Subacute Combined Degeneration Caused by Nitrous Oxide Intoxication: Case Reports

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Abstract-

Purpose: Case reports with a comprehensive review of the current literature concerning subacute combined degeneration induced by nitrous oxide inhalation. A differential diagnosis should be considered when young patients present with progressive myelopathy because that the misuse of nitrous oxide has potentially serious outcomes.

Cases Report: Three young patients aged from 18 to 24, one male and two females, were diagnosed with progressive ascending numbness in four limbs or both legs and ataxia. They all had been inhaling nitrous oxide from whipped-cream containers for several months. A cervicothoracic magnetic resonance imaging scan revealed long segmental hyperintensity changes at the posterior column of the spinal cord. Serological examination showed a low level of vitamin B12. Subacute combined degeneration of the spinal cord was diagnosed and the etiology was considered related to nitrous oxide misuse. Their neurological status, neuroimage, and neurophysiologic condition improved after vitamin B12 supplementation and cessation of nitrous oxide inhalation.

Conclusion: Iatrogenic usage of nitrous oxide apparently resulted in subacute combined degeneration in our three patients. Recently, nitrous oxide misuse has increased among young people. Subacute combined degeneration of the spinal cord should be considered as a possible outcome of such abuse.

Key Words: nitrous oxide, vitamin B12 deficiency, subacute combined degeneration, methionine, nagging, nanging

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INTRODUCTION

Subacute combined degeneration is characterized by myelopathy and peripheral neuropathy caused by vitamin B12 deficiency, which is usually caused by a strict vegetarian diet without vitamin supplementation. Stomach surgery can also cause this problem[1,2]. Inhalation of nitrous oxide, used as an anesthetic agent, is a common iatrogenic etiology of subacute combined degeneration in patients with vitamin B12 deficiency. The condition is most common after intra-operative exposure or use in dental procedures[3,4,5]. However, an increasing number of people have been using nitrous oxide as a recreational drug. Here, we report on three

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young patients who presented with myelopathy and peripheral neuropathy due to long-term nitrous oxide misuse, which is a rare etiology of subacute combined degeneration.

CASE REPORT

Case 1

A 24-year-old male university student reported intermittent numbness and weakness in his four distal limbs. He had no significant medical history, and his family history was also unremarkable. He had been inhaling nitrous oxide from bottles (1000 L per bottle) at the rate of four bottles per week. He discontinued this when he experienced intermittent ascending numbness in his fingers and toes. He went to a local hospital and was treated with intramuscular methylcobal injections (1000 mg every day) for five consecutive days. However, his condition progressively deteriorated and he developed an unsteady gait. He was, then, referred to our neurology ward for further evaluation and management.

Neurological examination revealed mild weakness by manual muscle tests (MMT 4+ /5) and hyperreflexia with clonus in the bilateral lower limbs. Joint position sensations, vibration, and pinprick sensations were impaired below the sixth thoracic dermatome. A severe spastic gait and sensory ataxia with a positive Romberg sign were noted. There were no cerebellar signs but autonomic dysfunctions such as constipation, urinary retention, and loss of morning erection were found. Myelopathy involving the posterior column and the bilateral corticospinal tract and possible polyneuropathy with sensory and autonomic involvement were suspected.

Initial tests showed no anemia (Hb, 13.5 g/dl) but an increased mean corpuscular volume (MCV) (100 fL; normal range 89+10fL). The level of vitamin B12 was low (149 pg/ml) when it was measured at local hospital, but they were normal after oral and intramuscular vitamin B12 supplementation. Parietal cell antibody levels, HIV antibody levels, and the autoimmune profile were within normal ranges. Nerve conduction velocity (NCV) showed reduced amplitude of CAMP in the right tibial and left peroneal nerves. Motor conduction velocity was slow in all sampled nerves of the lower limbs. Sensory conduction velocity in the left sural nerve was also slow. An F-wave study showed prolonged minimal F latencies in all sampled nerves of the lower limbs with A waves in the left peroneal nerve. The respiratory rate variability (RRIV) showed a reduced variance of RR intervals at rest and during deep breathing. The sympathetic skin response (SSR) was absent in bilateral soles. A sensorimotor polyneuropathy with autonomic dysfunction was diagnosed. The somatosensory evoked potential (SSEP) study revealed spinal cord involvement. Magnetic resonance imaging (MRI) scans (Fig. 1-A, B) showed long segmental hyperintensity changes at the posterior column from the second to the sixth cervical vertebrae. Analysis of the cerebrospinal fluid (CSF) revealed an elevated protein level without pleocytosis, 95 mg/dl initially and 71 mg/dl two weeks later. Superimposed inflammatory neuropathy was also considered as a possibility.

Because of poor response to vitamin B12 supplementation and the possibility of superimposed inflammatory neuropathy, he underwent plasmapheresis in addition to intramuscular vitamin B12 administration. Dramatic improvement was noted one week later. He could walk independently with only slight unsteadiness. He continued to receive vitamin B12 supplements and rehabilitation.

He did not inhale nitrous oxide during the outpatient clinic follow-up period. He had a steady gait and only mild numbness in the distal part of his four limbs after three months of vitamin B12 supplementation. The follow-up cervicothoracic MRI 3 months later showed that the previous lesions had resolved (Fig. 1-C, D). At the 1-year follow-up, his neurological condition remained satisfactory.

The severity of the polyneuropathy had improved, as indicated by follow-up NCV studies. The results of the SSR and RRIV studies were within normal limits.

Case 2

An 18-year-old female high-school student reported intermittent numbness in her lower limbs since two

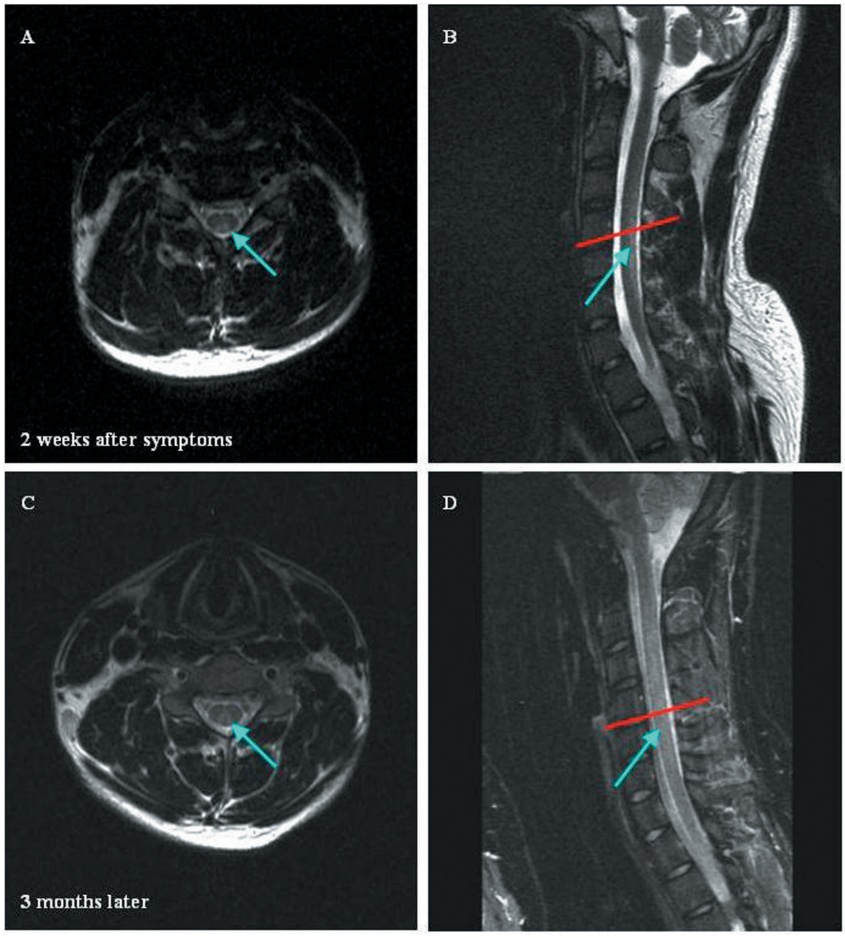

Figure 1. (A) (B): MRI of the cervical spine done two weeks after symptom showed long segmental hyperintensity change on T2WI at posterior column of spinal cord from the secondary to sixth cervical level (arrow), slightly more on the left and slightly fifth to sixth cervical level predominant. The lesion could be an inflammatory demyelination lesion or related to vitamin B12 deficiency. (C) (D): MRI of the cervical spine did three months later show faintly hyperintensity on T2WI at posterior paramedian spinal cord from the secondary to sixth cervical level. It is less prominent compared with the prior study.

months ago. The numbness was tingling in the beginning, but became hypoesthesia later, then ascending to bilateral hips one month prior to this admission. Numbness at finger tips was also noted. Her gait became unsteady and she fell down easily at walking. She had difficulties to put on and occasionally dropped her slippers. She also noted bilateral legs weakness so she had difficulties in climbing stairs up and down. Clumsiness was noted when she used chopsticks and wrote. Due to progressive unsteady gait, she was admitted to our ward for further management.

She had no significant medical history except an episode of oral ulcers was noted at gingiva, upper palate and pharynx with fever two months ago. Enterococcal infection was told by a local medical doctor and her oral ulcer improved. She started to use nitrous oxide in recent years at party. The frequency was about once a month in recent few years and the frequency increased to sequential 2-3 days per week since three months ago.

Neurological examination revealed mild weakness with scores of MMT 4-4+ /5 and hyporeflexia in four limbs. Joint position and vibration sensation over lower limbs, and pinprick sensations below the second thoracic dermatome were impaired. Cautious, high steppage gait

Table 1. Summary of clinical features in 3 cases of subacute combined degeneration after abuse of nitrous oxide inhalation

Case	Sex	Age (year/ old)	Initial symptom	Duration of inhalation of NO	Neurophysiology Study	Spinal cord MRI	Laboratory data
1	M	24	Four limbs numbness	4L per week for 2 months	NCV: axonal sensori-motor polyneuropathy RRIV/SSR: autonomic dysfunction SSEP: spinal cord lesion	hyperintensity changes at the posterior column (2^{nd} to 6^{th} cervical cord)	Hb: 13.5 g/dl MCV: 100 fL Vitamin B12: 149 pg/ml (at local hospital)
2	F	18	Both legs numbness	2-3 days per week for 3 months (volume not sure)	NCV: motor-predominant polyneuropathy SSEP: axonal polyneuropathy and posterior column lesion of the spinal cord	hyperintensity changes at the posterior column (2^{nd} to 6^{th} cervical cord)	Hb: 12.9 g/dl MCV: 101.2 fL Vitamin B12: 275 pg/ml
3	F	20	Both legs weakness and numbness	2-3 canisters per day for 2 months (volume not sure)	NCV: axonal sensorimotor polyneuropathy with demyelinating features	hyperintensity changes at the posterior column (2^{nd} to 7^{th} cervical cord)	Hb 12.8 g/dl MCV: 101.6 fL Vitamin B12 237 pg/ml

NCV: nerve conductive velocity

SSEP: somatosensory evoked potential

RRIV: respiratory rate variability

SSR: sympathetic skin response

Normal range for laboratory: MCV: 89±10fL; Vitamin B12: 179-1132 pg/ml

Motor Conductive Velocity

		distal latency (ms)	amplitude (mV)	NCV (m/s)
Case 1.	Median. R	4	12.7	50
	Ulnar. R	3.4	16.78	54
	Median. L	4	13.41	52
	Ulnar. L	3.3	15.09	55
	Peroneal. R	5.8	2.079	36
	Tibial R.	5.5	2.475	40
	Peroneal L.	6.1	0.887	34
	Tibial L.	5.8	4.331	37
Case 2.	Median. R	4	9.324	50
	Ulnar. R	3.2	13.32	46
	Median. L	3.8	10.51	51
	Ulnar. L	2.9	10.9	51
	Peroneal. R	5.3	1.178	34
	Tibial R.	4.2	5.887	35
	Peroneal L.	5.3	1.343	32
	Tibial L.	4.3	3.842	33
Case 3.	Median. R	4.5	8.7	54
	Ulnar. R	3.5	11.6	51
	Median. L	4.4	12.2	48
	Ulnar. L	3.7	11.5	47
	Peroneal. R	5.8	2.3	31
	Tibial R.	6.1	8.7	29
	Peroneal L.	7	3.9	30
	Tibial L.	8.5	8.6	33

Sensory Conductive Velocity

	latency (ms)	amplitude (μV)	NCV (m/s)

Case 1.	Median. R	2.4	56.25	58
	Ulnar R.	2.5	38.49	57
	Sural R.	3.4	11.82	41
	Median. L	2.5	54.06	56
	Ulnar L.	2.4	34.64	57
	Sural L.	3.6	12.04	39
Case 2.	Median. R	2.7	26.93	52
	Ulnar R.	2.7	15.69	51
	Sural R.	3.2	10.03	44
	Median. L	2.6	31.41	55
	Ulnar L.	2.8	14.07	51
	Sural L.	3.2	12.96	44
Case 3.	Median. R	2.8	33	50
	Ulnar R.	3.2	32	43
	Sural R.	absent		
	Median. L	3.2	40	44
	Ulnar L.	3.3	26	42
	Sural L.	absent		

F-waves

		min-lat (ms)	F-%	
Case 1.	Median. R	28.4	100	
	Ulnar. R	28	100	
	Median. L	27.4	100	
	Ulnar. L	27.8	100	
	Peroneal. R	56.5	100	
	Tibial R.	58	100	
	Peroneal L.	A-waves		
	Tibial L.	57	100	
Case 2.	Median. R	25.6	50	
	Ulnar. R	25.9	100	relatively uniform shape
	Median. L	24.7	60	
	Ulnar. L	26.3	100	
	Peroneal. R	A-waves		
	Tibial R.	52.3	100	relatively uniform shape
	Peroneal L.	54.8	83.3	elatively uniform shape
	Tibial L.	52.7	100	
Case 3.	Median. R	22.9	80	
	Ulnar. R	29.4	100	
	Median. L	32.1	90	
	Ulnar. L	31	90	
	Peroneal. R	63.8	50	
	Tibial R.	68.3	90	
	Peroneal L.	61.7	60	
	Tibial L.	69	100	

H-reflexes

		latency (ms)
Case 1.	Tibial. L	34.4
	Tibial. R	33
Case 2.		Not performed
Case 3.	Tibial. L	absent
	Tibial. R	absent

Autonomic nerve tests

	RRIV Resting (%)	Deep breathing (%)	SSR Palm	Sole
Case 1.	10.7	14	+	-
	10.8	12.7		
	9.95	13		
Case 2.	19.7	30	+	+
	16	24.5		
	14.9	27.1		
Case 3.	17.4	33.3	+	+
	16.6	27.6		
	20.3	31.3		

Somatosensory evoked potential

		N1 (ms)	P1 (ms)	N2 (ms)	P2 (ms)	N3 (ms)
Case 1.	Median. R	22.4	30.4			
	Median. L	21.2	30			
		P1 (ms)	N1 (ms)	P2 (ms)	N2 (ms)	
	Peroneal. R	67.2				
	Peroneal L.	66				
		N1 (ms)	N13 (ms)	N9 (ms)	N1-N13	N13-N9
Case 2.	Right side	19.8	13.5	10	6	3.8
	Left side	19.5	13.4	9.6	6.2	3.6
Case 3.		Not performed				

Table 2. Review of literature for SCD related with N_2O inhalation

Author (et al)	No. of Patient	Sex/Age	Route of N_2O	Diagnosis	Country	Year	Reference
Tatum WO	1	M/25	Abuse for 3-4 years	SCD with pseudo-Guillain-Barre yndrome	USA	2009	23
Renard D	1	M/46	Anesthesia	SCD	France	2009	22
Singer MA	1	M/27	Anesthesia for dental procedures	SCD	USA	2008	6
Cartner M	1	F/20s	Abuse for 10 days	SCD	Australia	2007	10
Wu MS	1	F/26	Abuse	SCD	Taiwan	2007	13
Cohen Aubart F	2	*	Anesthesia	SCD	France	2007	20
Lin CY	1	M/41	Abuse for 10 years	SCD	Taiwan	2007	21
Shulman RM	1	F/23	Abuse for 8 months	SCD	Australia	2007	12
Vasconcelos OM	1	M/36	Anesthesia	SCD	USA	2006	19
Ahn SC	1	M/NR	Anesthesia	SCD	USA	2005	3
Ilniczky S	2	M/52	Anesthesia	SCD	Hungary	2002	4
Jongen JC	4	3F1M/49-74	Anesthesia	SCD	Germany	2001	24
Sesso RM	1	F/63	Anaesthesia, previous macrocystic anemia	Cervical myeloneuropathy	Spain	1999	5
Girón JM	1	**	Anesthesia	SCD	Spain	1998	25
Beltramello A	1	F/73	Anesthesia	SCD	Italy	1998	17
Flippo TS	5	NR	Anesthesia	SCD	USA	1992	26
Stacy CB	2	NR	Prolonged exposure (occupation: NR)	Severe myeloneuropathy and Macrocytic anemia	USA	1986	14
Blanco G.	1	NR	Dentist, abuse for 8 months	Severe myeloneuropathy and Macrocytic anemia	USA	1983	8
Layzer RB	15	NR	14 dentists; 13 N_2O abused from 3months to several years	Axonal sensori-motor polyneuropathy myelopathy, post/lateral column	USA	1978	27

* Article in French ** Article in Spanish

NR: not recorded

Abbreviation: SCD: subacute combined degeneration; N_2O: nitrous oxide

and positive Romberg sign were noted. There was no cerebellar sign. In addition, she reported mild constipation.

Initial tests showed no anemia (Hemoglobin, 12.9 g/dl) but increased MCV (101.2 fL, normal range 89+10fL). The level of vitamin B12 was above lower limits (275 pg/ml; normal range 179-1132 pg/ml) but high homocysteine level (71.77μmol/L; normal range 3.4-15.6μmol/L) was noted. Parietal cell antibody and HIV antibody levels and the autoimmune profile were within normal ranges. The NCV study showed reduced compound muscle action potential amplitudes and slowing of motor conduction velocities in bilateral tibial and peroneal nerves. The F-waves study showed prolonged F-wave latencies in bilateral tibial and peroneal nerves with A-waves in the right peroneal nerve and a relatively uniform shape of F-waves in the right ulnar, tibial and the left peroneal nerves The results of SSR and RRIV studies were within normal limits. Motor-predominant polyneuropathy or cervical and lumbosacral polyradiculopathy was impressed. The SSEP study suggested coexistence of axonophic polyneuropathy and posterior

column lesion of the spinal cord. MRI scans showed long segmental hyperintensity changes at the posterior column from the second to the sixth cervical vertebrae. Analysis of the CSF revealed normal protein and cell counts.

Under the impression of cervical myelopathy and polyneuropathy, related to Vitamin B12 deficiency from nitrous oxide abuse, intramuscular Vitamin B12 was administered. However, she lost follow up after discharge.

Case 3

A 20-year-old female had frequent drinking and smoking. She also inhaled nitrous oxide at a rate of 2-3 canisters per day for two months before this episode. A progressive ascending numbness were noted in her both legs followed by distal weakness and gait disturbance since she began to inhale nitrous oxide. The numbness then ascended to abdomen, thorax, upper limbs, and clavicles. She had difficulty in standing up from chair and putting on slippers. Objects she grasped frequently dropped. She had decreased hot sensation when taking a shower. She felt like something between her feet and floor when standing on the ground. In the dark environment, she couldn't move well. She went to our emergency service for help. Initial tests showed an increased MCV (101.6 fL; normal range 89+10fL) but no anemia (hemoglobin, 12.8 g/dl) and the level of Vit.B12 was 237 pg/ml (normal range 179-1132 pg/ml). Parietal cell antibody and HIV antibody levels and the autoimmune profile were within normal ranges. Analysis of CSF revealed normal protein (26.6 mg/dl) and cell counts. The NCV study showed prolonged distal motor latencies in all sampled nerves and slowing of motor and sensory conduction velocities in most of the sampled nerves, especially in lower limbs and absent SNAP in bilateral sural nerves. The F-wave studies showed prolonged minimal latencies in all sampled nerves, especially in lower limbs, except right median and ulnar nerves. The H-reflex was also absent in bilateral tibial nerves. The results of RRIV and SSR studies were within normal limits. Sensorimotor polyneuropathy with demyelinating feature was impressed. MRI showed long segmental hyperintensity changes at the posterior column from the second to the seventh cervical cord. Under the impression of cervical myelopathy and polyneuropathy, related to Vitamin B12 deficiency from nitrous oxide abuse, intramuscular Vitamin B12 therapy was started. She lost follow up after discharge.

DISCUSSION

An impaired uptake of vitamin B12 has long been recognized as a cause of cobalamin deficiency. Cobalamin deficiency occurs because of malnutrition, absence of intrinsic factor, or damage to the ileum, such as that found in Crohn's disease. Less commonly, cobalamin deficiency may result from the inactivation of the B12 metabolism induced by the inhaled anesthetic nitrous oxide[6,7]. Nitrous oxide intoxication can cause vitamin B12 deficiency in otherwise normal individuals [6,8].

Vitamin B12 deficiency can result in nerve injury for several reasons. Firstly, vitamin B12 is an important cofactor in the conversion of homocysteine to methionine and tetrahydrofolate, one of the important cofactors in the metabolism of nucleic acids[14]. Secondly, inactivation of the vitamin B12 metabolism leads to a failure of the methylation of proteins in the myelin sheaths, which results in axonal swelling and eventually axonal loss[5]. Nitrous oxide is a colorless, non-inflammable gas with a weak anesthetic but useful analgesic action[9]. Although the complications of using nitrous oxide as an anesthetic agent are well documented, few reports deal with the complications of this recreational drug (Table 2). "Nagging" or "nanging" are terms used to describe the recreational use of nitrous oxide, derived from the repetitive sound distortions experienced by nitrous oxide users[10] like our patients to inhale the gas directly from a compressed nitrous oxide gas container. Nitrous oxide interacts with vitamin B12 in elective inhibition of methionine synthetase[1] and directly affects DNA synthesis and nerve axon integrity[14]. Thus, nitrous oxide induces subacute combined degeneration through the inactivation of the vitamin B12 metabolism.

Subacute combined degeneration of the spinal cord

is a recognized complication of vitamin B12 deficiency. The other common neurological manifestations of vitamin B12 deficiency include polyneuropathy, but rare in dementia and optic neuropathy[13]. The neuropathological changes in the spinal cord in patients with subacute combined degeneration include initial swelling and irregularity of the myelin sheath, followed by demyelization and loss of axons[15]. The former is reversible while the later is not. Myelopathic changes complicated by vitamin B12 deficiency initially occur in the lower cervical and upper thoracic segments of the spinal cord and then spread longitudinally and transversely[16]. This occurs in the central regions of the posterior columns and, to a lesser extent, in the posterolateral regions of the spinal cord. The changes manifest as high-signal lesions on T2-weighted MRI scans due to increased water content secondary to edema[4,16]. They present as demyelination, Wallerian degeneration, and gliosis[16]. The diagnosis of subacute combined degeneration is mainly based on clinical diagnosis, including subacute onset of spastic paraparesis and impaired sensation, in addition to a history of pernicious anemia, gastric surgery, a vegetarian diet, or even nitrous oxide exposure[1]. Although the diagnosis could be confirmed by an abnormal signal of the spinal cord on MRI and low serum vitamin B12 levels, the findings of these two tests could sometimes be normal[3,19]. Functional vitamin B12 deficiency may be responsible for the condition in patients with normal vitamin B12 levels[18].

The treatment for nitrous oxide-related myeloneuropathy involves ceasing nitrous oxide use and administering vitamin B12 supplements. Reported recovery periods vary. Partial versus full recovery will depend on the extent of the neuropathological damage to the spinal cord[10]. The absence of sensory deficits and Romberg and Babinski signs is associated with a higher complete resolution rate[19]. Methionine has also been reported as a treatment for nitrous oxide-induced myelopathy[14]. In our first case, the patient received additional plasmapheresis in addition to vitamin B12 supplementation. Tatum et al.[23] reported a 25-year-old female with myeloneuropathy due to nitrous oxide abuse that mimicked the presenting features of the Guillain-Barre syndrome-subtype[23]. The reported female had a normal Vitamin B12 level (466 pg/mL) and received a 5-day course of methylprednisolone at 1000 mg per day before supplemental vitamin B12 administration. Our first patient had received intramuscular vitamin B12 injection but still had clinical deterioration. The elevated protein levels in the CSF and the dramatic response to plasmapheresis in our first patient indicated the possibility of superimposed inflammatory polyneuropathy. But it is a pity that the two female patients did not come back for continuous treatment and follow up after discharge. To be re-creational usage of nitrous oxide or other toxin deserved worrying (Table 1). From a result of high frequency of nitrous oxide usage showed under a questionnaire-based study for 1782 students in Auckland, New Zealand, the presentation of substance myelopathy in an otherwise fit young person should prompt an enquiry about the use of nitrous oxide[11]. Though there is not nitrous oxide related neurological complication focused in this paper. We can find the age of patients with subacute combined degeneration and nitrous oxide decreases in these years (Table 2), also in our patients; and they are usually not iatrogenic but addition.

Subacute combined degeneration is a nutrition-related myelopathy caused by vitamin B12 deficiency. Although vitamin B12 deficiency is common in malnutrition, after gastroentric surgery, and in individuals on a vegetarian diet, the use of nitrous oxide concomitant with low vitamin B12 levels can also result in subacute combined degeneration of the spinal cord. The misuse of nitrous oxide has potentially serious outcomes and should be discussed as one of the issues related to harm minimization and health promotion[12]. A differential diagnosis of nitrous oxide induced subacute combined degeneration should be considered when patients present with progressive myelopathy. Herein, we reported three cases of nitrous oxide misuse that resulted in neurological complications due to vitamin B12 deficiency.

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