

# Nitrous oxide recreational abuse presenting with myeloneuropathy and mimicking Guillain-Barre syndrome

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**SUMMARY** The recreational use of nitrous oxide (N<sub>2</sub>O) is increasing in festivals, university parties, clubs, private residences, and parks. The abuse of N<sub>2</sub>O has serious complications of the central and peripheral nervous system. In this article, we report a case of a 28-year-old previously healthy man who presented with a three-day history of rapidly progressive leg numbness, tingling, and weakness with gait instability and frequent falls. He had a history of marijuana use and daily inhalation of N<sub>2</sub>O (approximately 20 whippets daily over 2-3 years). He was admitted with a presumptive diagnosis of Guillain-Barre syndrome and was started on intravenous immunoglobulin. Three days after admission, paresthesia ascended to the level of nipple line, and his weakness in the lower limb increased significantly. MRI of the cervical spine showed focal non-enhancing lesions extending from C4 to C6. Serum analysis showed low vitamin B12 level, elevated methylmalonic acid, and elevated homocysteine level. Supplemental 1000 µg/day of vitamin B12 intramuscular injections and 15 mg of folic acid tablets were given. The patient showed gradual improvement. This is a rare case of N<sub>2</sub>O recreational abuse presenting with myeloneuropathy and mimicking Guillain-Barre syndrome. This case highlights the importance of detailed history and physical examination in patients who arrive at the hospital with clinical features of Guillain-Barre syndrome. This is especially true if there are red flags such as drug abuse or discrepancy between clinical and para-clinical (investigations) parameters. Neuroimaging of the brain and spinal cord might be necessary to score the final diagnosis in such cases.

**Keywords** nitrous oxide, recreational abuse, myeloneuropathy, Guillain-Barre syndrome

## 1. Introduction

Nitrous oxide (N<sub>2</sub>O), also known as the laughing gas, dinitrogen oxide or dinitrogen monoxide, is a colorless (at room temperature and atmospheric pressure) non-flammable gas with a chemical formula N<sub>2</sub>O. Since its discovery, it has been used in the food industry, fuel booster, dissociative anesthesia, and pain control. It has also been used for the treatment of withdrawal of nicotine, opioids, and cocaine (1). When used in anesthesia, it is considered a weak anesthetic agent for dental and surgical procedures (2).

The recreational use of N<sub>2</sub>O is increasing in festivals, university parties, clubs, private residences, and parks. It is the second most popular recreational drug amongst young people affecting 7.6% of youth 16-24 years old in Wales, England annually (3). There are no data about the

rates of N<sub>2</sub>O or inhalant use in Saudi Arabia as evident by a thorough literature review using multiple databases such as Ovid, Medline, EMBASE, ProQuest, Science Direct, Google Scholar, and PubMed. Worldwide, it is the seventh most used drug according to the world drug report 2016 (4). It is commonly sold in bulks online presented for use as a whipped cream propellant. It is prepared in prefilled balloons or small pressurized metal canisters which are then transferred into a dispenser (whippets or cracker) (5).

In this article, we report a case of nitrous oxide recreational abuse presenting with myeloneuropathy and mimicking Guillain-Barre syndrome.

## 2. Case Report

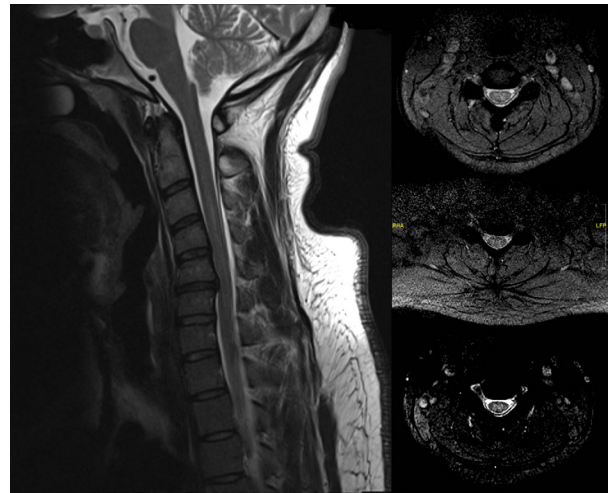
A 28-year-old previously healthy man presented

with a three-day history of rapidly progressive leg numbness, tingling, and weakness with gait instability and frequent falls. He denied any history of preceding upper respiratory tract infection, gastroenteritis, or vaccination. There was no history of bowel or bladder dysfunction, head or neck pain, seizures, or memory impairment. There was no past medical history of any endocrine, metabolic, or surgical diseases, and he denied any history of trauma. He was single, high-school-educated with a history of marijuana use and daily inhalation of N<sub>2</sub>O. Approximately 20 whippets daily over 2-3 years were used as a means of recreation. No history of other illicit drug use, but he smokes tobacco.

General examination including vital signs was normal. Neurologically, higher mental functions and cranial nerves were normal. He was anxious and depressed. Motor examination showed flaccid bilateral symmetrical upper and lower limb weakness, distal more than proximal with bilateral foot drop. The weakness distally was 2/5 and proximally 4-/5. The tone was reduced in all limbs with reduced pinprick sensation in a patchy distribution with the lower limbs being more involved than the upper limbs. Vibration and joint position sense were impaired bilaterally on the tip of his big toe. Reflexes were +2 in the arm and +1 at the knee with absent ankle jerks and bilateral downgoing toes. Cerebellar examination showed no dysmetria on the finger to nose test, and gait assessment was difficult to assess due to weakness. There was no bulbar weakness or respiratory symptoms.

He was admitted with a presumptive diagnosis of Guillain-Barre syndrome. Laboratory checkup revealed normal complete blood count, renal profile, electrolyte, thyroid function test, and liver function test. Chest x-ray, urinalysis, toxicology screen, and electrocardiogram were normal. Cerebrospinal fluid (CSF) analysis on admission revealed no white blood cells or red blood cells with normal glucose and protein without oligoclonal bands. He was started on intravenous immunoglobulin (IVIG) 400 mg/kg per day for five days.

Three days after admission, paresthesia ascended to the level of nipple line, and reflexes became brisk bilaterally with bilateral upgoing toes (Babinski sign). His weakness in the lower limb increased significantly, and his power was 0/5 distally and proximally. In the upper limbs, his weakness was the same. A repeated CSF analysis ten days after admission revealed again a normal analysis with no albuminocytological dissociation and negative microbiology and cytology. Nerve conduction studies twelve days after admission showed classical axonal length-dependent polyneuropathy. MRI of the cervical spine showed focal non-enhancing lesions extending from C4 to C6 (Figure 1). Serum analysis showed normal folate level at 7 µg/L (normal 2-20 µg/L), low vitamin B12 level at 124 µg/L



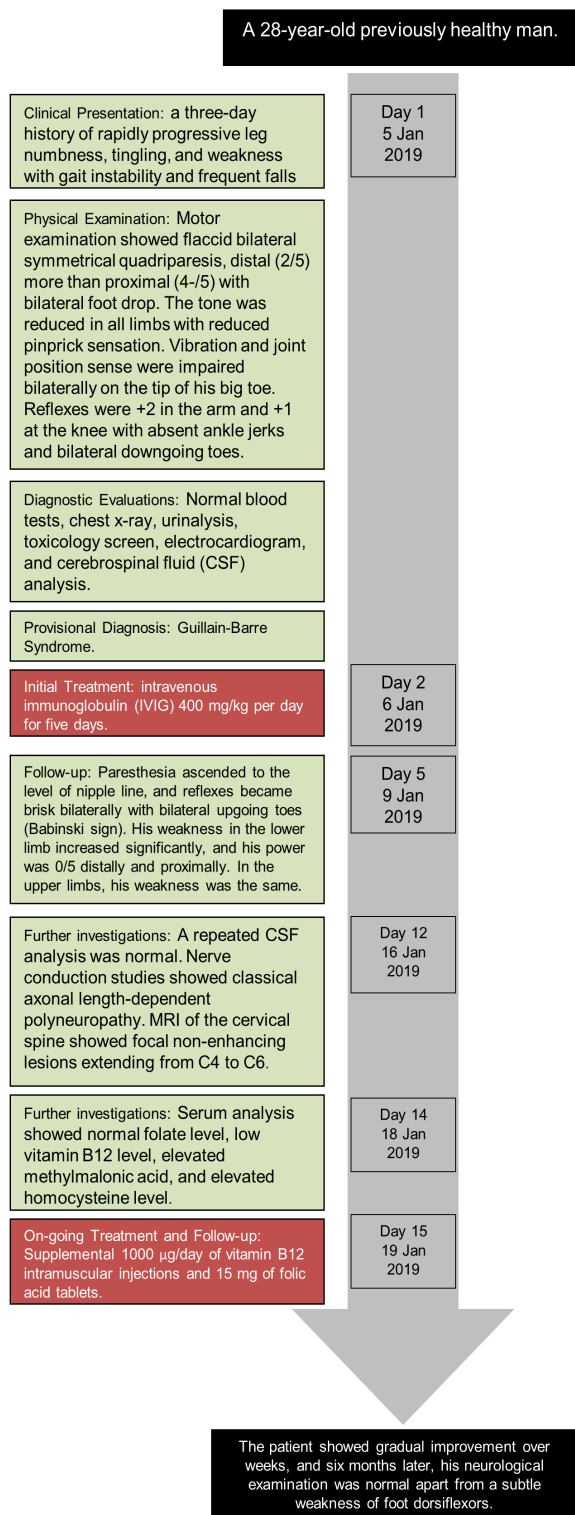
**Figure 1.** MRI of the cervical spine showing focal non-enhancing lesions extending from C4 to C6.

mL (normal 150-800 µg /mL), elevated methylmalonic acid at 3.7 µmol/L (normal 0-0.4 µmol/L), and elevated homocysteine level at 98 (4-20 µmol/L). Supplemental 1000 µg/day of vitamin B12 intramuscular injections and 15 mg of folic acid tablets were given. The patient showed gradual improvement, and six months later, his neurological examination was normal apart from a subtle weakness of foot dorsiflexors (Figure 2).

### 3. Discussion

In 1793, the English scientist Joseph Priestley was the first to synthesize N<sub>2</sub>O gas. In 1799, N<sub>2</sub>O was administered to visitors of the pneumatic institute by Sir Humphry Davy. He astutely noted the analgesic effect of the gas and gave it for the first time the term “laughing gas”. In the early 1800s, the gas became a popular public entertainment and fashionable addition to British high-society parties due to its euphoric properties (6). It also creates a state of depersonalization, derealization, sound distortion, and lightheadedness. The first reported medical use of N<sub>2</sub>O was by Horace Wells, an American dentist, who used the gas for his own tooth extraction in 1844 (7).

N<sub>2</sub>O causes its harmful effect by oxidizing the cobalamin (B12) cobalt atom from its 1+ to 3+ valence state rendering methylcobalamin inactive on a co-factor of methionine synthase. This inhibits the conversion of homocysteine to methionine and 5-methyltetrahydrofolate to tetrahydrofolate. Methionine is necessary for myelin production and to replenish the one carbon donor pool and tetrahydrofolate is necessary for DNA synthesis. In addition, cyanocobalamin is necessary for the conversion of methyl-malonyl CoA to succinyl-coenzyme A (8). Accumulation of methyl-malonyl CoA and homocysteine in the serum can be measured by a special laboratory and are used as a surrogate



**Figure 2. Timeline figure for our case.**

marker of vitamin B12 deficiency. Accumulation of methyl-malonate provides abnormal substrates for fatty acids synthesis, and subsequently, these abnormal fatty acids may be incorporated into the myelin sheath. Proper synthesis of succinyl CoA is important as an intermediate in the Krebs cycle (9). Other postulated

mechanisms of action include a decrease in excitatory neurotransmission throughout the central nervous system via non-competitive glutamate inhibition and acting on a partial mu, kappa and delta opioid receptor agonists modulation dopamine activity and noradrenergic nociceptive pathways (10). In our patient, the clinical picture was that of myeloneuropathy with low vitamin B12 and high methylmalonic acid and homocysteine. The positive history of N<sub>2</sub>O abuse, presence of clinical features of subacute clinical myeloneuropathy, and biochemical changes have confirmed the diagnosis of N<sub>2</sub>O toxicity.

Unfortunately, the gas is also called "legal high" due to easy availability. It has a rapid onset with a peak of around one minute after inhaling and then fading away for 2 minutes. Each canister contains 8 grams of N<sub>2</sub>O in a volume of 10 cm<sup>3</sup> can be bought for £2. It produces approximately 8 liters of N<sub>2</sub>O gas. It has a rapid onset with a peak of around one minute after inhaling and then fading away after 2 minutes (11).

The use of N<sub>2</sub>O is not as innocent as many people think especially if used in high daily doses (more than ten bulbs) for a prolonged duration. A recent systematic review of the literature by Garakani et al. (12) found a total of 72 cases with neurological sequelae to N<sub>2</sub>O abuse. They were categorized into four different groups: myeloneuropathy (31 cases), subacute combined degeneration of the spinal cord (17 cases), polyneuropathy (15 cases) and myelopathy (14 cases) (12). Nitrous oxide abuse can produce a sense of psychotic and neurological symptoms. Among psychotic symptoms are anxiety, depression, hallucinations, impulsive and aggressive behaviors, manic delusions, and psychosis (13). Neurological symptoms include weakness, numbness, ataxia, visual symptoms, falls, and paresthesia, confusion, and forgetfulness (14).

A unique finding in our case was the involvement of two different areas in the neuroaxis that are the cervical spinal cord and peripheral nerves. The diagnostic exercise of localization in our case was unique, which was guided by repeated daily history and detailed neurological examination. This was accompanied by timely-ordered investigations. The initial clinical features were suggestive of an acute peripheral neuropathy, which were followed a few days later by clinical features of spinal cord involvement in the cervical segment. Cervical segment involvement was suggested by sensory level, bladder control disturbance, and brisk reflexes. The rapid onset, progressive course, and history of N<sub>2</sub>O abuse also guided us to the correct diagnosis.

The neuroradiological changes of N<sub>2</sub>O toxicity in the posterior and lateral columns of the spinal cord are those seen in cobalamin deficiency. They include an abnormally high T2 signal intensity that occurs predominantly in the cervical segment of the spinal

cord (12).

Treatment is aimed primarily at stopping the exposure and administering B12. There is no standardized B12 regimen, but a commonly accepted plan is 1000 µg intramuscularly for five days and then intermittently until symptoms resolve. An alternative plan is 1000 µg – 2000 µg orally daily for 1-2 weeks and then 500 µg daily for three months (15).

Our case report is unique for several reasons. Firstly, although N<sub>2</sub>O abuse is common in both developed and developing countries, to date, this is the first case reported from Saudi Arabia as evident by a thorough literature review using multiple databases such as Ovid, Medline, EMBASE, ProQuest, Science Direct, Google Scholar, and PubMed. Secondly, this is the second case of N<sub>2</sub>O toxicity presenting as Guillain-Barre syndrome (16). Thirdly, our patient was treated aggressively by vitamin B12 injections, folate, and IVIG with an excellent outcome. Finally, our report presents interesting imaging, neurophysiology, and review the important aspects of the topic.

In conclusion, the abuse of N<sub>2</sub>O has serious complications of the central and peripheral nervous system. It is a great mimicker, and early diagnosis and treatment are crucial. If the affected patient does not disclose his recreational N<sub>2</sub>O abuse or the neurologist fails to inquire about it, diagnosis may be difficult. This case highlights the importance of detailed history and physical examination in patients who arrive at the hospital with clinical features of Guillain-Barre syndrome. This is especially true if there are red flags such as drug abuse or discrepancy between clinical and para-clinical (investigations) parameters. Neuroimaging of the brain and spinal cord might be necessary to score the final diagnosis in such cases.

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