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CASE REPORT

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아산화질소 가스 남용 이후 발생한 아급성 연합성 척수변성증에 동반된 다발성 운동 신경 병증

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Motor Dominant Polyneuropathy with Subacute Combined Degeneration of the Spinal Cord following Nitrous Oxide Abuse

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Nitrous oxide (N_2O) is known to induce cobalamin (vitamin B12, Cbl) deficiency, leading to myeloneuropathies. We describe two patients who present Cbl deficiency after N_2O abuse for several months. They complained weakness of both lower limbs and gait disturbance. Their magnetic resonance imaging demonstrated high signal intensities on the dorsal columns of the spinal cord at C2-C5 on T2 weighted images, suggestive of subacute combined degeneration (SCD). Initial electrodiagnostic studies resulted in demyelinating and axonal motor dominant polyneuropathies (PNs). In these cases, Cbl deficiency due to N_2O inhalation was suspected as the primary cause for SCD. Cbl deficiency, however, is mainly known to affect sensory nerves, and therefore difficult to account for the motor dominant PNs in our cases. Based on such fact, we suggested that N_2O-induced motor dominant PN may occur independently from Cbl deficiency in SCD patients.

Keywords: Subacute combined degeneration, Polyneuropathy, Nitrous oxide

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Introduction

Nitrous oxide (N_2O) is utilized mainly for anesthetic purposes. However, these days the gas is abused in a form dubbed 'happy balloon' among the young generation for recreational purposes in nightclubs or bars. N_2O gas interferes with cobalamin (Cbl) metabolisms, leading to axonal degeneration and a failure of myelin maintenance in the spinal cord [1]. This process results in subacute combined degeneration (SCD) of the spinal cord. SCD is characterized by demyelination and axonal loss in the dorsal and lateral columns and can usually cause dorsal column dysfunctions, such as ataxic gait and loss of vibratory and proprioceptive sense [1,2].

Cbl deficiency derived peripheral polyneuropathies (PPN) are

mostly symmetrical, length-dependent axonal sensory neuropathies, or less commonly sensorimotor neuropathies [3,4]. Patients with PPN due to Cbl deficiency were less likely to have pain or lower limb weakness [4].

We report two cases of SCD concomitant with motor dominant polyneuropathies (PNs), who present motor weakness, especially in bilateral lower extremities, as well as sensory abnormalities.

Case report

Case 1

A 22-year old female patient was admitted to another hospital due to weakness of both lower limbs, gait disturbance and urinary incontinence for 2 weeks. She was taking anti-depressant and had habit of inhaling N_2O daily more than 100 'happy balloon's for the past 6 weeks. She was transferred to our hospital 3 weeks after symptom onset. Physical exams showed lower limbs motor grades of 3 (fair), bilateral hypoesthesia of the T4 dermatomes and below, impaired proprioception and vibration, hyperactive knee and ankle jerks, positive Romberg sign and ataxic gait. Pathologic reflexes were absent. Her standing and gait balance was poor, resulting in a Berg balance scale (BBS) of 32 points out of 56.

Serologic tests conducted 2 weeks after onset revealed a mean corpuscular volume (MCV) 95 fL (normal range 81-99 fL); hemoglobin 10.9 g/dl (12-15g/dL); Cbl level 165 pg/ml (200-1000 pg/ml); homocysteine 20.9 umol/L (3.7-13.9 umol/L). She received intramuscular (IM) injection of Cbl in previous hospital. Follow-up serologic tests at admission showed normal range of Cbl (530.4 pg/ml), folic acid and other vitamins. Autoantibodies were negative.

Initial whole spine magnetic resonance imaging (MRI) was taken 2 weeks after initiation of symptoms and showed no spinal cord signal abnormalities. However, follow-up MRI taken 1 week later demonstrated high signal intensities on the dorsal columns of the spinal cord at C2-C5 on T2 weighted images (Fig. 1A, B), suggestive of SCD.

Initial electrodiagnostic studies (EDX) was conducted 3 weeks after symptom onset. Motor nerve conduction studies (NCS) demonstrated prolonged latencies and low amplitudes of the right peroneal and bilateral tibial compound motor unit action

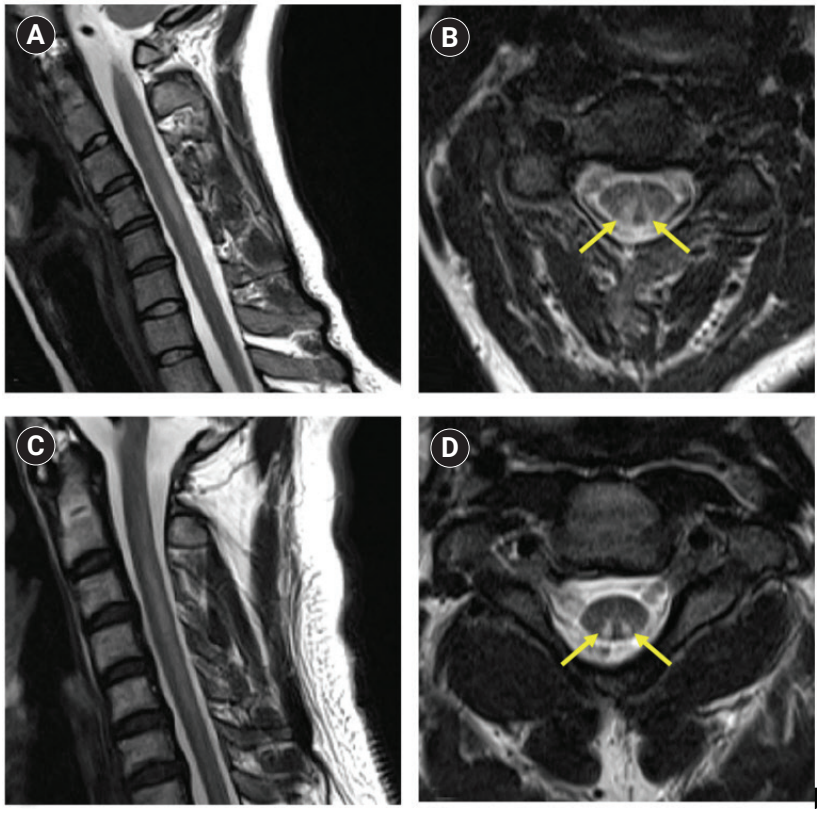

Fig. 1. Sagittal (A) and axial (B) spine MRI images of case 1, taken 3 weeks after symptom onset. Sagittal (C) and axial (D) spine MRI images of case 2, taken 5 months after symptom onset. Swelling of myelin sheaths and patchy myelopathic spongy vacuolation of the posterior columns are shown as hyper-intense lesion on T2-weighted MRI in the form of typical inverted V signs (arrows).

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potentials (CMAPs). The left peroneal CMAP revealed low amplitude and decreased nerve conduction velocity. Sensory NCS were within normal limits, except low amplitude of the left superficial peroneal sensory nerve action potential (SNAP). The F-waves were prolonged with the bilateral peroneal and tibial nerves stimulation. The H-reflexes were prolonged, bilaterally (Table 1). Needle electromyography (EMG) demonstrated abnormal spontaneous activities (ASA) and reduced motor unit recruitments in the right first dorsal interosseous, gastrocnemius, and tibialis anterior muscles. Initial EDX resulted in demyelinating and axonal PNs, mainly involving the motor nerves.

Additional treatment were administered after admission; daily intramuscular (IM) injections of cobamamide (1 mg) for 12 days and daily oral Cbl supplementation (1.5 mg) for the following 20 days. Her urinary incontinence and sensory symptoms at all dermatome levels resolved 7 weeks after symptom onset. Although she had improvement of motor grade of the both lower extremities improved to grade 4+ (good +) and gait performance (BBS 40), she still had difficulties to keep dynamic standing balance. Follow-up EDX exhibited some improvements: normalization of the H-reflex latencies, amplitude increments of CMAPs of the median nerve (Table 1).

Case 2

A 33-year old male with a history of N_2O abuse two or three times a week (about 20 'happy balloon's at a time) for 7 months complained gait difficulty and weakness of bilateral lower limbs for 1 months. At the first time, he only complained numbness of

Table 1. Motor and Sensory Nerve Conduction Study Results of Case 1

Initial (3 weeks after symptom onset)								
Motor NCS			Stimulation site	Recording site	Latency (msec)	Amplitude (mV)	NCV (m/sec)	F wave (msec)
	Right	M	Wrist	APB	2.7	8.2	52	24.8
		U	Wrist	ADM	1.9	15.5	56	25.8
		T	Ankle	AH	5.8*	2.3*	44	55.8*
		P	Ankle	EDB	6.4*	1.0*	42	54.6*
	Left	T	Ankle	AH	5.6*	7.1	43	55.8*
		P	Ankle	EDB	4.4	1.3*	33*	56.0*
		H-reflex	Right	36.1*	Left	36.2*		
Sensory NCS			Stimulation site	Recording site	Peak latency (msec)	Amplitude (uV)	Distance	
	Right	M	Digit III	Wrist	2.7	28.0	12.0	
		U	Digit V	Wrist	2.4	36.5	11.0	
		S	Ankle	Leg	2.6	9.9	10.5	
		S.P	Ankle	Leg	2.3	7.4	9.5	
	Left	S	Ankle	Leg	2.1	15.3	8.0	
		S.P	ankle	Leg	2.6	4.2*	10.5	
Follow up (7 weeks after symptom onset)								
Motor NCS			Stimulation site	Recording site	Latency (msec)	Amplitude (mV)	NCV (m/sec)	F wave (msec)
	Right	M	Wrist	APB	3.5	13.2	52	28.0
		U	Wrist	ADM	2.9	12.4	50.0	27.0
		T	Ankle	AH	5.5*	2.6*	47.0	54.0*
		P	Ankle	EDB		NR*		
		P	Fibular head	TA	4.2	1.0*	9.0	43.0
		H-reflex	Right	34.9*	Left	34.2*		
Sensory NCS			Stimulation site	Recording site	Peak latency (msec)	Amplitude (uV)	Distance	
	Right	M	Wrist	Digit III	3.6	49.0	14	
		U	Wrist	Digit V	3.9*	44.0	14	
		S	Leg	Ankle	4	14.0	14	
		S.P	Leg	ankle	4	6.0	14	

NCS: nerve conduction study, NCV: nerve conduction velocity, M: median nerve, U: ulnar nerve, T: tibial nerve, P: peroneal nerve, S: sural nerve, S.P: superficial peroneal nerve, APB: Abductor pollicis brevis, ADM: abductor digiti minimi, AH: abductor hallucis, EDB: Extensor digitorum brevis, NR: no response.
*Abnormal values are presented with an asterisk.

trunk and below and ataxic gait. After 3 months, weakness and gait disturbance developed and he admitted another hospital. Serologic test conducted 3 months after symptom onset showed that increased MCV (106 um3) and decreased hemoglobin (10.2 mg/dL) and Cbl level (130 pg/ml). Spine MRI taken 3 months after symptom initiation revealed high signal intensities on the dorsal columns of the spinal cord C2-C6 on T2 weighted images. He was diagnosed with SCD and received mecobalamin IM injection (1mg) for 5days. After treatment, Cbl level (617.3 pg/ml) was normalized and numbness had improved. He admitted to our hospital and took further evaluations since weakness and gait disturbance persisted 5 months from the initial symptom onset.

Physical exams showed motor grades of 2 (Poor) for both ankle and below, bilateral hypoesthesia of the C5 dermatomes and below, impaired proprioception and vibration, hyperactive knee and ankle jerks and positive Romberg sign. His dynamic standing and gait balance was poor (BBS 37).

Serologic examination at admission showed normal levels of hemoglobin, MCV, folic acid and various vitamins including Cbl. The anti-intrinsic factor antibody was negative. Compared to initial MRI, follow-up spine MRI still showed abnormalities of spinal cord C2-C6 (Fig. 1C, D).

EDX were also performed upon admission. Motor NCS revealed prolonged latencies and low amplitudes of the right median and left tibial CMAPs. The right tibial and the bilateral peroneal CMAPs were unobtainable. The superficial peroneal SNAP showed low amplitude on the right side, and was unobtainable on the left side. The F-waves were unobtainable with the bilateral tibial and peroneal nerves stimulation. The bilateral H-reflexes were prolonged (Table 2). On the needle EMG, ASA and polyphasic motor unit potentials with reduced recruitments

Table 2. Motor and Sensory Nerve Conduction Study Results of Case 2

Initial (4 weeks after symptom onset)								
Motor NCS			Stimulation site	Recording site	Latency (msec)	Amplitude (mV)	NCV (m/sec)	F wave (msec)
	Right	M	Wrist	APB	4.5*	1.9*	52	29.5
		U	Wrist	ADM	2.5	5.5	56	28.3
		T	Ankle	AH		NR*		NR*
		P	Ankle	EDB		NR*		NR*
	Left	T	Ankle	AH	5.9*	0.2*	54	NR*
		P	Ankle	EDB		NR*		NR*
		H-reflex	Right	32.3*	Left	32.9*		
Sensory NCS			Stimulation site	Recording site	Peak latency (msec)	Amplitude (uV)	Distance	
	Right	M	Digit III	Wrist	2.9	48.3	13	
		U	Digit V	Wrist	2.7	20.3	12	
		S	Ankle	Leg	2.7	8.5	9.5	
		S.P	Ankle	Leg	2.3	5.8	9	
	Left	S	Ankle	Leg	2.5	10.8	9	
		S.P	Ankle	Leg		NR*		
Follow up (8 weeks after symptom onset)								
Motor NCS			Stimulation site	Recording site	Latency (msec)	Amplitude (mV)	NCV (m/sec)	F wave (msec)
	Right	M	Wrist	APB	3.9	3.7*	50	28.6
		U	Wrist	ADM	3.5	6.1	55	29
		T	Ankle	AH	4.8*	0.2*	40	NR*
		P	Ankle	EDB		NR*		NR*
		H-reflex	Right	32.2*	Left	32.0*		
Sensory NCS			Stimulation site	Recording site	Latency (msec)	Amplitude (mV)	Distance	
	Right	M	Wrist	Digit III	3.3	26.0	14	
		U	Wrist	Digit V	3.7	27.0	14	
		S	Leg	Ankle	3.9	5.0	14	
		S.P	Leg	ankle	3.9	5.0	14	

NCS: nerve conduction study, NCV: nerve conduction velocity, M: median nerve, U: ulnar nerve, T: tibial nerve, P: peroneal nerve, S: sural nerve, S.P: superficial peroneal nerve, APB: Abductor pollicis brevis, ADM: abductor digiti minimi, AH: abductor hallucis, EDB: Extensor digitorum brevis, NR: no response.
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were noted in the right flexor carpi radialis and first dorsal interosseous muscles and the bilateral tibialis anterior, peroneus longus and gastrocnemius muscles. EDX were suggestive of motor dominant PNs.

Additional treatment including daily IM injections of cobamamide (1 mg) for 13 days and oral Cbl supplement (1.5 mg) and folic acid (3 mg) for the following 32 days were administered. Six months after symptom onset, his gait balance (BBS 46) and motor grades bilateral lower extremities (grade 4, Good) were improved. In spite of clinical improvements, follow-up EDX showed not significant change except for some improvement in the right median CMAPs (Table 2).

Discussion

Cobalamin (Cbl) plays a key role in the synthesis and maintenance of the myelin sheath, because it is an important cofactor of methionine synthases and L-methyl-malonyl-coenzyme A mutase [3].

N_2O inhibits the function of Cbl by oxidizing the cobalt, resulting in the failure of myelin maintenance and axonal degeneration in the spinal cord, finally leading to SCD [1]. SCD refers to a demyelination of the dorso-larteral columns and especially involves the fasciculus gracilis, which is a nerve tract in the dorsal-medial leminiscus pathway and carries sensory inputs from the legs [2,5]. The commonest clinical symptom of SCD is symmetrical distal sensory symptoms manifested by diminished vibration and proprioception, usually beginning in the lower limbs. Ataxic gait, positive Romberg's signs and Lhermitte's sign and hyper- or hypo-reflexia can also manifest [2].

Many SCD cases with typical sensory deficits similar to our patients have been reported in previous literature [1,2,6], but there are only few SCD cases showing severe motor weakness [7]. As our two patients presented low Cbl levels and typical sensory deficits of SCD, Cbl deficiency would be suggested as a main cause of SCD. Meanwhile, they also complained severe weakness of the bilateral legs and motor symptoms were persisted even after sensory symptoms were resolved following repletion of Cbl and discontinuance of N2O inhalation. Motor dominant PNs were suggested on EDX of two patients, accounting for the weakness of the bilateral lower limbs. As myeloneuropathies resulting from Cbl deficiency are known to predominantly involve the sensory nerves, not the motor nerves [3,4], there is possibility of other causes of motor dominant PNs of axonal type in our patients.

Increased homocysteine (Hcy) levels are known to be related to PN, especially in diabetes mellitus patients. Some argues that high Hcy may cause worse motor peripheral nerve functions in old ages [8], but another review revealed that sensory deficits are predominant in Hcy-related PN [9].

One study evaluating the clinical and EDX findings of N_2O-induced PN suggested that N_2O-induced PPN were usually an axonal type, showing marked reductions of CMAPs in lower extremities compared to other toxic related PPNs [10]. They also reported that N_2O-induced axonal PPN were unaffected by Cbl or Hcy levels.

There is limitation that we did not know homocysteine level of case 2. However, considering that our patients were young and had no diabetes history, the EDX of our cases (motor dominant axonal type PNs) hinted towards the possibility that N_2O-associated motor neuropathies can develop besides Cbl deficiency induced SCD following N_2O abuse.

We described two cases of SCD concomitant with motor dominant PPN. Through these cases, N_2O induced motor dominant PN may occur irrespectively of Cbl deficiency in SCD patients. Therefore, when a SCD patient showing motor weakness has a history of N_2O exposure, it is highly recommended to check for the possibility of N_2O-induced PN. Furthermore, clinicians have to alert that motor syndrome could persist after normalization of Cbl level and last much longer than just Cbl deficiency-induced SCD symptoms.

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