Two Cases of Nitrous Oxide-induced Functional Vitamin B12 Deficiency

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Background

Progressive weakness and sensory changes are two common presenting neurological symptoms. True muscle weakness can arise from abnormalities anywhere along the pathway between the motor cortex and the muscle, including the corticospinal tracts, anterior horn cells, spinal nerve roots, peripheral nerves, and neuromuscular junction. A detailed neurological exam assessing motor strength, deep tendon reflexes, and related sensory changes is crucial in localizing where along this pathway the abnormality lies. Once the lesion has been localized, the etiology of the lesion can fall into one of many categories including genetic, immunologic, infectious, neoplastic, toxic, or metabolic. A detailed family, travel, and social history can help rule out or rule in several of these etiologies. Laboratory and electromyographic studies can assist in confirming a diagnosis.

Case Descriptions

Patient A was a 40-year old male with four months of progressive weakness and sensory changes. The symptoms began with tingling of the feet that ascended to the arms within five weeks of onset. He then began to lose his balance and could not stand up due to the weakness in his legs, causing him to become wheelchair bound. He also reported weakness in his hands. For several months before the weakness started, he inhaled up to 100 nitrous oxide cartridges per day for anxiety. On examination, he was sitting in a wheelchair and could not stand up unassisted. Strength was 4/5 in the deltoids, 3/5 in the finger flexors and extensors, 2/5 in the hip flexors, and 0/5 in the ankle flexors and extensors. Pinprick and vibration sense were decreased in the feet up to the shins, and proprioception was impaired in the lower extremities. DTRs were diffusely absent. The remainder of the exam was normal. EMG was consistent with severe axonal sensorimotor neuropathy. On laboratory studies, B12 level was 246 ng/mL; copper level, SR, ANA, TSH, IFPE, and HbA1c were normal. Homocysteine level was 44.6 µmol/L, and methylmalonic acid level was 309 nmol/L, near the upper limit of normal.

Patient B was a 46-year old male with progressive weakness and sensory changes. The symptoms began eight months prior to presentation with weakness and numbness of the hands and feet, poor balance, and severe pain in the fingertips. For several months before the weakness started, he started inhaling whipped cream nitrous oxide chargers, up to 400 per day. On examination, he was sitting in a wheelchair and could not stand up. Strength was 3/5 in the hip flexors and 0/5 in the ankle extensors. Pinprick and vibration sense were decreased in the feet up to the shins, and proprioception was impaired in the lower extremities. DTRs were diffusely absent on the left. EMG was consistent with predominantly demyelinating sensorimotor polyneuropathy. B12 level, copper level, SR, ANA, TSH, SPEP, and HbA1c were normal; serum MMA was high.

Results

Patient A was initially treated with high dose intramuscular vitamin B12, 1000 µg per day for 14 days followed by 1000 µg per week for 14 weeks, and physical therapy with a presumed diagnosis of nitrous oxide toxicity leading to functional vitamin B12 deficiency. The patient was also instructed to discontinue all use of inhaled nitrous oxide. One month after treatment initiation, he reported improvement of the sensory symptoms in the arms and legs. Four months after treatment initiation, the patient was no longer wheelchair-dependent, walking with a walker. He was able to walk confidently with no symptoms in the arms. However, he still had residual bilateral foot drop, numbness in the feet, and poor balance. Serum MMA had decreased to 140 nmol/L. He was then given 1000 µg vitamin B12 monthly for the next six months. At follow up, he reported continued improvement, now walking with a cane. Strength improved to 5/5 in the deltoids, finger flexors and extensors, and hip flexors and 2/5 in the ankle flexors and extensors. Knee reflexes were normal.

Patient B was initially treated with 2 mg intramuscular vitamin B12 weekly and physical therapy with the same presumed diagnosis. He was instructed to abstain from nitrous oxide use with follow up in two months.

Discussion

Nitrous oxide is a gas that is used in many different disciplines from anesthesia to automotive racing. It is also found in aerosol spray propellants which are commonly found in household items such as whipped cream cans and cooking sprays. Due to their widespread availability and affordable cost, nitrous oxide chargers, known colloquially as "whippits" (Figure 1), have begun to be used recreationally to achieve a state of euphoria. Occasional use rarely leads to adverse long-term outcomes. However, heavy abuse has been documented to cause polyneuropathy and ataxia, often giving the clinical picture of subacute combined degeneration seen in vitamin B12 deficiency.

Figure 1

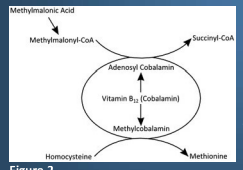

Figure 2

Vitamin B12 is necessary for both the conversion of homocysteine to methionine as well as the conversion of methylmalonyl-CoA to succinyl-CoA as illustrated in Figure 2. Nitrous oxide, through oxidation of cobalt ions in vitamin B12, converts the active monovalent form of vitamin B12 to its inactive bivalent form. This prevents methylation of myelin proteins leading to demyelination within the central and peripheral nervous systems.

Discussion (continued)

Therefore, with nitrous oxide toxicity, though vitamin B12 levels may be normal since vitamin B12 is only being inactivated, and there is no true deficiency, patients will have a functional vitamin B12 deficiency. Though vitamin B12 levels may be normal, as they were in these two patients, homocysteine and methylmalonic acid levels will still often be increased as seen in vitamin B12 deficiency due to the inactivation of vitamin B12 by nitrous oxide. After initiation of therapy, homocysteine and methylmalonic acid levels can be monitored for progress.

The clinical presentation of nitrous oxide-induced functional vitamin B12 deficiency varies. In most reported cases, the presentation is that of a myelopathy particularly affecting the dorsal columns, or subacute combined degermation of the spinal cord. There have been documented cases, however, with no clinical evidence of myelopathy and normal spinal cord imaging. In these cases, there was clinical evidence of a sensorimotor neuropathy with demyelinating features on electromyographic studies. This presentation can be confused with Guillain-Barré syndrome. However, lack of response to intravenous immunoglobulin therapy, relationship between symptom onset and nitrous oxide inhalation, and serum laboratory studies can help differentiate between the etiologies of the neurological symptoms.

The recommended treatment for nitrous oxide-induced functional vitamin B12 deficiency is high-dose intramuscular vitamin B12 replacement. Though homocysteine and methylmalonic acid levels may quickly return to normal after treatment initiation, symptomatic improvement can take months to years. It is also not uncommon to see incomplete recovery with residual motor or sensory deficits.

Though thought to be benign, nitrous oxide inhalation, especially with heavy use, is toxic to the human body, particularly the nervous system. Patients with symptoms consistent with vitamin B12 deficiency or Guillain-Barré syndrome should be asked about recreational nitrous oxide use. Early nitrous oxide cessation and vitamin B12 supplementation often lead to improvement, if not reversal, of neurological deficits.

References

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