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Nitrous oxide abuse-induced subacute combined degeneration: A case report highlighting vitamin B_{12} metabolic dysfunction and its implications

[1]Yixin Bao, [1]Xiaoyun Lei, [2]Chun Sun

[1]Department of Neurology, the Second Affiliated Hospital of Jiaxing University, Jiaxing, Zhejiang, China; [2]Department of Urology, the Second Affiliated Hospital of Jiaxing University, Jiaxing, Zhejiang, China.

Abstract

Subacute combined degeneration (SCD) of the spinal cord is typically caused by vitamin B_{12} deficiency and represents a progressive neurological disorder. We report here a 21-year-old male admitted to the Neurology Department of the Second Affiliated Hospital of Jiaxing University with a 10-day history of progressive tetraparesis and paresthesias. Comprehensive investigations were conducted, including blood tests, cerebrospinal fluid analysis, and head magnetic resonance imaging (MRI), all of which yielded normal results. Electrophysiological studies demonstrated evidence of multifocal peripheral neuropathy. Imaging of the cervical spine revealed patchy long T2 signal abnormalities with an inverted V-sign extending from C2 to C5. Further detailed inquiry into his medical history disclosed a long-standing history of nitrous oxide inhalation. Based on these findings, the patient was diagnosed with SCD of the spinal cord induced by disrupted cobalamin metabolism associated with prolonged nitrous oxide inhalation. The patient was treated with daily intravenous injections of 1000 μg of mecobalamin and oral administration of 5 mg folic acid tablets. Following treatment, the patient exhibited some improvement in his symptoms. Early recognition, cessation of nitrous oxide exposure, and high-dose mecobalamin therapy led to partial neurological recovery.

Keywords: Nitrous oxide (laughing gas), subacute combined degeneration, vitamin B_{12} deficiency, hyperhomocysteinemia, methylmalonic acid

INTRODUCTION

Nitrous oxide (N_2O), often referred to as laughing gas, is a colorless gas widely utilized for its anesthetic properties in medical settings and as an additive in the food industry.[1] In recent years, its non-medical abuse as a recreational hallucinogenic and euphoric drug has become a growing global concern. The oxidized cobalt ions inhibit the activity of methionine synthase, leading to functional vitamin B_{12} deficiency.[2] Vitamin B_{12} is essential for neuronal integrity as it plays a key role in myelin synthesis, DNA methylation, and neurotransmitter metabolism. Vitamin B_{12} deficiency can disrupt these processes, resulting in impaired nerve conduction and repair.[3]

Vitamin B12 deficiency is a well - documented cause of subacute combined degeneration (SCD) of the spinal cord, a neurological disorder featuring demyelination of the spinal cord's posterior and lateral columns, and impacting both sensory and motor pathways, as shown in several studies.[4] Nevertheless, SCD cases triggered by nitrous oxide - induced vitamin B12 deficiency are often neglected in clinical settings, especially when typical hematological abnormalities of vitamin B12 deficiency are absent.

This report presents a young male case who developed SCD after long - term nitrous oxide inhalation. The case report illustrates the diagnosis of drug - abuse - induced SCD and provide a reference for preventing and managing substance - abuse - related neurological complications, particularly in adolescents.

Address correspondence to: Chun Sun, Department of Urology, the Second Affiliated Hospital of Jiaxing University, No. 1518 Huancheng North Road, Nanhu District, Jiaxing 314000, Zhejiang, China. E-mail: sunchun0626@163.com

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CASE REPORT

A 21-year-old man presented with progressive numbness and weakness in the extremities over 10 days, becoming unable to walk when he arrived at our hospital. The patient reported that before the onset of the disease, he used 200 cartridges of nitrous oxide per week for one year, with intermittent use. The last use was two weeks before the onset of the disease. He denied smoking tobacco, drinking alcohol or abusing other controlled substances. The patient reported a balanced diet and denied a history of pernicious anemia, autoimmune diseases or chronic gastrointestinal disorders. His blood routine test and stool routine and occult blood test showed no obvious abnormalities. The abdominal CT scan showed no significant abnormalities. Therefore, we have largely ruled out the possibility of chronic gastrointestinal diseases. There was no significant change in weight since the onset of the disease.

The distal extremities showed slightly reduced strength at 4/5 based on the Medical Research Council (MRC) scale, while proximal muscle strength remained normal at 5/5. The patient had difficulty walking. The superficial sensation of the limbs was symmetrically reduced. The range of superficial sensation reduction in the upper limbs was from the fingertips of both hands to the elbows, and in the lower limbs, it was from the toes of both feet to the root of the thighs. The vibration and joint sensation of the limbs were reduced. A comprehensive bladder residual urine assessment was conducted, revealing a post-void residual volume of 0 mL. The patient reported smooth bowel movements with daily defecation, indicating normal urinary and gastrointestinal function. Blood pressure measurements showed: 130/79 mmHg in the supine position, 128/76 mmHg immediately upon standing, 125/77 mmHg after one minute of standing, 131/73 mmHg after three minutes, and 129/73 mmHg after five minutes. No significant orthostatic hypotension was observed. The patient laboratory tests, including a complete blood count, liver and renal function, electrolyte analysis, vitamin B12 level measurement, and thyroid function tests were within normal ranges. A lumbar puncture was performed, revealing an opening pressure of 210 mm water column. The cerebrospinal fluid biochemical analyses and ganglioside antibody assays were normal. We performed magnetic resonance imaging (MRI) examinations of the patient's head and cervical spine. The brain MRI showed no abnormalities; however, the cervical spine MRI demonstrated prolonged T2 hyperintensities with a distinctive inverted V sign involving the C2 to C5 segments as shown in Figures 1A and B.

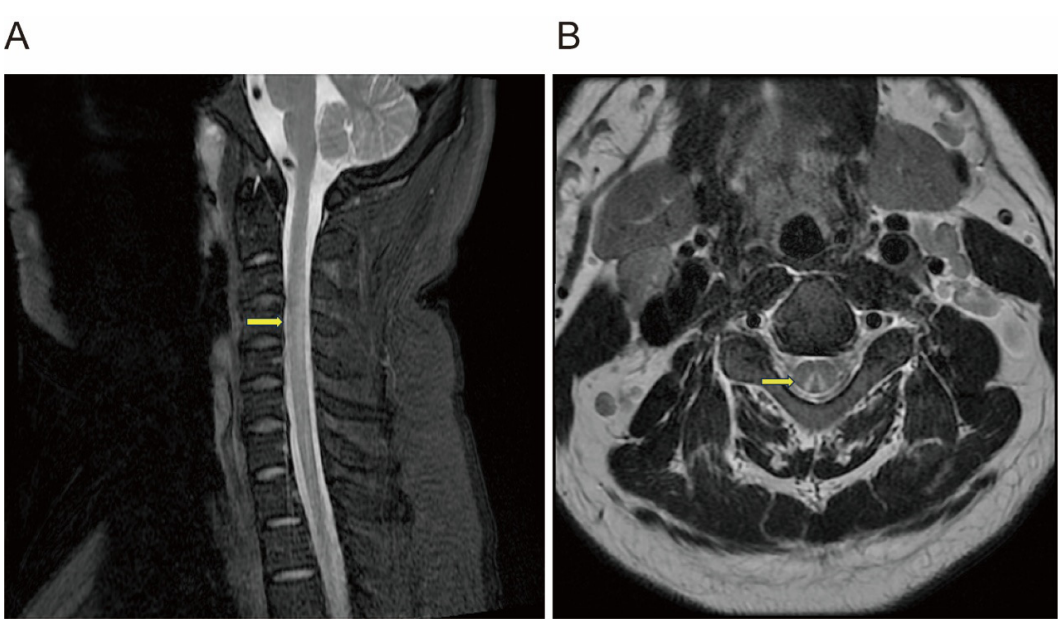

Figure 1. Image A depicts a sagittal view of the cervical spine, reveals abnormal long T2 signal intensities within cervical spinal cord segments C2 to C5, while Image B presents an axial cross-section, characterized by an inverted V-sign (yellow arrow).

In light of the clinical and radiological findings, the patient was diagnosed with spinal cord SCD. We performed a comprehensive serum vitamin B12 assay for the patient. The patient's serum vitamin B12 concentration was measured at 270.28 pg/ml, which falls within the established normal reference interval of 187–833 pg/ml. The serum methylmalonic acid (MMA) level was measured at 96.71 ng/mL, exceeding the reference range of <47.2 ng/mL. Serum homocysteine level is measured at 110.10 μmol/L, which significantly exceeds the upper normal reference limit of 15 μmol/L. To investigate potential etiologies, we conducted further assessments including blood biochemistry, ferritin levels, HIV antigen-antibody testing, and HTLV-1 screening, which ruled out neuropathies secondary to renal dysfunction, diabetes, iron deficiency, or specific infections. Serum copper and ceruloplasmin tests were not performed.

DISCUSSION

SCD typically involves the posterior and lateral columns of the spinal cord. In this case, however, the patient exhibited concomitant peripheral neuropathy in addition to spinal cord involvement. Clinical manifestations included prominent limb numbness. Electrophysiological studies revealed decreased sensory nerve conduction velocity and reduced amplitude of sensory nerve action potentials, while motor nerve conduction velocity was relatively preserved in comparison. Furthermore, electromyography indicated that the peripheral neuropathy was predominantly axonal in nature, with greater involvement of the lower extremities compared to the upper extremities, and sensory nerves affected more severely than motor nerves. These electrophysiological findings align with the characteristic features observed in SCD patients with associated peripheral neuropathy. The detailed electromyography (EMG) findings are presented in Table 1.

In this case, the patient is diagnosed with impaired vitamin B12 function secondary to nitrous oxide abuse, the patient was treated with daily intravenous injections of 1000 μg of mecobalamin, which is the active form of vitamin B12 in vivo, and oral administration of 5 mg folic acid tablets. Following five days of treatment, the patient reported improvement in the numbness and weakness of his limbs. However, he remained unable to walk independently. The patient was subsequently

Table 1: Electromyography (EMG) test report

	Motor nerve conduction velocity					
The name of nerve	**NCV(m/s)**		**Lat(ms)**		**Amp(mv)**	
	R	**L**	**R**	**L**	**R**	**L**
Tibial nerve	38	36	4.3	5.5	1.1	2.1
F-wave			60.1	59.1		
Common peroneal nerve	38	37	6.4	5.4	2.1	0.9
Median nerve	50	50	4.2	4.3	10.4	8.3
F-wave			30.1	30.0		
Ulnar nerve	51	51	3.0	2.9	7.2	7.5
F-wave			30.5	28.7		
	Sensory nerve conduction velocity					
The name of nerve	**NCV(m/s)**		**Lat(ms)**		**Amp(mv)**	
	R	**L**	**R**	**L**	**R**	**L**
Superficial peroneal nerve	38	40	2.8	2.5	3.3	6
Sural nerve	36	48	2.2	1.8	1.6	4.6
Median nerve	51	48	2.2	2.1	12.5	10.7
Ulnar nerve	55	58	1.9	2	13.2	9.9

NCV: Nerve Conduction Velocity; Lat: Latency; Amp: Amplitude

discharged with a prescription for mecobalamin tablets and instructed to continue oral therapy. Following discharge, the patient ceased the use of nitrous oxide and initiated oral administration of 1500 micrograms of mecobalamin tablets and 5 milligrams of folic acid tablets daily. At present, the patient is able to walk indoors with assistance, and the numbness in the limbs has shown significant improvement compared to the condition before treatment.

SCD of the spinal cord is a neurodegenerative disorder that impacts both the central and peripheral nervous systems; it is primarily caused by vitamin B_{12} deficiency, which may result from impaired intake, absorption, binding, transport, or metabolism. A case series from Taiwan[5] documented SCD linked to nitrous oxide abuse among adolescents, reporting that 6 of 9 patients exhibited low serum vitamin B_{12} levels. Similarly, another case study highlighted lower serum vitamin B_{12} levels.[6]

Our patient exhibited normal serum vitamin B12 levels; however, elevated methylmalonic acid (MMA) and homocysteine levels upon further testing indicated a functional deficiency of vitamin B12. Methylmalonic acid (MMA) is a metabolite in the homocysteine metabolic pathway. Elevated MMA levels[7] typically reflect aberrations in methylmalonyl-CoA metabolism, which are commonly associated with deficiencies in vitamin B12, folate, or methyl donor metabolism. Compared with the direct measurement of serum vitamin B12 (cobalamin), MMA[8] provides a more accurate reflection of functional vitamin B12 status, as it is directly influenced by the synthesis and degradation pathways of methylmalonyl-CoA in vivo. Consequently, in the diagnosis or risk assessment of sickle cell disease (SCD), the "sensitivity" of MMA lies in its ability to signal underlying functional vitamin B12 insufficiency even when serum B12 levels are within the normal range or only slightly reduced, thereby enabling earlier detection of metabolic abnormalities. Given that the patient denied a long-term vegetarian diet and demonstrated normal complete blood count results, further evaluation with intrinsic factor and parietal cell antibody testing was not pursued. Deficiency of intrinsic factor produced by gastric parietal cells or autoimmune gastritis may lead to malabsorption, resulting in functional vitamin B12 deficiency. However, metabolic markers such as methylmalonic acid (MMA) often better reflect the functional status than serum B12 levels.[9] Therefore, intrinsic factor/parietal cell antibody testing was not performed in this case, which limits direct assessment of whether malabsorption is attributable to autoimmune or atrophic gastritis.

SCD mainly affects the posterior and lateral funiculi of the spinal cord and the peripheral nerves. The role of electromyography (EMG) in the diagnosis of SCD of the spinal cord is limited but remains of auxiliary value.[10] EMG can aid in the assessment of coexisting peripheral neuropathy, which may accompany SCD despite its primary involvement of the dorsal and lateral columns of the spinal cord. As demonstrated in this patient, EMG findings reveal a more pronounced reduction in sensory nerve conduction velocity compared to motor conduction velocity. Additionally, lower limb nerves are more prominently affected than upper limb nerves, with a marked decrease in the amplitude of the sural nerve sensory nerve action potential (SNAP). Both motor and sensory nerves were affected, with the lesions predominantly involving the lower extremities. As demonstrated by the analysis of electromyography in 110 cases of subacute combined degeneration of the spinal cord induced by nitrous oxide abuse by Yu, M. *et al*., the electromyographic findings revealed mixed axonal and demyelinating damage.[11] These electrophysiological characteristics may assist in differentiating SCD from other neurological disorders such as Guillain-Barré syndrome, amyotrophic lateral sclerosis, and multiple sclerosis.

For the diagnosis and treatment of this disease, we have outlined the following key clinical considerations:

When to consider nitrous oxide-induced subacute combined degeneration of the spinal cord

Demographic characteristics: Young patients, individuals with recreational drug use history, healthcare professionals, and food service workers; absence of conventional risk factors for vitamin B12 deficiency (non-vegetarian diet, no history of gastrointestinal disorders).
Characteristic clinical manifestation profile: Classic symptom triad (Paresthesia, ataxia, and limb weakness); Neurological examination findings (Impaired deep sensation, superficial sensory deficits, abnormal tendon reflexes, positive pathological signs, and ataxic gait); Autonomic dysfunction (Bladder dysfunction, bowel dysfunction, and orthostatic hypotension); Disease progression features (Subacute onset,

progressive worsening, symmetrical distribution, sensory symptoms predominating over motor symptoms).

Which tests to order (homocysteine, possibly MMA) when serum B_{12} is normal.

Essential complete examination: determination of serum methylmalonic acid (MMA) (more sensitive than serum vitamin B12, reflecting the functional status of vitamin B12 in cells); Serum homocysteine determination (reflecting methionine synthase activity, complementing MMA, and enhancing diagnostic sensitivity); Serum folic acid determination (for identifying folic acid deficiency and guiding treatment)

Typical MRI pattern and role of EMG

Characteristic neuroimaging findings include: On axial views: Bilateral posterior column symmetrical T2 hyperintensity presenting as an "inverted V sign" or "inverted triangle sign." On sagittal views: A continuous linear T2 hyperintensity along the posterior columns, spanning multiple spinal cord segments, most commonly observed in the cervical and upper thoracic regions.
Role of EMG in diagnosis: Electrophysiological examinations provide objective confirmation of peripheral neuropathy and its characteristics in subacute combined degeneration, which characteristically involves not only the spinal cord (posterior and lateral columns) but also frequently affects the peripheral nerves. *Characterization of Lesion pathology and distribution:* Axonal vs. demyelinating, sensory vs. motor nerves, upper vs. lower limbs.
Assessment of Lesion Severity: The extent of amplitude reduction reflects the degree of axonal damage, while the number of affected nerves indicates the scope of pathology, providing an objective basis for treatment and prognosis evaluation.

The therapeutic regimen[12] primarily involves cessation of nitrous oxide exposure and supplementation with vitamin B12. The recommended dosages are as follows: methylcobalamin 500–1000 μg administered via intramuscular injection or oral route daily for 4 consecutive weeks, followed by an adjustment to 1000 μg per dose[13], 2–3 times per week for the subsequent 2 to 3 months. Thereafter, maintenance therapy with oral supplementation is instituted.

The prognosis of this disease is primarily associated with the extent of pathological involvement, the timeliness of medical consultation, the patient's age, and whether standardized vitamin B12 therapy has been administered promptly. A retrospective analysis of 68 cases with subacute combined degeneration of the spinal cord revealed that favorable prognoses were associated with younger age, shorter disease duration, and early therapeutic intervention.[14] Generally, patients with early-stage presentation (symptom duration less than three months), mild or purely sensory manifestations, younger age, and those who receive timely and standardized vitamin B12 supplementation tend to have more favorable outcomes, with complete recovery achievable in 30% to 40% of cases.[15]

In recent years, the misuse of nitrous oxide among adolescents has become increasingly prevalent due to the erroneous perception that it is both "legal" and "harmless". Approximately 30% of global[16] SCD cases reported in recent years have been linked to nitrous oxide exposure. However, excessive or prolonged exposure to nitrous oxide can inactivate vitamin B_{12} by oxidizing its cobalt center, thereby inhibiting methionine synthase activity. This leads to a functional B12 deficiency, impaired DNA synthesis and myelin production, and ultimately, SCD of the spinal cord.

We present a case of subacute combined degeneration of the spinal cord in a young male patient who presented with the primary clinical manifestations of progressive tetraparesis and paresthesias. The patient had a history of nitrous oxide abuse spanning over one year. Cervical MRI performed after admission revealed a characteristic inverted V-shaped lesion. Although serum vitamin B12 levels were within the normal range, elevated methylmalonic acid and homocysteine levels suggested functional vitamin B12 deficiency. Management involved prompt cessation of nitrous oxide exposure and initiation of vitamin B12 supplementation. Following a course of methylcobalamin, the active form of vitamin B12, the patient's symptoms partially improved, and he was able to ambulate short distances with family assistance upon discharge. Prognosis in such cases depends on early diagnosis and intervention; if treatment is initiated more than six months after symptom onset, patients may develop permanent sequelae, such as severe spinal cord degeneration. This case also affords us the following insight:

strengthening regulatory control over nitrous oxide distribution and enhancing health education initiatives, especially those targeting adolescents, are critical to mitigating the rising incidence of SCD.

DISCLOSURE

Ethics: The study was approved by the Medical Ethics Committee of the second Hospital of Jiaxing (protocol code 2025-CA-16 of 9, June, 2025). Written informed consent was obtained from the patient to publish this paper.

Data availability: The data used to support the findings of this study are available from the corresponding author upon request.

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Conflict of interest: None

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