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Nitrous oxide abuse and associated neurological diseases

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Abstract

Objectives Nitrous oxide has long been used as an anesthetic agent. The recreational use and abuse are rapidly increased in Western countries and lead to many neurological complications.

Methods Retrospectively review of seven patients.

Results Seven patients aged 19–32 years, mean 22.6 years. They inhaled nitrous oxide between 1 month to 1 year prior to the symptom onset. They all presented with acute or subacute ataxia or motor, and sensory dysfunction. The two had coexisting encephalopathy. Electrodiagnosis showed sensorimotor axonal polyneuropathy. All patients had borderline or low serum vitamin B12 level. Two had high serum homocysteine or methylmalonic acid levels. Cervical spine MRI in two patients showed posterior column lesion. At average 2 month-follow up, all patients had minimal improvement. While at more than 6 month-follow up, most patients had moderate to complete recovery.

Conclusion Seven patients with nitrous oxide induced neurological disease are reported. All patients present with acute myelopathy and sensorimotor polyneuropathy. Short term outcome is generally not favorable while long term outcome shows remarkable improvement.

Keywords Nitrous oxide, Myelopathy, Neuropathy, Neurological illness, Vitamin B12 deficiency

Introduction

Nitrous oxide, commonly known as "laughing gas," has been utilized extensively in both industrial and medical applications [1–3]. In the medical field, it serves as an anesthetic and has been in use since the 1800s, in both major and minor surgeries. However, recreational misuse is becoming more prevalent due to its stimulating effects on the nervous system, inducing a sense of euphoria and trance. Unfortunately, this has led to addiction issues, especially among teenagers and young adults seeking decent entertainment [4, 5]. The misuse of nitrous oxide poses a significant public health concern due to its adverse effects on the nervous and cardiovascular systems [1–3]. This issue has been reported in Western countries but there is no report to date in Asian countries.

Nitrous oxide disrupts the B12 pathway primarily by oxidizing the cobalt in the cobalamin cofactor, converting it to cob(III)alamin, which renders it inactive. This inhibition impairs the conversion of methylcobalamin to adenosylcobalamin, which is crucial for methionine synthesis by methionine synthase and finally impacts DNA synthesis and methylation processes. Despite normal B12 levels, functional deficiency may occur in some cases and

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can be diagnosed by high methymalonic acid and homocysteine levels. The elevation of plasma homocysteine levels post-nitrous oxide anesthesia had been reported and could be explained by the influence of methylenetetrahydrofolate reductase gene polymorphisms on homocysteine concentrations after nitrous oxide exposure, highlighting the clinical implications of nitrous oxide-mediated disruption of the B12 pathway [6, 7].

Symptoms of nitrous oxide exposure vary based on the duration and amount of exposure. Short-term exposure may result in fainting or mild symptoms, while prolonged exposure can lead to tingling in limbs, difficulty in balancing, altered cognitive functions, and, in severe cases, permanent damage to the nervous system or death [3].

Patients exposed to large amounts of nitrous oxide may experience symptoms similar to hypoxia, necessitating urgent treatment involving oxygen administration and airway management. Blood tests to check vitamin B12 levels and subsequent supplementation, if required, are essential to address the side effects of nitrous oxide exposure [1–3].

Long-term exposure, even to small amounts, can lead to vitamin B12 deficiency, affecting the nervous system and potentially exacerbating existing health conditions. In most reported cases, especially neurological presentations, symptoms have been linked to a vitamin B12 deficiency, with reduced or borderline vitamin B12 blood levels [8].

This report discusses seven cases of this illness resulting from nitrous oxide inhalation from two hospitals in Thailand. The purpose of this report is to explore the correlation between nitrous oxide exposure and the characteristics of neurological symptoms, along with the outcome.

Materials and methods

A retrospective review was conducted on seven patients with a history of nitrous oxide abuse and neurological symptoms. The review included an analysis of clinical data, investigations, and follow-up information. Human Research Ethics Committee of Thammasat University (Medicine) (COA No. 069/2024, MTU-EC-IM-0-265/66) and Bangkok Hospital Institutional Review Board (COA No. 2023-28) have approved this study protocol.

Results

Clinical manifestations and laboratory findings from seven patients were summarized in Table 1.

The baseline characteristics of the seven patients in this case series reveal a mean age of 22.6 years, ranging from 19 to 32 years, with a majority being female (6 females, 1 male). Underlying diseases included depression in one patient, ataxic neuropathy due to B12 deficiency in another, and GERD in a third patient. Nitrous oxide (N_2O) usage varied widely, with durations ranging from daily for 2 years to every day for 1 week.

Investigative findings highlighted common clinical symptoms such as numbness, ataxia, confusion, imbalance, and weakness, with motor and sensory dysfunction present in all patients but distributed variably. Nerve conduction studies demonstrated sensorimotor axonal polyneuropathy with mixed features in three patients, severe sensorimotor polyneuropathy in one, and motor-predominant polyneuropathy in two. Blood levels for B12 displayed a mean of 176.55 pg./mL, ranging from 65.2 to 434 pg./mL, while some patients exhibited elevated homocysteine and methylmalonic acid levels which confirmed functional B12 deficiency status. MRI findings were suggestive of cervical myelopathy in four cases, with no abnormal findings in the remaining three.

Management involved B12 replacement through intramuscular injections for all patients, supplemented with specific medications such as B1, calcium, and oral cyanocobalamin, tailored to individual needs. Treatment durations varied between 1 week and 3 months. The follow up period were at 2–4 weeks, 2 months and every 3 months. However, some cases had lost follow up. In these cases, telephone follow up were used instead. The outcome was mainly focused on the weakness, gait/ambulation and functional status. Patient outcomes showed a spectrum of improvement, ranging from minimal to significant, observed over follow-up periods varying from 1 month to 1 year.

Patient 1

A 23-year-old patient presented with numbness and ataxia persisting for the past five months. She had a history of prolonged daily use of laughing gas for over two years, with a daily intake of up to 2000 milligrams. Although she ceased usage two months ago, mild cravings persisted. The patient had a background of untreated depression, hypothyroidism, and non-alcoholic steatohepatitis. Clinical symptoms included bilateral hand and foot numbness, progressively worsening imbalance, and persistent ataxia. Despite discontinuing laughing gas, symptoms remained unchanged. Physical examination revealed weakness in hip flexion, tibialis anterior, and extensor hallucis longus, with diminished joint perception sensation and absent deep tendon reflexes. Nerve conduction studies and electromyography indicated sensorimotor axonal polyneuropathy with mixed axonal and demyelinating features, associated with neurogenic weakness in the lower limbs. Vitamin B12 level was low(160.1 pg./ml) Vitamin B12 deficiency from nitrous oxide abuse was suspected. Treatment involved a 7-day course of daily intramuscular vitamin B12 injections and calcium replacement. After 4 weeks, the patient showed improvement with reduced numbness in hands and slight

Table 1 Clinical characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (year)	23	32	19	21	20	23	20
Underlying disease	Depression	No	Gastroesophageal Reflux Disease	No	Heterozygous Alpha Thalassemia	No	Depression
Concomitant medication	venlafaxine, aripiprazole, diazepam	No	lansoprazole	No	promethazine, tramadol	No	venlafaxine
Previous N_2O use	Every day for 2 years	Twice a week for 6 months	Twice a week for 2 months	Once a week for 1 year	Every day for 9 months	Once a week for one year and every day for 1 week	Every day for 2 years
Clinical Presentation	Numbness and ataxia for 5 months	Confusion, Heightened numbness in both feet, and deteriorated in stability for 1 day	Progressive numbness and weakness in both legs for over one month	Numbness in both feet especially toes for two weeks	Ataxia for 4 days	Alteration of consciousness for 1 day	Foot drop and inability to walk for 1 month
Motor dysfunction	+ (LL, distal predominant in TA)	+ (LL, distal)	+ (LL, distal)	+ (LL, distal predominant in TA, gastrocnemius, and EHL)	+(all extremities, distal predominant)	+(all extremities, proximal predominant)	+(LL, distal predominant)
Sensory dysfunction	+ (LL, distal)	+ (LL, distal)	+(both hands and LL)	+ (LL, distal)	+ (LL, distal)	+(all extremities)	+ (LL, distal)
Ataxia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Areflexia	+	-	+	-	+	+	+
Diagnostic Tests							
Nerve conduction study and EMG	sensorimotor axonal polyneuropathy with mixed axonal and demyelinating features	severe sensorimotor polyneuropathy	severe motor predominant, axonal polyneuropathy in both lower limbs, severe coexisting bilateral peroneal neuropathy	motor predominant polyneuropathy in both feet, Acute denervation at both TA and gastrocnemius.	moderate to severe mixed axonal and demyelinating sensorimotor polyneuropathy	moderate degree of asymmetrical sensorimotor axonal polyneuropathy, more severe in both lower limbs	severe sensorimotor polyneuropathy
Blood level for B12 (Normal 187-771 pg/mL)	160.1	434	65.2	198	165	135	352
Homocysteine level (Normal <15 mcmole/mL)	ND	ND	ND	ND	90.2	111.6	101
Methylmalonic acid (normal < 0.4 mcmol/mL)	ND	ND	ND	ND	2.66	8.84	11.2
ANA profile	Negative	Positive	Weakly positive	Not done	Not done	Not done	Not done
CBC	Normal	Normal	Macrocytic anemia MCV 100 fL	Normal	Hypochromic microcytic anemia MCV 65 fL	Macrocytic anemia MCV 108 fL	Normal
MRI Result	Normal	Normal	Cervical spine showed segmental T2 hyperintense foci at the posterolateral cord (inverted V appearance) along C2-5 levels.	Normal	Brain: Normal Cervical spine: hypersignal intensity at posterior aspect of spinal cord along C4-C7 levels	Cervical spine showed hypersignal intensity at posterior aspect of spinal cord along C1-C7 levels	Symmetrical non-enhancing hyperintensity at dorsal column C2-C6 levels with inverted V sign

Table 1 (continued)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Outcome	Minimal improvement	Able to do some standing on one foot but not stable	Minimal improvement	Minimal improvement	Moderate improvement	Marked improvement	Complete recovery
Follow up	1 month	1 year	2 months	1 month	6 months	10 months	9 months

LL, lower limb; ND = not done, CBC, complete blood count; MCV = mean corpuscular volume

improvement in feet, though stability remained an issue. Follow-up blood tests indicated low vitamin D and B12 levels, and the patient was advised on further care and precautions.

Patient 2

A 32-year-old patient had a medical history of ataxic neuropathy resulting from B12 deficiency due to nitrous oxide abuse one year ago. Despite oral B12 supplementation, there had been intermittent compliance, with the patient taking the B12 supplement (Methycobal®) irregularly. Additionally, the patient had resumed nitrous oxide usage, indulging once or twice a week. Presenting symptoms included confusion, heightened numbness in both feet, and a further deterioration in stability. Physical examination revealed a wide-based gait, a positive Romberg test, and instability during the tandem walk. Pin sensation was decreased up to the ankle, with significant diminishment in joint position sensation and vibration perception in both feet and ankles. Mild weakness in both ankle and toe movements was observed. Diagnostic tests indicated severe sensorimotor polyneuropathy, with absent sural responses in both feet, abnormal blood levels for B12 and B1, and positive results for antiparietal cell antibody and anti-intrinsic factor tests. The diagnosis was polyneuropathy due to a deficiency of B12 caused by nitrous oxide abuse. Treatment involved daily IM B12 (1,000 micrograms) and IV B1 (100 milligrams) for five days. After three months of treatment, the patient showed some improvement in standing on one foot but remains unstable.

Patient 3

A 19-year-old patient with a medical history of acid reflux has a history of using nitrous oxide, averaging twice a week continuously for two months. She presented to the hospital with symptoms of numbness and weakness that worsened over the past two weeks. Upon examination, motor weakness at both legs was observed, graded as 3 out of 5 (MRC scale) with a distal predominant pattern. There was a decrease in pinprick sensation, loss of proprioception, sensory ataxia with a positive Romberg test, and areflexia. Nerve conduction study and electromyography revealed severe motor-predominant axonal polyneuropathy in both lower limbs. There was a probable coexisting bilateral peroneal neuropathy associated with severe motor axonal loss and acute denervation at both tibialis anterior muscles. The serum B12 level was 65.2 pg./mL, and a complete blood count showed an MCV of 100 fL. MRI findings of the cervical spine indicated segmental T2 hyperintense foci at the posterolateral cord (inverted V appearance) along C2-5 levels, suggesting myelopathy. After 2-month- follow up, the symptoms minimally improved, with residual footdrop, distal foot numbness and ataxia.

Patient 4

A 21-year-old patient with no underlying disease, had been inhaling nitrous oxide once a week for a year. She presented with a gradual progression of numbness and weakness in both legs over one month, with a particular focus on numbness in both feet, especially the toes, persisting for two weeks. Despite discontinuing the use of nitrous oxide, minimal improvement was noted. The physical examination revealed motor dysfunction with distal predominance in the lower limbs, particularly in the tibialis anterior, gastrocnemius, and extensor hallucis longus muscles. Sensory dysfunction was observed distally in the lower limbs. The patient exhibited ataxia, and deep tendon reflexes were absent at the ankle joint. Diagnostic tests indicated motor-predominant polyneuropathy in both feet with normal sensory nerve conduction studies. Additionally, there was acute denervation at both the tibialis anterior and gastrocnemius. Blood tests revealed a B12 level of 198 pg./mL. The patient showed minimal improvement after one month of treatment, and lost follow up.

Patient 5

A 20-year-old patient had a history of daily laughing gas use for 9 months and occasional promethazine and tramadol use. She experienced hallucinations after initial nitrous oxide use and ceased it for 5 months. Then she resumed a more frequent inhalation pattern a month before the present illness. Over four days, she reported feeling drowsy, dizzy, and unsteady, with weakness in her arms and legs but no numbness, prompting her to discontinue gas inhalation. The physical examination revealed alertness, pallor, and weakness in all extremities (grade 3 out of 5 MRC score), as well as upper proximal

weakness (grade 4 out of 5). Deep tendon reflexes were decreased, and absent at the patella and Achilles tendon. A wide-based gait, positive Romberg test, normal pinprick, and temperature sensation were noted, along with significantly diminished joint position sensation and vibration perception in all extremities.

Diagnostic tests indicated moderate to severe mixed axonal and demyelinating sensorimotor polyneuropathy, more severe in both lower limbs, with low B12 levels and elevated homocysteine and methylmalonic acid. MRI of cervical spine also showed hypersignal intensity at C4-7 levels. Treatment included a 7-day course of daily intramuscular vitamin B12 injections, followed by weekly injections and oral cyanocobalamin and ketosteril. After 6 months of follow up, moderate improvement was noted with remaining mild ankle and toe weakness.

Patient 6

A 23-year-old patient with no underlying disease had been using nitrous oxide every day for one week. She presented with alterations in consciousness lasting one day. Upon admission, she was found to have quadriparesis (more severe in lower limbs) and hyporeflexia. Diagnostic tests revealed a moderate degree of asymmetrical predominantly motor axonal polyneuropathy, more severe in both lower limbs, along with acute denervation at both the tibialis anterior and gastrocnemius. Blood tests showed a low B12 level, high homocysteine and methylmalonic acid level. The patient demonstrated moderate improvement after B12 IM treatment one month, once weekly and followed by oral vitamin B12. After 10 months of follow up, marked improvement was noted with remaining mild toe weakness.

Patient 7

A 20-year-old patient with a history of depression and use of venlafaxine had a two-year history of daily laughing gas use. She presented with foot drop and incapacity to ambulate for one month. Physical examination showed reduced pin and touch sensation in both hands and feet (up to the wrist and knee), weakness in quadriceps (grade 4 out of 5), ankle (grade 1 out of 5), toes (grade 0 out of 5), and gastrocnemius (grade 2 out of 5), rendering her unable to walk. Investigations revealed a B12 level of 352 pg/mL, homocysteine level of 101 mcmol/mL, and methylmalonic acid level of 11.2 mcmol/mL. MRI of the cervical spine revealed symmetrical and non-enhancing hyperintensity lesions at the bilateral dorsal column C2-6 levels. Nerve conduction study and EMG demonstrated severe sensorimotor axonal polyneuropathy with acute denervation and poor motor unit recruitment at distal leg muscles.

She was treated with B12 injections of 1000 mcg daily for one week, followed by weekly or biweekly injections for 6 weeks and oral long term B12 therapy. Repeat B12 level was >2000 pg/mL and homocysteine was reduced to 8.5 mcmol/mL At 6 months, nerve conduction study still showed moderate to severe sensorimotor polyneuropathy, but EMG found resolved acute denervation and marked improvement in motor unit recruitment. A follow-up examination showed overall improvement at 3 months and complete recovery at 9 months.

Discussion

In this case series, all patients were teenagers or young adults who were exposed to nitrous oxide for a long period of time. The onset is rather acute or subacute, than chronic neuropathy. This clinical presentation could be from recent increase in its usage. The correlation between exposure and severity of neurological symptoms were noted. Most patients were quite healthy at baseline but many of them has underlying psychiatric disease, particularly depression. Nevertheless, their illness and concomitant medications are not likely associated with B12 deficiency.

Regarding the laboratory result, most patients had borderline or low vitamin B12 level. In case of a high clinical suspicion of nitrous oxide abuse, homocysteine and methylmalonic acid should be measured to confirm causing functional B12 deficiency. Nevertheless, methylmalonic acid is not often tested based on our routine clinical practice. Its assay is not widely available in resource limited setting. In Thailand, it needs to be sent oversea. Therefore, this test may not be necessary if the diagnosis of functional B12 deficiency is quite clear.

MRI were performed in most patients and correlated with each patient's clinical syndrome. MRI of cervical spine is often done for quadriparetic or pararetic cases, while MRI brain may not be beneficial in these cases. Nevertheless, nerve conduction study and electromyography were more important, and they were performed in every case to diagnose and characterize polyneuropathy diagnosis.

In our cases, we used vitamin B12 injection 1 mg/day for 2 weeks, then 1 mg/week injection for 4 weeks, then 0.5 mg two or three times a day. Because of normal absorption in these cases, oral B12 form were used for long term supplement. After the initial treatment, the dosage may be adjusted, depending on the severity and vitamin B12 level during follow up period. The short term outcome was not favorable with remaining severe weakness or gait disorder. However, the long term functional outcome at 6 months or more showed marked improvement or complete recovery. Some had remaining ankle or toes weakness.

A retrospective observational study in the Netherlands, nitrous oxide poisoning from recreational use alarmingly increased after EU-legislation change. The incidence has

exponentially increased from 2010 to 2020, along with signs of peripheral neuropathy in these cases [9]. Due to its initial perception of its harmlessness, the public may not be aware of the potential consequences of regular abuse. The limitation of purchased amount of nitrous oxide to consumers may aid in reducing its recreational use, whether in a large cylinder or whip cream cartridge.

Regarding the clinical information, paresthesia is the most common complaint, predominantly in lower limbs which is associated with other spinal cord dysfunction signs and symptoms. Mid cervical (C3-6) spinal cord is the most affected level in MRI. It often reveals symmetrical non-enhancing hyperintensity at dorsal column with inverted V sign. The amount of nitrous oxide consumed correlates with methylmalonic acid level which is an important biomarker of functional B12 deficiency [10]. When facing the clinical syndrome of acute or subacute sensorimotor impairment, clinician should also look for other differential diagnosis such as Guillain Barre syndrome, polyneuropathy from nutritional deficiency or toxic substance, transverse myelitis and other causes of myelopathy syndrome.

Normal vitamin B12 level can be found in this syndrome. Therefore, the measurement of methylmalonic acid and homocysteine level should be performed for functional B12 deficiency. Discontinuation of nitrous oxide abuse is the extremely important, Early treatment with high dose parenteral B12 such as cyanocobalamin once daily, then follow by oral supplementation if the absorption is ensured. The patient should have a long term follow up and maintenance of B12 supplementation because recurrent use is quite common.

Presumptive B12 supplement may not aid in reducing this complication. Four chronic abusers who took oral vitamin B12 supplementation, as recommended by other users and online forums, still had functional B12 deficiency and developed subacute combined degeneration of spinal cord [11]. Not only myeloneuropathy form B12 deficiency, acute cognitive impairment, which was followed by myelopathy has been described as the initial manifestation of its toxicity in a regular abuser despite normal B12 level. The symptoms rapidly resolved with timely intravenous supplementation of vitamin B12 [12].

Long term prognosis in these chronic cases may not be favorable. Nine out of 22 cases still had ongoing neurological sequalae and required walking aids on discharge despite prolonged rehabilitation. At the average follow up of 183 days, only 10.5% of the patients were asymptomatic. Persistent sensory changes, weakness in the upper and lower limbs, and gait abnormality were noted in almost half of them [10]. However, in our series, most patients significantly improved or recovered in 6 months, despite the poor short term outcome. Minor distal leg and toe weakness were still noticeable. The prognosis may be affected by duration of the nitrous oxide use, early diagnosis and treatment.

Furthermore, social media posts and internet searches is also rapidly increased to obtain nitrous oxide among the student groups [13]. Educating parents about the potential dangers of nitrous oxide is crucial to prevent addiction problems in teenagers. Epidemiological data highlights the need for increased attention and monitoring of nitrous oxide use, especially in industrial settings where exposure can lead to adverse health effects.

Work-related nitrous oxide poisoning is not uncommon, often occurring during food preparation processes. Proper use of nitrous oxide is paramount, considering its toxic nature and widespread use in the food industry. Knowledge dissemination about correct usage, restricting it to industrial and experimental purposes, and implementing personal protection methods can mitigate the risk of illness and its severity [1, 3, 14].

The limitation of this study is its retrospective nature with small sample size, potential selection bias, and the lack of standardized assessment tools. Nevertheless, nerve conduction study and EMG, biochemical test and imaging have been performed to make a clear diagnosis. In general, it is quite difficult to estimate the exact amount of nitrous oxide used due to the variability in amount, means of use, frequency and other related factors. Many patients may be asymptomatic for a prolonged period and become diagnosed when severe weakness or gait deficit develop. Physicians should have high clinical suspicion when facing young patients with polyneuropathy or myelopathy, and the diagnosis should be confirmed with relevant tests. Further research could address these issues and lead to a better outcome.

Conclusion

Nitrous oxide abuse is becoming an epidemic worldwide. The neurological manifestation ranges from acute encephalopathy and chronic myeloneuropathy which leads to long term disability. Its wide range of clinical manifestation may mimic other diseases. A high index of suspicion, early diagnosis, and long-term follow-up with B12 supplementation are crucial for managing this treatable condition. This study underscores the need for increased awareness, education, and preventive measures to address the growing public health challenge posed by nitrous oxide misuse.

Abbreviations

ANA	Antinuclear antibody
CBC	Complete blood count
EU	European Union
IM	Intramuscular
LL	Lower limb
MCV	Mean corpuscular volume
MRC	Medical Research Council

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Author contributions
K. K.: conceptualization, methodology, supervision, data acquisition, writing – original and final draft, review and editing; P. C. and W. K.: data acquisition, writing- original draft, review and editing. All authors approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The institutional review board (IRB) takes responsibility for the anonymization of the patient. The Human Research Ethics Committee of Thammasat University (Medicine) (COA No. 069/2024, MTU-EC-IM-0-265/66) and Bangkok Hospital Institutional Review Board (COA No. 2023-28) have approved this study protocol. The informed consent has been waived by the institutional review board.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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