CASE REPORT

One month of nitrous oxide abuse causing acute vitamin B₁₂ deficiency with severe neuropsychiatric symptoms

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SUMMARY

A 21-year-old university student studying abroad in the USA presented to the emergency department with double vision, lower extremity weakness with difficulty ambulating and other neuropsychiatric symptoms. MRI of the brain and spinal cord were normal. Vitamin B₁₂ was 78 pg/mL (58 pmol/L, reference 211–911 pg/mL). The patient had been using nitrous oxide capsules used for whipped cream recharging, which she obtained from other students, a few times daily for a month for the purpose of anxiety relief. The patient was not a vegan or vegetarian. The patient was treated with intramuscular vitamin B₁₂ repletion with partial resolution of neurologic symptoms and discharged on vitamin B₁₂ supplementation.

BACKGROUND

Nitrous oxide (N₂O, or laughing gas) can cause severe B₁₂ deficiency.^{1–3} This is already established in the literature but we feel that there is not enough awareness about it. For example, the New England Journal of Medicine *Clinical Practice* review on Vitamin B₁₂ from 2013, which one would expect to be comprehensive and authoritative, does not even mention N₂O.⁴ Yet, N₂O abuse is common and case reports of vitamin B₁₂ depletion with N₂O use are increasingly common.

Even more ominous is that it rapidly causes B₁₂ deficiency (it has been reported as soon as 2 days) as opposed to vitamin B₁₂ deficiency of other aetiologies, which may catch physicians who expect B₁₂ deficiency to be something taking years to develop off guard.

This pathology is common. N₂O is widely used recreationally around the world. For example, in the UK, it was the second most popular recreational drug in 2015 (cannabis was number one).⁵ N₂O is readily available online and in clubs. In the USA, use of N₂O is less common for some reasons, but the authors have been in proximity to two such cases occurring in students studying abroad in the USA within only a few years. The purpose of this case report is to bring awareness to this serious and quite common drug effect to knowledge both for medical practitioners and lay people.

CASE PRESENTATION

Review of systems was positive for double vision, falls, dizziness, weakness in lower extremities and

anxiety. There was no upper extremity paraesthesia or weakness, respiratory difficulty or shortness of breath. The patient described three episodes characterised by then momentary syncope preceded by a prodrome of loss of vision followed by tinnitus.

On physical examination, the patient's extraocular muscles were intact, pupils were normal in size, and reactive to light and accommodation. The patient had 4/5 strength in the lower extremities. The Romberg test was positive. No orthostasis was present and respiratory effort was normal.

There was no significant medical history or family history of neurological diagnoses, genetic or metabolic disorders. The patient denied use of illicit substances or alcohol use. She smoked half a pack per day.

The patient had been using nitric oxide daily by means of 'cream chargers' obtained from other Chinese students studying abroad. She related that she had last used the N₂O 3 days prior to presentation. She had stopped using it because it was no longer helping the anxiety. Also, the patient had been trying to aggressively diet in order to lose weight she had gained after returning from vacation, although she had not been a vegan or vegetarian.

INVESTIGATIONS

Laboratory tests (reference ranges are in parentheses)

- ▶ Vitamin B₁₂: 78 pg/mL (211–911 pg/mL).
- ▶ Methylmalonic acid: 0.74 nmol/mL (<=0.40 nmol/mL).
- ▶ Homocysteine: 127.6 µmol/L (3.7–13.9 µmol/L).
- ▶ Folic acid 8.33 ng/mL (>5.38 ng/mL).
- ▶ Iron, total 26 µg/dL (50–150 µg/dL).
- ▶ Total iron binding capacity 174 µg/dL (270–440 µg/dL).
- ▶ Iron saturation 15.0% (20.0%–50.0%).
- ▶ Ferritin 125 ng/mL (7–292 ng/mL).
- ▶ Vitamin E (α-tocopherol): 4.9 mg/L (5.5–17.0 mg/L).
- ▶ Comprehensive urine drug screen, creatine phosphokinase, C reactive protein, erythrocyte sedimentation rate, thyroid-stimulating hormone, ceruloplasmin, serum protein electrophoresis and immunofixation, urine pregnancy test, HIV-1 p24 antigen and HIV-1/HIV-2 antibody: within normal limits or negative.
- ▶ Haemoglobin A1c 6.5% (4.0%–6.0%).

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- ▶ D-dimer: 2.87 (0.00–0.50 mg).
- ▶ Copper 0.75 µg/mL (0.75–1.45 µg/mL).
- ▶ Comprehensive metabolic panel: within normal limits except alkaline phosphatase 35 U/L (reference range 52–144 U/L), total bilirubin 2.1 mg/dL (reference range 0.2–1.2 mg/dL).
- ▶ Complete blood count with automated differential: WBC 3.1 10⁹/L, haemoglobin 77 g/L (reference range 120–160), platelets 184 10⁹/µL, hematocrit 22.6%, mean corpuscular volume 76 fL (80–100 fL), mean corpuscular haemoglobin 26.0 pg (27.0–33.0 pg), red cell distribution width 14.8% (11.6%–14.6%).

Imaging

- ▶ CT of the brain without contrast: Negative
- ▶ CT angiogram of the neck and brain: Negative
- ▶ CT angiogram of the chest: Negative
- ▶ MRI with and without contrast of the brain, cervical, thoracic, and lumbar spine: Negative

DIFFERENTIAL DIAGNOSIS

Multiple Sclerosis

Vitamin B₁₂ deficiency and other vitamin and nutrient deficiencies

Guillain–Barré syndrome, Miller Fisher variant

Neuromyelitis optica (Devic's disease)

Neurosyphilis

Subacute sclerosing panencephalitis

Lyme disease

Cerebellar ataxia (toxin mediated-alcohol, drugs vs infectious (prion, viral, toxoplasmosis)

Neoplasm (Lymphoma, meningioma etc)

Neurodegenerative disorders

Psychogenic ataxia

Conversion syndrome

Wilson's disease

TREATMENT

The patient was treated with 1000 mcg intramuscular injections of B₁₂ daily. Physical therapy at first requested for the patient stay in the hospital and then recommended to continue outpatient physical and occupational therapy. The patient was discharged on hospital day four. The patient was instructed to abstain from N₂O, continue intramuscular B₁₂ 1000 mcg for a week and subsequently take oral vitamin B₁₂ at 2500 mcg daily for a month. She was asked to follow-up with her primary caregiver and perform an outpatient evaluation with neuro-ophthalmology for further evaluation of diplopia.

OUTCOME AND FOLLOW-UP

After parenteral treatment, the patient had improvement in her gait, muscle strength and anxiousness. Serum vitamin B₁₂ prior to discharge was 1130 pg/mL (211–911 pg/mL).

DISCUSSION

In this case, the differential diagnosis was broad and there were many abnormal lab values. The patient had some unusual lab findings such as the low serum alkaline phosphatase (which can be seen in Wilson's disease but is not specific) as well as an elevated haemoglobin A1c. Nevertheless, the diagnosis was B₁₂ deficiency because B₁₂ deficiency was the single pathology that could explain almost all of the patient's manifestations. B₁₂ deficiency is notorious for masquerading as blood disorders and can also contribute to numerous non-specific symptoms (such as this patient's syncope episodes). Furthermore, on repletion, the

patient's symptoms improved as described above. It was thought that the B₁₂ deficiency was due to N₂O misuse and not aggressive diet because B₁₂ stores last for years.

N₂O (or laughing gas) is an odourless and colourless gas. Having been first synthesised in 1772, It is appealing in its anxiolytic, amnesic and analgesic properties. In fact, in 1844, American dentist Horace Wells started to employ it as an analgesic for extracting teeth.⁶

Vitamin B₁₂ is a cofactor for only two enzymes: methionine synthase and L-methylmalonyl coenzyme A mutase. Vitamin B₁₂ deficiency causes megaloblastic anaemia, demyelinating disease and non-specific neuropsychiatric symptoms.⁴ It can mimic hematologic cancers or rare neurologic conditions such as Guillain–Barré syndrome.

The mechanism of vitamin B₁₂ depletion by N₂O is thought to be by means of oxidation.^{7,8} As such, this form of B₁₂ deficiency can present much more rapidly than B₁₂ deficiency from inadequate intake, malabsorption or pernicious anaemia. N₂O-induced neurologic pathology was first described in 1978.⁹ N₂O toxicity from B₁₂ depletion can occur anywhere from 2 days to 2 months after starting use.⁶ Our patient developed it after 1 month of heavy use. It cannot be emphasised the rapidity with which N₂O starts to cause this deleterious effect. Evidence of this was presented in a 2008 study where exposure to 66% N₂O for just 4 h was found to cause plasma homocysteine levels to increase.¹⁰ Our patient was fortunate in that she did not develop myeloneuropathy on the MRI as do some other patients in similar cases.¹¹

Notably, while some case reports detail reversibility of neurologic symptoms with reversal of myelopathic changes on the MRI disappearing,¹¹ numerous case reports of vitamin B₁₂ deficiency from N₂O have found that even when repleted intramuscularly, the symptoms are not fully reversible.^{12,13} Patients who are malnourished or otherwise more vulnerable to B₁₂ deficiency are even more susceptible to B12 depletion. For example, one case reported symptoms which were thought to be Guillain–Barré syndrome in a sickle cell disease patient but then discovered that the patient had been using N₂O for pain crises.¹⁴

This case is similar to other case reports of B₁₂ deficiency from N₂O use. It is different in that here, the patient was using N₂O for anxiety control (as opposed to recreationally) and there was no history of anaesthesia with N₂O.

Learning points

- ▶ Nitrous oxide (N₂O, not to be confused with nitric oxide, NO) is used recreationally and sometimes still used clinically in anaesthesia. It can cause vitamin B₁₂ deficiency very rapidly, anywhere from 2 days to 2 months after starting use.
- ▶ Vitamin B₁₂ deficiency causes a wide range of hematologic and neuropsychiatric symptoms. It can mimic other diseases such as hematologic neoplasms, multiple sclerosis and Guillain–Barré syndrome.
- ▶ N₂O is legal and can easily be purchased over on internet or at clubs. It has anxiolytic, amnesic, analgesic, euphoric and even hallucinogenic properties.
- ▶ Even when vitamin B₁₂ is repleted, the neurologic effects may not be fully reversible.

Contributors MNA was the medical student who had this case. Together with JC, the junior resident, he wrote the case presentation part of the manuscript. MSL is the senior resident who wrote the discussion and the rest of the report as well as edited the case presentation after the attending, RT, reviewed it.

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