 201800588B0).

2.1. Literature review

A literature review was performed through searches of MEDLINE and PubMed databases, with the keywords "spinal cord degeneration nitrous oxide" and/or "myelopathy nitrous oxide" and/or "neurotoxicity nitrous oxide" with the studies limited to human studies and case reports. Reference lists of the selected studies were viewed as a secondary source.

Cases below 20 years of age who abused or used N_2O for recreational purposes were included. We excluded cases older than 20 years of age, those caused by N_2O anesthesia, with underlying vitamin B_{12} deficiency or following a vegetarian diet. The search yielded seven case reports. We summarized all adolescent cases and compared the characteristics with those in adults.

3. Results

Nine patients (eight girls and one boy) aged 14–19 years were included. Eight of these patients presented with numbness as the initial symptom, and three experienced hyperesthesia. All suffered from muscle weakness, including four with lower limb weakness alone and five with both upper and lower extremity involvement. Ascending weakness was noted in two cases and descending weakness in three. Eight patients eventually developed varying degrees of ataxia. When seeking medical help, the initial chief complaints included numbness or weakness (7/9), abdominal pain with constipation (1/9), and lower urinary tract symptoms (1/9). All patients had a history of N_2O abuse during the period of 6 months before onset of the symptoms, and seven of the patients had used N_2O over a long period of time (more than 6 months). None of the patients were veganists.

A decreased or absence of deep tendon reflex was found in all of the patients, and eight had proprioception defects. All of the patients had decreased muscle

power. Four of the patients had low levels of serum vitamin B_{12}, two of whom were within lower limits. Eight patients had an elevated serum homocysteine level, and only two patients had anemia. Six patients received neurophysiology studies. All had demyelinating features, four had evidence of spinal cord involvement and one had axonal degeneration.

Cervicothoracic MRI revealed degeneration of cervical areas in 6 patients, thoracic regions in 1, and simultaneous cervicothoracic involvement in the other. Table 1 summarizes the clinical features of the nine patients.

Cobamamide at a dose of 500–1500 μg per day was prescribed after the diagnosis in all patients, and all had full recovery of muscle power within 2 months. Five patients had persistent sensory deficits, and sensory ataxia persisted in one patient. Constipation was noted in one patient, while none of the patients had urinary tract symptoms.

A search of the literature found seven articles describing adolescent cases of subacute combined degeneration attributed to recreational N_2O abuse, including two males and five females. All of the patients had numbness/paresthesia and five had weakness, including two with an ascending pattern. Details of the published adolescent cases are summarized in Table 2. The characteristics of all adolescent cases with subacute combined degeneration of the spinal cord following recreational N_2O abuse are summarized in Table 3.

4. Discussion

N_2O-induced subacute combined degeneration of the spinal cord has been increasingly reported in recent years because of the increasingly popular use due to its euphoric effects [10]. The presentations should be included in the differential diagnosis of acute flaccid myelopathy, such as enterovirus 71 or D68 infection. N_2O destroys methylcobalamin, thus deactivates the enzyme methionine synthase. Impaired methylation of myelin sheath proteins caused by chronic vitamin B_{12} inactivation, which further results in axonal loss, is the main mechanism of N_2O-related spinal cord degeneration and myelopathy [11,12].

In adults, the most common initial symptom is paresthesia or ataxia [13]. In our case series, all of the patients developed muscle weakness, which was then followed by gait disturbance. Gait disturbance caused by loss of sensory input, in the early phase or mild form can be compensated by muscle strength, which is often stronger in adolescents than in elderly people, and this may explain the difference between the two groups. In adolescents, common symptoms include numbness, muscle weakness and ataxia, and rarely involuntary movements, dysuria, constipation and cognitive impairment. In adults, however, cognitive impairment has been reported to be a commonly associated neurotoxicity [5,14]. N-methyl-D-aspartate receptor antagonist toxicity and related cell death, of which adolescents are less vulnerable than adults, was suggested to be a probable mechanism in rodent models [15–17]. When seeking medical help, adolescents may present with abdominal pain, constipation or dysuria rather than an altered sensation in the limbs, which has not been reported in adult case series. The variability in adolescents not only raises certain difficulties in making a differential diagnosis, but also indicates the likely underestimation of N_2O abuse in this group.

The diagnosis of N_2O-induced subacute combined degeneration can be supported by clinical manifestations, neurologic examinations, MRI findings and distinct relationships to N_2O exposure. Posterior column sensory deficits followed by decreased muscle power with greater involvement of the lower limbs, and decreased tendon reflex are typical neurological findings in children. Dissociation between upper and lower limb reflexes, which has been frequently reported in adult [18], has not been reported in adolescents. Swelling of myelin sheaths and patchy myelopathic spongy vacuolation are characteristics of subacute combined degeneration [19,20], and can be detected by spinal MRI. An "inverted V" sign (Fig. 1), a symmetrical signal intensity abnormality limited to posterior or posterolateral columns, is a consistent feature [21]. Increased T2 signal intensity, reported to be most commonly involved in cervical and upper thoracic cords in adults [22], seems to affect the cervical and lower thoracic cords more in adolescents. Density of myelinated fibers in the fasciculus gracilis, which was reported highest in cervical area, could explain the vulnerability of cervical spine to nitrous oxide neurotoxicity in both groups [23].

In a systematic review of adult cases with N_2O abuse, 54.1% had neuroimaging changes and 72.2% had low or low-normal vitamin B_{12} serum levels [9]. In adolescents, in comparison, all had evidence of neuroimaging changes and less than half of them disclosed low levels of serum vitamin B_{12}. Most cases, however, had elevated levels of homocysteine. "Functional" vitamin B_{12} deficiency as assessed by measuring levels of methylmalonic acid and homocysteine, the substrates of reactions catalyzed by vitamin B_{12}, is a crucial clue for the diagnosis [24,25]. Therefore, an elevated homocysteine level appears to be a more characteristic feature than low vitamin B_{12} level both in adults and adolescents.

Withdrawal of exposure and prompt vitamin B_{12} supplements are essential treatments for N_2O-induced subacute combined degeneration [26]. Vitamin B_{12} therapy can be administered orally or intramuscularly [27]. Intramuscular supplements may be more suitable in patients who have undergone gastrectomy, however vitamin B_{12} deficiency can still be reversed easily with oral supplements [28]. Our case series received 500 to 1500 mcg cobamamide per day. Even though the dosage

Table 1
Clinical features of the 9 patients with nitrous oxide abuse.

Patient No.	Gender	Age	Symptoms			Neurological examination	Laboratory data		NCV Study* /SSEP study	Spinal MRI changes	N_2O abuse
			Numbness	Limbs weakness (Direction)	Others		Vit. B_{12} (pg/ml) (Ref. 197–771)	Homocysteine (μmol/L) (Ref. < 12)			
1	F	17	+	U + L	Hyperesthesia Ataxia	Decreased DTR Loss of P Decreased MP	221	12.1	Moderate motor neuropathy	C Spine	Heavily use, dose and duration not sure
2	F	16	+	U + L (Descending)	Ataxia	Absence of DTR Loss of P Decreased MP	219	10	Mild sensorimotor polyneuropathy/Normal	C1-C6 T7-T8	4L/day for 3 months
3	F	15	+	U + L (Descending)	Hyperesthesia Ataxia	Decreased DTR Loss of P Decreased MP	114	43	Mild polyneuropathy/ Spinal cord involvement	C2-C6	4-10*L* weekly for 6 months
4	F	18	+	U + L	None	Decreased DTR Loss of P Decreased MP	309	31	Moderate axonal sensorimotor polyneuropathy/Spinal cord involvement	NP	1 year, dose and frequency not sure
5	F	16	+	L (Descending)	Dizziness Hyperesthesia Ataxia	Decreased DTR Decreased MP	380	81.9	NP	C3-C6	Heavily use around 1 year, dose not sure
6	F	16	+	L	Ataxia LUTS	Absence of DTR Loss of P Decreased MP	112	119.6	NP	T8-T11	1 cylinder (6 kg)/month for 1 year
7	F	18	+	U + L (Ascending)	Ataxia	Decreased DTR Loss of P	195	18	Extreme sensorimotor polyneuropathy/Spinal cord involvement	C Spine	1 cylinder (6 kg) share with others, 3–4 times/ week for 1 year
8	M	19	–	L	Ataxia Constipation	Decreased DTR Loss of P Decreased MP	422	29	Moderate axonal sensorimotor polyneuropathy/Spinal cord involvement	C2-C7	More than 1 year; dose and frequency not sure
9	F	14	+	L (Ascending)	Ataxia Constipation Cramping	Absence of DTR Loss of P Decreased MP	<83	82.1	NP	C2-C8	4L/week for more than 1 year

C: cervical; T: thoracic; DTR: deep tendon reflex; F: female; M: male; L: lower; U: upper; LUTS: lower urinary tract symptoms; MP: muscle power; MRI: magnetic resonance imaging; NCV: nerve conduction velocity; NP: not performed; P: Proprioception; Ref.: reference of normal limits; SSEP: somatosensory evoked potential.

* The severity of axonal neuropathy is based on Electrophysiological Severity Scale, modified from Mondelli et al. [33]. "Mild" meant decreased amplitude of sensory nerve action potential (SNAP), 20–50% decrease of compound muscle action potential (CMAP) amplitude, decreased by <25% with respect to lower limits of motor conduction velocity(MCV) or reduced interferential pattern at full effort with or without denervation activity at rest in electromyography (EMG); "moderate" meant absolutely decreased amplitude of SNAP with normal sensory conduction velocity (SCV), 50–99% decrease of CMAP amplitude, decreased by >25% with respect to lower limits of MCV or discrete interferential pattern at full effort in EMG; "severe" meant decreased SCV and amplitude of SNAP, absence of CMAP or single interferential pattern at full effort in EMG; "extreme" meant absence of SNAP or no motor unit action potential.

Table 2
Published cases of spinal cord degeneration/myelopathy in adolescents caused by the recreational use/abuse of nitrous oxide.

Date	Reference	Age/sex	Symptoms	Neurologic exam	Lab	MRI changes	Treatment	Outcome
2012	Hsu CK, et al.	19/M	4-limb numbness Gait imbalance for 1 month	Muscular weakness Areflexia Ataxic Positive Romberg sign Sensory level	Low Vitamin B12 (156 pg/nL)	Posterior& anterior column of C-spine	1000 μg/day vitamin B12 × 5 days then 1000 μg/week × 2 months	Full recovery after 2 months
2016	Chen HJ, et al.	20/F	Unsteady gait Involuntary movement Distal tingling sensation for 1 month	Dystonia Muscle power normal Hyperreflexia Extensor plantar-response Vibration/proprioception impairment	Vitamin B12 normal Normocytic anemia	Posterior column of C1-C6	2000 μg/day × 3 days then oral form, dose not mentioned	Involuntary movements disappeared, Walk independent slowly 3 weeks later
2011	Lin RJ, et al.	18/F	Lower limb numbness for 2 months, ascending Leg weakness Unsteady gait	Hyporeflexia Pinprick, joint position, vibration impairment Weakness Steppage gait Constipation	Vitamin B12 normal High homocysteine	Posterior column of C2-C6	Intramuscular vitamin B12, dose and duration unknown	Loss follow-up
2012	Ghobrial GM, et al.	19/M	Progressive numbness and weakness	Decrease muscle power Hyperreflexia Absence of vibration, proprioception and sensory light touch	Vitamin B12 normal	Posterior column of C2-C7	Intravenous methylprednisolone	Symptom resolution in 36 h
2015	Matthew Jones, et al.	18/F	Hand numbness Leg weakness Drop foot for 2–3 weeks	Decreased muscle power of lower limbs and tendon reflex Ataxic gait	Vitamin B12 normal MMA normal	Dorsal column of cervical and thoracic spine	Vitamin B12, dose not mentioned	Ambulate 100 ft when discharge
2015	Duque MA, et al.	20/F	Lower leg paresthesia for 3 weeks Difficulty walking	Hip flexor weakness Thoracic sensory level Reduced proprioception in distal lower limbs	Low Vitamin B12 (126 pg/mL) High MMA No anemia High folate	Dorsal column & around central canal	Vitamin B12, dose not mentioned	Full recovery in 1 month
2017	Yuan JL, et al.	20/F	4 limb progressive paresthesia Unsteady gait for 15d	Mild cognition impairment, Decreased vibration & proprioception, bilateral hyporeflexia, sensory ataxia, positive Babinski sign and Romberg sign	Low folic acid No anemia Normal vitamin B12 and homocysteine	Posterior column of C1-T12	Intramuscular Vitamin B12 1 mg/day	Resolved markedly in 3 months

MRI: magnetic resonance imaging; C: cervical; T: thoracic.
MMA: methylmalonic acid.
Data collected from references [8,34–39].

Table 3
Summary of the 16 adolescent cases with subacute combined degeneration of the spinal cord following recreational nitrous oxide abuse.

Characteristics	n	%
Gender (n = 16)		
Male	3	19
Female	13	81
Age (years)	17.7 (14–20)	
Symptoms (n = 16)		
Numbness/paresthesia	15	94
Weakness	14	88
Lower limb	14	88
Upper limb	7	44
Ascending	3	19
Descending	3	19
Ataxia	14	88
Involuntary movement	1	6
Impaired cognition	1	6
Lower urinary tract symptom	1	6
Constipation	3	19
Neurological exams (n = 16)		
Loss of proprioception/vibration	13	81
Decreased muscle power	14	88
Hyporeflexia/areflexia	13	81
Hyperreflexia	2	13
Sensory level	2	13
Dystonia	1	6
Laboratory exams (N = 16)		
Anemia	3	19
Vitamin B12 (n = 15)		
Decreased/ lower limit	5/2	47
Normal	8	53
Homocysteine (n = 11)		
Normal	2	18
Elevated	9	82
Methylmalonic acid (n = 2)		
Normal	1	50
Elevated	1	50
Spinal cord involvement (n = 15)		
Cervical spine	14	93
Thoracic spine	5	33
Treatment (n = 16)		
Vitamin B12	15	94
Steroid	1	6
Prognosis (n = 13)		
Full recovery	6	46
Good recovery	5	38
Remained sequela	2	15

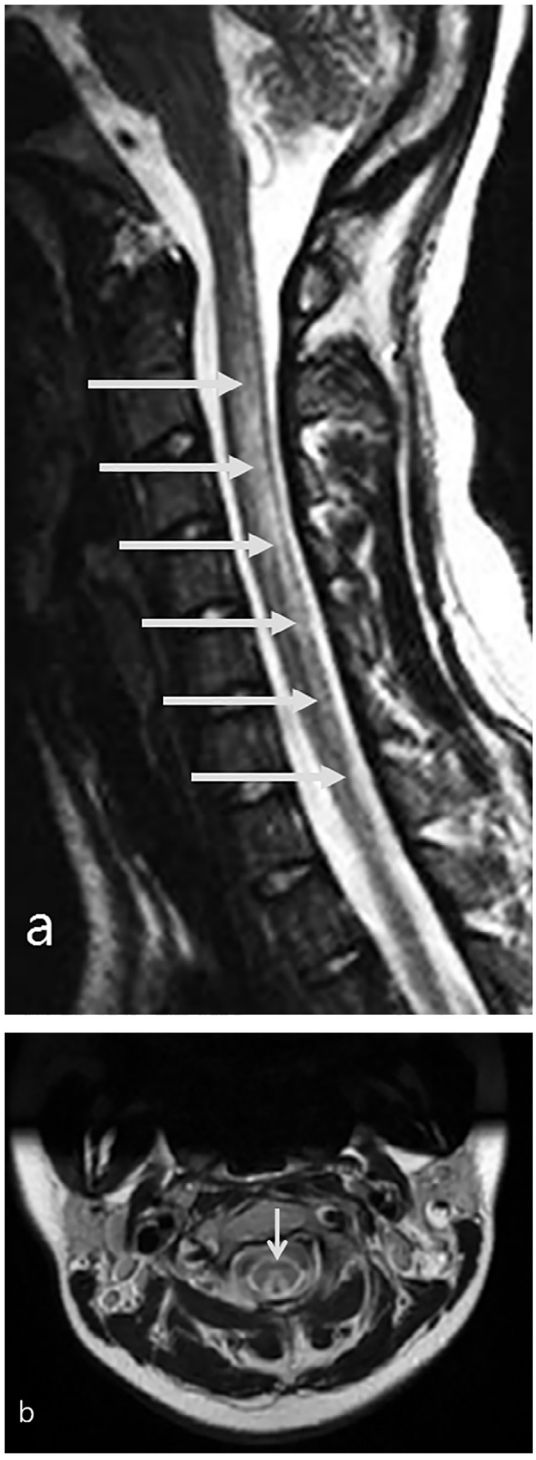

Fig. 1. A 15-year-old female suffered from N_2O-induced subacute combined degeneration. Magnetic resonance images of her spinal cord disclosed abnormal hyperintensities within the cervical dorsal column (a). Typical inverted V-shaped T2 signal intensity was noted on axial series (b).

was lower than that usually recommended (1000–2000 mcg per day) [27,29], the outcome was favorable. Full recovery was found 46% of the adolescents, which is much higher than that reported in adults (14–17%) [9,18]. The factors for favorable prognosis include a younger age, less severe neurologic deficits, less extensive spinal cord lesions on MRI, absence of anemia and early treatment [18]. Notably, no muscle weakness was reported on follow-up in our case series. N_2O-associated severe motor neuropathy, which has been reported to be independent of functional vitamin B_{12} deficiency [30,31], was not found in our adolescents.

Previous studies have reported that males are more likely to have experienced N_2O inhalation recreationally and also to be more likely to suffer from neurological symptoms [22,25,32]. In adolescents, however, we inci-

dentally found a female predominance in recreational N_2O-induced subacute combined degeneration. Further studies with a larger sample size are needed to evaluate potential gene-based associations.

The interpretation of the results in this study should be carried out in light of following limitations. First, this is a retrospective study with small sample size. However, the largest case series and the novelty in pediatric group may outweigh the limitation of small numbers. Second, serum methyl malonic acid (MMA) and homocysteine are both the most sensitive and specific markers of functional vitamin B_{12} deficiency, which meant better metabolic indicators of deficiencies at the tissue level. In our case series and literature review, nevertheless, few pediatric cases reported both. Third, it is preferable to use a combined preparation such as hydroxocobalamin in vitamin B_{12} deficiency so that both adenosylcobalamine and methylcobalamine, two active form can be replenished. However, only cobamamide was available as oral form in our medical setting. Finally, lack of formal cognitive testing and inconsistent duration of follow up may both affect the outcome of the interpretation. A prospective study may overcome these bias.

5. Conclusion

Our case series and literature review highlight the significance of N_2O-induced subacute combined degeneration of the spinal cord in adolescents. The increasingly popular use of N_2O among young people, the remarkable neurotoxicity, and the favorable outcome when diagnosed and treated earlier highlight the need for greater attention to be paid to adolescents who abuse N_2O.

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Declarations of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2018.12.003.

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