Nitrous Oxide-induced Subacute Combined Degeneration Presenting with Dystonia and Pseudoathetosis: A Case Report

Hung-Ju Chen, Chih-Shan Huang

Abstract-

Purpose: Nitrous oxide (N_2O) is neurotoxic by interfering with vitamin B_{12} bioavailability. The clinical picture is indistinguishable to that of subacute combined degeneration (SCD). A movement disorder might occur though it is not a characteristic feature. We report a patient with N_2O-induced SCD, exhibiting a combination of different involuntary movements.

Case Report: A 20-year-old woman presented with one month of progressive unsteady gait, involuntary movements and tingling sensation in a stocking-glove distribution. She had used N_2O and ketamine intermittently for recreational purposes for about two years. Neurological examination demonstrated normal cranial nerve functions except for dystonia in the facial muscle and tongue. Her muscle strength was full, but there were bilateral hyperreflexia and extensor plantar response. She exhibited dystonia in four limbs with athetoid movement in fingers and toes, worsened by eye closure. Vibration and proprioception were impaired. Laboratory tests revealed anemia (Hb: 9.9 g/dl) with normal mean corpuscular volume (85.7 fL) and decreased iron level (22 μg/dl) while other results were normal including serum vitamin B_{12} level (626 pg/ml). Magnetic resonance imaging showed a hyperintense lesion from C1 to C6 level in the posterior column. She was diagnosed as having SCD caused by N_2O abuse, presenting with generalized dystonia and pseudoathetosis. The involuntary movements disappeared with vitamin B_{12} supplementation.

Conclusion: Movement disorders may be the rare manifestations of SCD associated with N_2O abuse. Early recognition of the etiology is vital because it is treatable with vitamin B_{12} and methionine.

Key Words: Nitrous oxide, subacute combined degeneration, dystonia, pseudoathetosis

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INTRODUCTION

Subacute combined degeneration (SCD) of the spinal cord is a result of vitamin B_{12} deficiency and characterized by weakness, abnormal sensations, mental problems and visual difficulties[1,2]. Nitrous oxide (N_2O), a weak anesthetic gas used commonly for surgical and dental procedures[3], is neurotoxic by interfering with vitamin B_{12} bioavailability[4]. Neurological sequelae of prolonged exposure include potentially irreversible axonal peripheral

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neuropathy and myelopathy[5]. The clinical picture is virtually identical to that found in SCD with posterior and lateral column injury[6]. An increasing number of people have been using N_2O as a recreational drug[7] and the level of abuse is generally underestimated[3]. A quick search of the internet reveals multiple websites with instructions on where to buy N_2O and techniques for inhalation[8]. Despite its easy access and common use, presentations for known complications from abuse of this drug are uncommon and perhaps underdiagnosed[9]. Moreover, a movement disorder, not a characteristic feature of N_2O neurotoxicity[10], could be one of the rare manifestations. We describe a patient with SCD caused by N_2O abuse exhibiting a combination of different involuntary movements.

CASE REPORT

A 20-year-old woman presented with one month of progressive unsteady gait, involuntary movement in the four limbs and mild tingling sensation in a stocking-glove distribution. She was previous healthy without a contributory family history. Further questioning with regard to her habits and social history revealed that she had used N_2O and ketamine intermittently for recreational purposes for about two years; however, she did not give the detailed information about the dosage or the frequency. She had difficulty in walking independently, feeling that she was unable to control her lower limbs voluntarily rather than weakness. She also had problem in writing or using chopsticks. She had to hold a spoon effortfully while having meals. No symptom implying autonomic dysfunction was noted. Neurological examination demonstrated normal mental status and cranial nerve function except for mild stuttering in speech and dystonia in the facial muscle and tongue, especially while she was trying to protrude her tongue or make more facial expression. Manual test revealed full muscle strength. Hyperreflexia and extensor plantar response were present bilaterally. She exhibited dystonia-like posture in four limbs and athetoid movements in fingers and toes, worsened by eye closure. Sensory examination showed impaired vibration and proprioception distal to wrists and ankles. There was no significant cerebellar signs though she did not perform those tests smoothly, interfered by the involuntary movements. She needed support to keep in a broad-based stance and merely made few steps unsteadily with assistance.

Initial laboratory tests revealed anemia (Hb: 9.9 g/dl), normal mean corpuscular volume (MCV) (85.7 fL; normal range 81-99 fL), increased red cell distribution width (RDW) (29.8%; normal range 11-16%), decreased iron level (22 μg/dl; normal range 50-175μg/dl) and normal serum vitamin B_{12} level (626 pg/ml; normal range 180-914 pg/ml). Iron deficiency anemia (IDA) with suspected megaloblastic anemia was diagnosed. Since the patient stated she had taken some pills containing vitamin B complex before admission, the vitamin B_{12} level was presumably corrected. Serum copper, zinc, ceruloplasmin and thyroid function were within normal ranges. She had negative results in human immunodeficiency virus (HIV) antibody, nonreactive serologic tests for syphilis (STS) and the autoimmune profile (ANA, anti-ENA, RA factor). Analysis of the cerebrospinal fluid (CSF) was normal. Nerve conduction study (NCS) showed sensorimotor polyneuropathy (Table 1, 2). Visual evoked potentials (VEP) study suggested impaired bilateral visual conduction pathway. The results of somatosensory evoked

Table 1. Motor nerve conduction study

Nerves	Distal (8cm)	CV (m/s) Iatency (ms)	Amplitude (mV)	F wave (ms) distal/proximal
Median, L	4.4	50	8.4/7.2	31
Ulnar, L	3.4	54	11.7/12.1	28.9
Peroneal, R	absent	absent	absent	absent
Peroneal, L	absent	absent	absent	absent
Tibial, R	absent	absent	absent	absent
Tibial, L	5.8	27	0.2/0.2	absent

R: right, L: left, CV: conduction velocity

The patient refused examination in the right upper limb because of intolerable discomfort upon stimulation

Table 2. Sensory nerve conduction study

Nerves	Distal (14cm) Iatency (ms)	CV (m/s)	Amplitude (μV)
Median, L	2.8	50	22
Ulnar, L	3.2	43	13
Sural, R	absent	absent	absent
Sural, L	absent	absent	absent

R: right, L: left, CV: conduction velocity

The patient refused examination in the right upper limb because of intolerable discomfort upon stimulation

Table 3. VEP and SSEP

	Left	Right	Reference range*
VEP: P100 (ms)	140	128	100±5
Median nerve SSEP			
N9 (ms)	10.3	10.1	9.19±0.56
N13 (ms)	absent	absent	12.5±0.98
N20 (ms)	absent	absent	18.2±1.15
Tibial nerve SSEP	absent	absent	

VEP: visual evoked potential; SSEP: somatosensory evoked potential; *values represent mean±SD

potentials (SSEP) were suggestive of impaired both central sensory conduction and peripheral sensory conduction over bilateral extremities (Table 3). Magnetic resonance imaging (MRI) of spinal cord showed long segmental hyperintense lesion from C1 to C6 level without obvious enhancement with gadolinium in the posterior column. MRI of brain showed unremarkable findings. (Figure 1, 2)

Based on the history, clinical presentation, image findings and laboratory tests, she was diagnosed as SCD caused by N_2O abuse, presenting with generalized dystonia and pseudoathetosis. The patient was treated with high-dose intravenous vitamin B_{12} supplementation (2000 μg per day) for the first three days followed by oral supplementation. Her balance and gait improved gradually as well as the involuntary movement after treatment. With rehabilitation, she could walk independently slowly three weeks later.

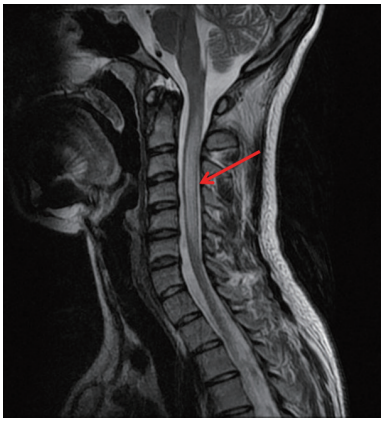

Figure 1. Sagittal T2W MRI showing longitudinal high signal intensity at C1-C6 level (arrow).

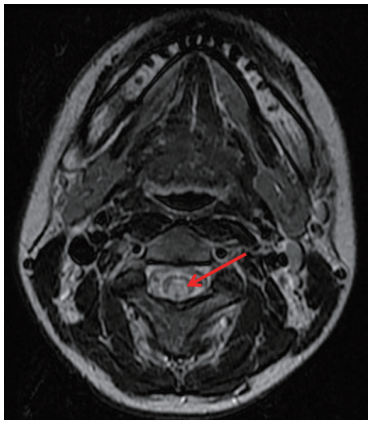

Figure 2. Axial T2W MRI showing high signal intensity prominent in the posterior column of cervical cord (arrow).

DISCUSSION

Movement disorders are uncommon presentations in patients suffering from N_2O neurotoxicity or even in SCD cases. Coexistence of different involuntary movements is rarer; furthermore, to our best knowledge, orolingual dystonia demonstrated in our patient has not been described in other cases with N_2O abuse.

Methionine synthase is of central importance for both DNA synthesis and to replenish the one carbon donor pool[11]. N_2O causes its harmful effects by irreversibly oxidizing the cobalt ion of cobalamin (vitamin B_{12}) from the (+) 1 to the (+) 2 valence state[12]. Oxidation of the cobalt ion prevents methylcobalamin from acting as a coenzyme of methionine synthase in the production of methionine and subsequently S-adenosylmethionine, which is necessary for methylation of myelin sheath phospholipids[4,13,14]. A failure of the biochemical pathway results in decreased myelin formation along with axonal swelling and eventually axonal loss[4,13,14,15]. Another cobalamin-dependent enzyme, methylmalonyl-CoA mutase, participating in the enzymatic conversion of methylmalonyl-CoA to succinyl-CoA, may not be so much affected by N_2O as methionine synthase. Proper synthesis of succinyl-CoA is important for fatty acid metabolism and is also an intermediate in the Krebs cycle[14].

Vitamin B_{12} deficiency is the cause of SCD. Normal vitamin B_{12} level in our patient was presumed to be the result of supplementation before she was presented to our clinic. The prior level could have been even lower. Nevertheless, it has been reported that neurotoxicity resulting from recreational abuse of N_2O occurs in patients with normal cobalamin levels[16,17]. Functional vitamin B_{12} deficiency may be responsible for that condition[18]. Measurement of methylmalonic acid (MMA) and homocysteine (HC) may be more sensitive indicators of disease in contrast to actual vitamin B_{12} levels[19]. In clinical practice, when symptoms persist despite treatment and cessation of abuse, effect can be corroborated by a measuring and confirming normalization of HC and MMA levels[20]. Macrocytic anemia is a common manifestation of vitamin B_{12} deficiency. Our patient had anemia with normal MCV in which presence of mixed macrocytic and microcytic anemia associated with concomitant IDA was reasonable according to the increased RDW. Macrocytosis was not demonstrated in several previously reported cases with nitrous oxide-induced vitamin B_{12} deficiency[8,9,20]. Patients with good folic acid intake may not develop the hematologic effects of B_{12} deficiency despite overt neurologic dysfunction[8].

Pathologically, SCD usually begins in the thoracic cord[21,22]; however, cervical cord involvement seems more common. The involvement of the anterior column in SCD is noted[23], that is, the corticospinal tracts may also be involved4 although lesions in the posterior column are characteristic pictures. The sensorimotor polyneuropathy in our patient was compatible with documented peripheral neuropathy as evidenced by axonal degeneration with or without demyelination[7,12]. Abnormal VEP may represent vitamin B_{12} deficiency-related asymptomatic optic neuropathy[1].

A literature review of movement disorders related to N_2O exposure (Table 4) revealed that Dehring et al. reported a young, healthy female outpatient who developed severe extrapyramidal symptoms such as opisthotonus and torticollis after an uneventful anesthetia with thiopentone,

Table 4. Cases reviewing of N_2O-related movement disorders

Age/Sex	Manifestations	MRI findings	Reference
32/F	opisthotonusand torticollis	not mentioned	Dehring et al.[24]
8 months/M	hypotonia, fine tremor, and athetoid movements	not mentioned	Felmet et al.[25]
19/M	pseudoathetosis of the fingers	T2W hyperintensity at posterior and anterior column of cervical cord	Hsu et al.[3]
75/M	dystonic posture of the left arm and severe athetoid-like movements of fingers and hands at rest.	T2W hyperintensity at posterior column (C1-C5)	Reggio et al.[26]
26/F	myoclonus (after vitB_{12} used)	T2W hyperintensity at posterior column (C2-C7)	Wu et al.[10]

fentanyl, enflurane, and N_2O for 50 minutes. A tentative diagnosis of central anticholinergic syndrome was proposed[24]. Felmet et al. reported an 8-month-old boy demonstrating profound hypotonia, fine motor tremor, and athetoid movements after being exposed to N_2O during an operation[25]. It is well established that pseudoathetosis, an athetoid-like movement always occurs in association with a severe proprioception deficit[26]. Although posterior column involvement with impaired proprioceptive sensation is almost inevitable in SCD, pseudoathetosis is found far less than expected like the 19-year-old case of Hsu et al[3]. Reggio et al. reported a 75-year-old Caucasian man with markedly reduced serum vitamin B_{12} level and cervical cord lesions exhibiting dystonic posture of the left arm and severe athetoid-like movements of fingers and hands at rest, which were worsened by eye closure and mental stress[26]. Our patient also displayed simultaneous dystonic posture and pseudoathetosis which involved four limbs rather than limited in upper limbs. Although diffusion-weighted image was not obtained, spinal cord infarction was excluded because the time course (progression for one month) and the anatomy involved (predominant in the posterior column) were not characteristic of a spinal cord stroke. Also, abnormal movements of the face could not be attributed to the spinal cord lesions. Most important, based on the gradual resolution of involuntary movements with vitamin B_{12} treatment, we assume N_2O neurotoxicity was responsible for those movement disorders. We hypothesize that our patient's orolingual dystonia resulted from dysfunction of the nervous system above the cervical cord which was not detected by MRI. A similar situation has been reported by Alt et al. in which prominent clinical manifestations were present with normal images[20].

Treatment for cobalamin deficiency and N_2O toxicity is cobalamin and possibly methionine supplementation[13,14]. It is worth noting that the sudden availability of vitamin B_{12} may result in a temporary imbalance of the complicated metabolic pathways of cobalamin[27,28], leading to transient deterioration of the disease paradoxically. It might explain the manifestations in a 26-year-old woman with N_2O intoxication reported by Wu et al., developing propriospinal myoclonus after beginning of vitamin B_{12} supplementation[10].

Neurologic recovery has been described as occurring from weeks to months after treatment is begun, with some patients never fully recovering[8]. Occasionally, the neurological toxicity can lead to severe disability[5]. The absence of sensory deficits, Romberg and Babinski signs is associated with a higher complete resolution rate[29]. There are no specific tests to document N_2O exposure; hence, a detailed history is the basis of diagnosis[30]. Perhaps as a result of its relative "legality" and gaseous form, many patients could fail to report their use of this substance[9].

The potential for encountering suspicious cases with paresthesia, gait disturbance or, of course, movement disorders in emergency departments is not insignificant, given the increasing incidence of N_2O abuse, particularly among adolescents[31]. N_2O abuse should be considered as a differential diagnosis of dystonia, pseudoathetosis or the complex presentation with both these two involuntary movements. Facial muscle and the tongue could be involved as well. Early recognition is vital because it is treatable and potentially reversible. Institution of combination therapy with methionine and vitamin B_{12} is recommended[5]. Further investigation is required to elucidate the pathogenic mechanism and the nature of the different movement disorders in association with N_2O.

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