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Myeloneuropathy from Nitrous Oxide Abuse: Unusually High Methylmalonic Acid and Homocysteine Levels

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ABSTRACT

A 23-year-old patient developed diffuse paresthesias and sensory loss. He had mildly reduced serum vitamin B_{12} (B_{12}) concentration with unusually high levels of methylmalonic acid (MMA) and homocysteine and no evidence of B_{12} malabsorption. Following parenteral B_{12} administration, his neurological deficit promptly resolved and B_{12} and MMA levels normalized, but elevated levels of homocysteine persisted. One year later, he admitted to inhaling nitrous oxide (N_2O). After halting N_2O abuse his homocysteine level normalized. This case demonstrates the importance of serum homocysteine level measurements in cases of suspected N_2O toxicity.

INTRODUCTION

Nitrous oxide abuse is relatively common[1,2] and may cause significant neurological disability. The mechanism of N_2O neurotoxicity is interference with vitamin B_{12} bioavailability[3] and the resulting neurological syndromes are indistinguishable from B_{12} deficiency due to malabsorption or low dietary intake.[4-6]

Diagnosing N_2O-induced neurologic disease may be difficult if the affected patient does not disclose his inhalation activity, or the examiner fails to inquire about it. Serum concentrations of melthylmalonic acid (MMA) and homocysteine are sometimes the only clues about the N_2O exposure since vitamin B_{12} levels may be normal.[6]

CASE REPORT

A 23-year-old man described 6-8 weeks of progressive numbness and paresthesias affecting his hands and feet. He denied any weakness, difficulty walking, bowel or bladder dysfunctions, or cognitive problems.

Approximately 2 weeks prior to the onset of his symptoms he began taking carbamazepine for mood control. His psychiatrist initially ascribed his symptoms to possible carbamazepine toxicity but his paresthesias progressed despite the discontinuation of carbamazepine.

His medical history included schizoaffective disorder but he had not used psychotropic medications for over a year. Close family members were free of neurodegenerative conditions. He denied toxic exposure or any substance abuse, but admitted using some "street drugs" in the past. He tested negative for HIV on several occasions. He ate a regular diet.

On neurological examination, his mental status, speech, and cranial nerves were normal. Motor examination showed normal muscle bulk, tone, and power. Muscle stretch reflexes were normal. Sensory examination showed markedly decreased vibratory sensation in his feet and legs, in a stocking pattern, normal proprioception, and no significant abnormality of pain, temperature, and light touch sensations. His Romberg test was negative, but he had slight difficulty on tandem gait testing.

Nerve conduction study and needle electromyography were normal, but quantitative sensory testing (QST) showed markedly abnormal thresholds for vibratory stimuli in lower extremities with normal thresholds for thermal stimuli. Complete blood count was normal except for mild increase in mean corpuscular volume at 96 fl/RBC (82-95). Serum creatinine, blood urea nitrogen, hemoglobin A_1C, aspartate aminotransferase, alanine aminotransferase, electrolytes, and serum protein electrophoresis were normal. Venereal Disease Research Laboratory test and Lyme titer were negative. ANA titer was minimally elevated at 1:40. Red blood cell folate level was normal at 444

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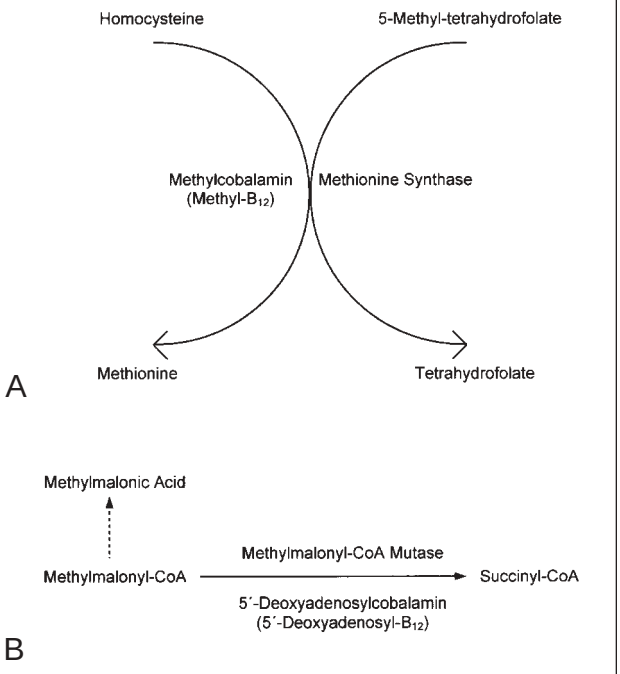

Figure 1A, B. Vitamin B_{12}-dependent metabolic pathways.

ng/ml (145-500). Serum B_{12} level was mildly below normal level at 136 pg/ml (150-800). There was severe elevation of MMA at 4.1µmo/l (0.0-.4). Homocysteine level was also very elevated at 114 µmol/l (4-20). Schilling test was normal. Anti-parietal cell and anti-intrinsic factor antibodies were negative. Magnetic resonance imaging of the head was normal.

The patient was prescribed intramuscular B_{12} injections with a 1000 µg dose daily for 5 days and then 1000 µg every 3 to 4 weeks. His symptoms completely resolved within a few weeks after initiation of B_{12} supplementation and his neurological examination 8 weeks later was normal. His B_{12} and MMA levels normalized within 2 months, but very high homocysteine levels persisted and unexpectedly rose to 164 µmol/l (10 times upper range of normal). The patient remained asymptomatic with intramuscular (IM) B_{12} treatment for a number of months, but subsequently he admitted inhaling, daily, large amounts of N_2O from cartridges used as propellants for decoration of baked goods. For several months before his symptoms developed he inhaled N_2O from between 24 to 60 cartridges per day, and on some weekends he would expend up to 240 cartridges. He complied with advice to halt N_2O abuse and his homocysteine level was normal on a follow-up visit 4 weeks later. Following the change to oral vitamin B complex supplementation (1 tablet twice a day) his B_{12}, MMA, and homocysteine levels remained normal and on subsequent follow-up visits he continued to be symptom free with normal neurological examination.

DISCUSSION

Nitrous oxide oxidizes the B_{12} (cobalamin) cobalt atom from its 1+ to 3+ valence state, rendering methylcobalamin (one of the active forms of cobalamin) inactive as a cofactor of methionine synthase.[3] This inhibits conversion of homocysteine to methionine (Figure 1A), a precursor of S-adenosylmethionine, which is necessary for myelin production, and also inhibits production of tetrahydrofolate (Figure 1A) which is essential for DNA synthesis.[3,6] Functional B_{12} (5´-deoxyadenosylcobalamin) is also necessary for conversion of methylmalonyl CoA to succinyl CoA (Figure 1B). Biochemical indicators of B_{12} deficiency are elevated serum concentrations of homocysteine and MMA, a result of their impaired metabolism.

The neurological syndromes caused by N_2O toxicity may occur in two different clinical situations. A subgroup of patients develop symptoms after prolonged, repeated exposure (usually abuse), and those patients typically have normal B_{12} levels. Another group are patients who usually have mild, subclinical B_{12} deficiency, and may become symptomatic after even a single exposure to N_2O.[6] The diagnosis of the N_2O toxicity syndromes may be elusive in patients presenting with normal serum B_{12} unless N_2O exposure is noted. Elevated MMA and homocysteine levels may be the only clues indicating disturbed B_{12} metabolism in these patients.

The patient in this report presented with paresthesias, profound loss of vibratory sensation ("large fiber" sensory loss) and preservation of pain and temperature ("small fiber" function). This clinical pattern, confirmed by QST, with unremarkable nerve conduction studies, suggested that his neurologic deficit was caused predominantly by dysfunction of the posterior columns of the spinal cord. Coexisting peripheral nerve involvement, below the detection threshold of the nerve conduction studies technique, was likely, with mostly distal sensory deficit. Therefore, his neurological syndrome could be referred to as myeloneuropathy.

The high MMA and homocysteine levels indicated that impaired B_{12} metabolism was the culprit of the neurological deterioration. Moreover, his symptoms completely resolved with high dose parenteral B_{12} administration. However, the persistent homocysteine levels remained unexplained until finally the patient ad-

mitted, on subsequent evaluations, chronic N_2O abuse. Once the patient quit N_2O inhalation, the homocysteine levels promptly normalized.

Mildly low level of B_{12} on initial measurement in our patient is of uncertain cause since N_2O should not compromise the absorption of B_{12}, his Schilling test was normal, and there was no dietary deficiency. We cannot rule out entirely impaired food-B_{12} absorption since the chicken serum test was not performed.[7] It is also possible that the oxidation of the B_{12} cobalt core might have interfered with the immunoassay employed in B_{12} level measurement by changing the configuration of the cobalamin molecule.

Interestingly, a similar case was reported in 1978 by Sahenk et al,[1] who described a patient inhaling whipped cream propellant, although the authors did not associate N_2O oxide toxicity with disturbance of B_{12} metabolism. In 1997 Brett[2] described a 21-year-old patient with ataxia, weakness, sensory loss, Lhermitte's sign, and acute anxiety secondary to N_2O toxicity from whipped cream bulbs (up to 200 per week). Similarly to our case, she had low serum B_{12} level at 56ng/L (200-1000) despite normal Schilling test. She was successfully treated with intramuscular B_{12}.

This is the first report documenting such high levels of homocysteine and methylmalonic acid levels in a patient with nitrous oxide abuse. It demonstrates the potential magnitude of metabolic derangement in N_2O abusers, and how challenging evaluation of these patients may be if they do not admit to substance abuse on initial evaluation.

As demonstrated in our patient, the homocysteine level appears to be more sensitive, and therefore a more useful biochemical marker of disturbed B_{12} metabolism in cases of N_2O toxicity than MMA. In our opinion this syndrome is probably underdiagnosed, and may be completely missed if homocysteine level is excluded in laboratory testing of these patients.

REFERENCES

1. Sahenk Z, Mendel JR., Couri D, et al. Polyneuropathy from inhalation of N_2O cartridges through a whipped-cream dispenser. *Neurology.* 1978;28:485-487.
2. Brett A. Myeloneuropathy from whipped cream bulbs presenting as conversion disorder. *Aust N Z J Psychiatry.* 1997;31:131-132.
3. Green R, Kinsela LJ. Current concepts in the diagnosis of cobalamin deficiency. *Neurology.* 1995;45:1435-1440.
4. Blanco G, Peters H.A. Myeloneuropathy and macrocytosis associated with nitorus oxide abuse. *Arch Neurol.* 1983;40:416-418.
5. Marié RM, Le Biez E, Busson P, et al. Nitrous oxide anesthesia-associated myelopathy. *Arch Neurol.* 2000; 57:380-382.
6. Kinsella, LJ, Green R. "Anesthesia paresthetica": Nitrous oxide-induced cobalamin deficiency. *Neurology.* 1995;45:1608-1610.
7. Carmell R. Malabsorption of food cobalamin. *Baillieres Clin Hematol.* 1995;8:639-655.

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