Nitrous Oxide-Induced Cervical Myeloneuropathy involving Posterior Column with Normal Range Vitamin B12

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Abstract: A 22-year-old man with heavy use of nitrous oxide as a recreational inhalant, presented with generalized paraesthesia, sensory loss and significant gait disturbance. He had clinical as well as radiological signs of involvement of the posterior column of the cervical spinal cord. Although, his vitamin B12 level was within normal limit, his methylmalonic acid and homocysteine levels were noted to be elevated. The thoracic part of the spinal cord is commonly affected in vitamin B12 deficiency-related neurological syndromes. However, in this case report the cervical part of the spinal cord was primarily involved. Following vitamin B12 and methionine replacement, his symptoms improved promptly.

Key words: NO - nitrous oxide, BMI – body mass index, HIV – human immunodeficiency virus, CMV – cytomegalovirus

Introduction
Nitrous oxide is an inhaled anaesthetic agent commonly used in anaesthesia, dentistry, and the food industry (aerosol dispensers). Many reports have described the neurotoxicity related to nitrous oxide use in various medical procedures and after occupational exposures (2-6). We describe a case of cervical myeloneuropathy involving the posterior column secondary to chronic use of nitrous oxide (NO). The vitamin B12 level was within normal limits. The level of vitamin B12 in our case was higher than those that were documented in previously published reports.

Case report
A 22-year-old man presented with numbness and paresthesia below the level of the base of the neck, and worsening clumsiness and gait disturbance of two weeks duration, after increased use of nitrous oxide in the last 3 months of presentation. He was found to have dysmetria, poor proprioception, decreased sensation to vibration and light touch over the extremities, and a positive Romberg sign. He denied any weakness, bladder or bowel symptoms, or cognitive dysfunction.

His medical history is significant for poly-substance abuse (methamphetamine, cocaine, and nitrous oxide inhalation--sixty canisters per week), anxiety and mild stable asthma. He also has long standing depression, and occasional suicidal ideation; but is currently not on treatment.

His close family members did not have any neurodegenerative disorders.

On general examination, he was alert, oriented and cooperative, and his nutritional status was normal with a BMI of 24.

On neurological examination his mental state, speech, and cranial nerves were normal. Motor examination showed normal muscle bulk, tone, power and reflexes.

Sensory examination showed only vibration and proprioception deficits in a stocking-glove pattern in upper and lower extremities. The rest of the sensory modalities were normal and the Romberg sign was positive.

The remainder of the physical examination was unremarkable.

The complete blood examination was normal except for a raised mean corpuscular volume of 95.2 fL. Biochemical panels were normal. The vitamin B12 level was 276 pico moles per litre (normal range 140-700). This is, notably, the highest vitamin level reported in case reports thus far in NO related vitamin B12 complications. The folate level was normal. However, the methylmalonic acid was raised at 3.35 micromoles per litre (normal 0.10-0.50) and the homocysteine level was elevated at 26 micromoles per litre (normal range 4-14). The thyroid function test was normal.
Viral serology was negative for hepatitis, HIV, CMV, enterovirus, varicella and herpes. CSF examination did not suggest any abnormality.

While the MRI head was normal, the MRI of the spine showed hyper-intense signal in the long segment dorsal column without signal enhancement. This symmetrical change present throughout the cervical cord creates what is known as the inverted V-sign or inverted rabbit ears sign (1). Nerve conduction studies were normal.

MRI-1, a hyperintense long signal can be observed in the cervical area.

MRI-2, an inverted V sign or inverted rabbit ears sign in cervical area.
The patient was given intramuscular B12 injections—1000 micrograms daily for a week, and then fortnightly followed by monthly. He was also given methionine one gram three times a day. His paraesthesia and gait abnormality improved significantly within three days. On follow-up two weeks later, his proprioception had mildly improved, and he could walk normally. He had become independent with activities of daily living.

Discussion

Nitrous oxide is an inhaled anaesthetic agent commonly used in anaesthesia, dentistry, and the food industry (aerosol dispensers). Many reports have described the neurotoxicity related to nitrous oxide use in various medical procedures and after occupational exposures (2-6).

Nitrous oxide inactivates cobalamin, the active derivative of vitamin B12, and an essential cofactor for the transfer of the methyl group from methyltetrahydrofolate to homocysteine to form methionine. This reaction subsequently decreases the quantity of methyl groups in myelin sheath phospholipids. The end result is demyelination of the nervous system involving the spinal cord (6) and rarely, in severe cases, peripheral neuropathy, optic atrophy, and encephalopathy. The early symptoms of polyneuropathy such as numbness tend to be unrecognized if they are not suspected during patient assessment (7).

The diagnosis of myelopathy is often delayed and can be difficult if the patient fails to disclose the use of nitrous oxide. A detailed history and thorough examination are essential in suspected cases of vitamin B12 deficiency.

In a mammalian cell, there are two different coenzyme forms of vitamin B12

- Methylcobalamin is used by the enzyme methionine synthase to convert homocysteine (HCY) into methionine. Methionine is further converted to the important methyl donor, S-adenosylmethionine.
- S'-deoxyadenosylcobalamin is used by the enzyme methylmalonyl-CoA mutase to convert methylmalonyl-CoA to succinyl-CoA.

Nitrous oxide oxidizes the cobalt atom of vitamin B12 from its 1+ to 3+ valence state. This new molecule inactivates methylcobalamin, as a cofactor of methionine synthase (8). This reaction inhibits conversion of homocysteine to methionine, a precursor of S'-adenosylmethionine, which is necessary for myelin production. NO also inhibits methionine synthase and that results in inhibition of production of tetrahydrofolate which is an essential factor for the synthesis of DNA (9, 10). (Fig. 1)

An active form of vitamin B12, adenosylcobalamin, is essential for the conversion of methylmalonyl-CoA to succinyl-CoA. In conditions where vitamin B12 is deficient, methylmalonyl-CoA levels increase. Methylmalonyl-CoA is then converted to
methylmalonic acid (MMA) which accumulates in the blood and urine. Since vitamin B12 is the only coenzyme required in this pathway, the MMA level is the best indicators of a B12 deficiency. (Fig. 2). Although, the total serum homocysteine is a sensitive indicator of vitamin B12 deficiency; its utility is limited as a sole confirmatory test because homocysteine levels are also elevated among patients by familial hyperhomocysteinemia, levodopa therapy, renal insufficiency and folate deficiency (11).

Figure 2

The patient described in this case report had impaired proprioception with preservation of pain and temperature sensation. This pattern of clinical findings was consistent with involvement of the posterior column of the spinal cord. Vitamin B12 deficiency affects vibration and proprioception (large fibres) more than pain and temperature sensations (small fibres) for unclear reasons.

The elevated levels of methylmalonic acid and homocysteine are indicative of qualitative or quantitative deficiency of vitamin B12. In this patient methylmalonic acid and homocysteine levels were elevated, and vitamin B12 level was within normal range. We believe that this patient has vitamin B12 dysfunction, rather than a quantitative deficiency.

MRI is the best modality of imaging in these groups of patients, which typically shows hyperintense signal with no enhancement, and usually begins in the upper thoracic region with ascending or descending progression (11). Although in this case report the posterior part of the cervical region was primarily affected, any part of the cervical cord can be affected including rare cases of anterior cervical cord involvement.

Comment

Nitrous oxide causes irreversible inactivation of vitamin B12 by oxidation leading to the development of myelopathy and in severe cases polyneuropathy. Neurological findings are primarily due to functional deficiency of vitamin B12 and in these cases the measured level of vitamin B12 may be normal. In patients with neurological complications due to vitamin B12 deficiency, anaemia and macrocytosis are often not present (12). A detailed history and thorough physical examination are of paramount importance in a patient with suspected vitamin B12 deficiency. Early diagnosis and treatment is crucial to avoid long term neurological complications.

We suggest in clinically suspected cases of vitamin B12 deficiency, methylmalonic acid and homocysteine levels should also be tested in conjunction with vitamin B12 level to detect qualitative as well as quantitative deficiency.

References

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