Clinical-radiological dissociation of a patient with nitrous oxide-induced subacute combined degeneration: A case report

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Case report

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Abstract

Background: A number of recent studies have reported subacute combined degeneration (SCD) induced by nitrous oxide (N2O) abuse. However, none have reported the association between the dynamic neuroimaging evolution and clinical manifestations of a patient with N2O-induced SCD. Case presentation: We describe a 24-year-old man who developed SCD with inverted V-sign hyperintensities over the posterior aspect of the spinal cord caused by frequent, excessive N2O inhalation. One month after treatment, his weakness and paresthesia resolved and his serum vitamin B12 level had improved above normal, but the hyperintensities on T2-weighted images had extended horizontally and longitudinally, compared to the initial magnetic resonance images (MRI). Two months after treatment, the patient had some remaining distal limb numbness and normal serum homocysteine level; however, the abnormal signals seen on cervical T2-weighted images had only slightly decreased compared to those seen on the one-month follow-up MRI. The evolution of conventional MRI findings lagged behind the clinical manifestation, suggesting a clinical-radiological dissociation. Conclusions: The clinical-radiological dissociation may have occurred in this case because the T2-weighted imaging did not have sufficient sensitivity to reveal cytotoxic edema. Additionally, the serum vitamin B12 level was not a good indicator of cellular vitamin B12. Clinicians should, therefore, recognize this phenomenon, comprehensively assess the condition of patients with N2O-induced SCD, and avoid terminating treatment based on the resolution of clinical symptoms and serological results.

Background

Subacute combined degeneration (SCD), a neurological complication of vitamin B12 deficiency, is typically observed in elderly individuals who have malabsorption syndromes, inadequate intake, or inadequate B12 bioavailability1. Recently, several sporadic cases of otherwise healthy young adults with SCD induced by nitrous oxide (N2O) abuse have been described2. However, to the best of our knowledge, none have reported a relationship between the dynamic neuroimaging evolution and clinical manifestations of a patient with N2O-induced SCD. Patients who abuse N2O are often recalcitrant, and treatment is frequently discontinued by these patients once their neurological symptoms improve3. Moreover, guidelines for treatment duration have not yet been established for patients with SCD. Therefore, we report the case of a young man diagnosed with SCD caused by extensive N2O inhalation that led to a clinical-radiological dissociation, and further highlight that the condition of patients with N2O-induced SCD cannot be determined by imaging abnormalities, clinical manifestations, or serum vitamin B12 levels alone.

Case Presentation

A 24-year-old man in a wheel-chair presented with numbness of all extremities and worsening lower-extremity weakness for approximately 20 days. For recreation, he had inhaled N_2O through an approximate average of 100–200 "whippit" cartridges per day for at least three months. The patient demonstrated good dietary intake without alcohol use and had neither a history of smoking nor illicit drug

use. Neurologic examination showed clear consciousness with fluent speech, normal cranial nerve examination, mild weakness in the upper limbs (grade 4) and severe weakness in the lower limbs (grade 3), markedly increased deep tendon reflexes, impaired joint position and vibration sensation, sensory ataxia, a positive bilateral Babinski sign, and positive Romberg and Lhermitte's signs. Laboratory tests revealed decreased serum levels of red blood cells (RBC) (3.32×10^{12} /L, reference range $4.30–5.80\times10^{12}$ /L), hemoglobin (Hb) (118.4 g/L, reference range 130–175 g/L), vitamin B_{12} (98.2 pmol/L, reference range 145–637 pmol/L), and folic acid (8.38 nmol/L, reference range 8.83–60.80 nmol/L). Serum homocysteine (Hcy) was strongly elevated (>50 μmol/L, reference range 5.46–16.20 μmol/L), indicating a functional vitamin B_{12} deficiency at the cellular level. Assessments of cerebrospinal fluid (CSF) yielded normal results, and inflammatory, infectious, and immune biomarker findings of both the CSF and serum were unremarkable. Sagittal spinal cord magnetic resonance imaging (MRI) showed hyperintensities involving the posterior columns from C2 to C6 on T2-weighted images (Fig. 1a), with an inverted V-sign on axial MRI (Fig. 1b). The brain and thoracic MRI confirmed normal findings.

The patient was diagnosed with SCD of the spinal cord induced by N_2O consumption. Treatment with a high dose of supplementary intramuscular vitamin B_{12} injections (1.5 mg per day), oral folic acid (15 mg per day), and abstinence from N_2O led to a gradual improvement in the patient's symptoms. One month later, the symptoms of weakness and paresthesia had resolved; the patient was able to walk unsupported with remaining gait impairment. His serum RBC, Hb, and folic acid levels had improved to normal, and the serum vitamin B_{12} concentration had increased to more than 1476 pmol/L (the maximum measurable value). However, the patient's serum Hcy remained elevated (19.02 μmol/L). At this time, we observed the interesting phenomenon that, despite the patient's clinical symptoms and laboratory values improving , the hyperintensities on T2-weighted images had extended, both horizontally and longitudinally, from C1 to T2 (Fig. 1 c), resembling a "ball" on the axial images (Fig 1. d). It is important to note that the patient had had no exposure to hormones or N_2O. He was discharged with a prescription for vitamin B_{12} supplements. At the two-month follow-up, the patient's gait had improved and he left mild paresthesia of the distal limbs. His serum Hcy had improved to a normal level. In addition, the abnormal signals seen on T2-weighted images had decreased since the one-month follow-up MRI but were still more extensive than what was seen on the initial MRI (Fig. 1 e, f). It seemed a clinical-radiological dissociation had occurred, and conventional MRI findings had consistently lagged behind the clinical and laboratory manifestations.

Discussion And Conclusions

Though several cases of SCD associated with vitamin B_{12} deficiency induced by N_2O abuse have been described, the relationship between the dynamic neuroimaging evolution and clinical manifestations of a patient with N_2O-induced SCD has never been reported. To the best of our knowledge, this is the first report of a clinical-neuroimaging dissociation in a patient with N_2O-induced SCD.

N_2O induces SCD by irreversibly oxidizing the cobalt ion of vitamin B_{12} (cobalamin). The highly nucleophilic cobalamin (1+), created upon the methylation of Hcy to form methionine, commonly reacts

with methyltetrahydrofolate to regenerate methylcobalamin[4]. Once the cobalt ion is oxidized by N_2O, the methylcobalamin, as a cofactor of methionine synthase in transferring Hcy to methionine, subsequently inhibits S-adenosylmethionine, which is essential for the methylation of myelin sheath phospholipids[5]. Thus, inactivating vitamin B_{12} metabolism results in the demyelination of the spinal cord[6].

Few cobalamin-deficient patients have normal serum vitamin B_{12} levels. According to the metabolic pathway described above, a normal level of serum vitamin B_{12} is not indicative of the precise or timely cellular availability of vitamin B_{12}. Instead, elevated serum levels of Hcy or methylmalonic acid serve as better biomarkers for the diagnosis of cellular vitamin B_{12} deficiency[7]. Although the serum levels of vitamin B_{12} and folic acid of this patient returned to normal, the elevated Hcy showed greater value as an indicator of cellular vitamin B_{12} deficiency. That is to say, demyelination of the cervical spinal cord may still exist.

In addition, the lag of the conventional MRI findings behind the clinical manifestations is similar to that seen in central pontine myelinolysis (CPM). In 1996, SCD was classified as a pure myelinolytic disease with no apparent loss of myelin or areas of partial neuropathological remyelination[8]. Hence, we surmise that – similar to what may be observed in cases of CPM – the clinical-radiological dissociation observed in our case may relate to the neuropathological basis of intramedullary and interstitial edema. Hyperintensity on spinal cord diffusion-weighted imaging (DWI) and a corresponding hypointensity on the apparent diffusion coefficient maps have been previously reported in patients with SCD[9,10]. These acute demyelinating lesions manifested as restricted diffusion, indicating an energy failure that caused cytotoxic edema.

DWI provides quantitative and qualitative functional information on the microdiffusion of water molecules at the cellular level, and has been widely applied to evaluate a variety of brain disorders, such as acute cerebral infarction[11]. Similarly, DWI is superior to T2-weighted imaging for the diagnosis of cytotoxic edema in its early stages. Hence, we hypothesize that the T2-weighted imaging was not sensitive enough to reflect the early intramedullary and interstitial cytotoxic edema due to SCD, and may be another possible reason for the clinical-imaging dissociation of the present case.

In conclusion, we recommend that N_2O abuse should be considered when patients present with SCD – especially if the patient is young and otherwise healthy. The inability of serum vitamin B_{12} to reflect cellular vitamin B_{12} levels and T2-weighted imaging to reveal cytotoxic edema in the early stages may have contributed to the clinical-imaging dissociation. Clinicians should, therefore, comprehensively assess the condition of patients with N_2O-induced SCD, avoid terminating treatment due to the resolution of clinical symptoms and serological findings, and carefully evaluate worsening imaging results as a possible clinical-imaging dissociation.

Abbreviations

CPM, central pontine myelinolysis; CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; Hb, hemoglobin; Hcy, homocysteine; MRI, magnetic resonance imaging; N2O, nitrous oxide; RBC, red blood cells; SCD, subacute combined degeneration

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Written informed consent was obtained from the patient. A copy of the written consent is available for review by the editor upon request. We clarify that the consent covered the publication of the information included in the case report, as well as any associated images.

Availability of data and materials

Data has not been made accessible in the interest of protecting the patient's privacy.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JJ: concept and design of the study, interpretation of the data, drafting and revising the manuscript. XS: critical revision of the manuscript for important intellectual content, study supervision.

All authors have read and approved the manuscript.

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Figures

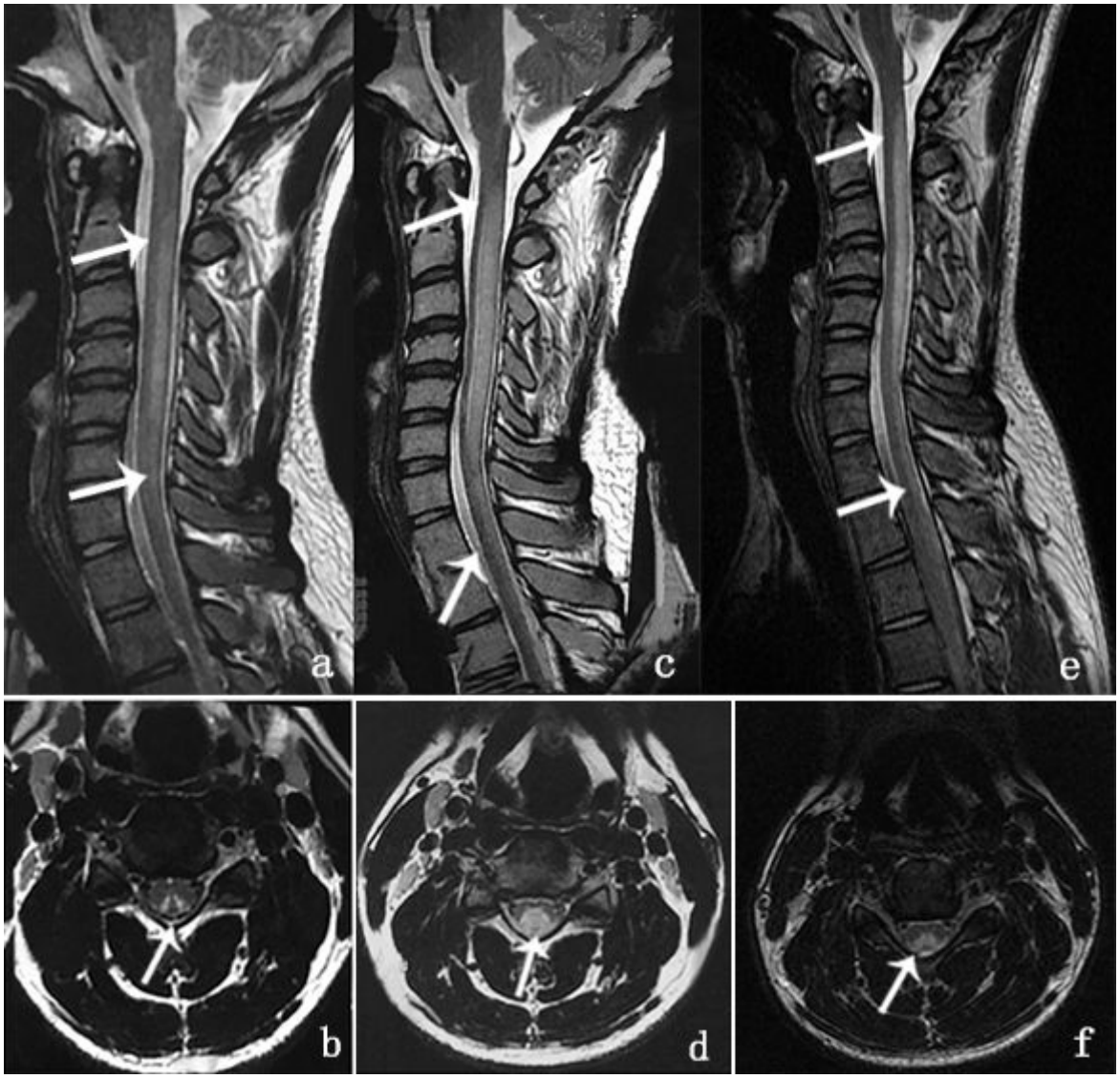

Figure 1

Magnetic resonance imaging of the cervical spinal cord a. Sagittal T2-weighted imaging showed increased intramedullary signal intensity along the posterior column of the spinal cord extending from C2 to C6 on August 3rd, 2018. b. A V-shaped hyperintensity on axial T2-weighted imaging at the C4 level was seen within the dorsal cervical spinal cord on August 3rd, 2018. c. Sagittal T2-weighted imaging showed abnormal, longitudinally and horizontally extensive hyperintensities involving the lateral and posterior columns of the spinal cord extending from C1 through T2 on September 3rd, 2018. d. Axial T2-weighted imaging at the C4 level showed a ball-shaped hyperintensity on September 3rd, 2018. e. Sagittal T2-weighted imaging showed hyperintensity along the posterior column of the spinal cord extending from C1 to T1 on October 4th, 2018. f. Axial T2-weighted imaging at the C4 level showed that the V-shaped hyperintensity had decreased compared to its size in September (d).

Supplementary Files

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