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Laughing gas abuse causing subacute combined spinal cord degeneration with psychiatric manifestations

Maria Ruxandra Docan[1], Mihaela Aftinia Marian[1,2], Anca Adriana Arbune[1], Elena Marin[1], Adriana Octaviana Dulamea[1,2]

[1]Fundeni Clinical Institute, Neurology Department, Bucharest, Romania
[2]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Background. Nitrous oxide, a nonirritating gas commonly used as an anesthetic, is increasingly abused by the young population for its euphoric effects due to its seemingly harmless nature. However, its neurological impacts can vary in intensity and sometimes result in permanent damage. Accurate diagnosis and treatment hinge on identifying nitrous oxide use through anamnesis, clinical and paraclinical findings, as demonstrated in the following case report.

Case report. A 27-year-old female with psychiatric history presented with progressive paresthesia and walking difficulty, admitting to recent nitrous oxide use, alongside other substances. Clinical examination revealed mild tetraparesis, coordination disturbances, generalized hyporeflexia, and sensory deficits. Electromyography showed severe sensory neuropathy, and spinal MRI indicated subacute combined degeneration (SCD) of the spinal cord. Laboratory tests revealed hyperhomocysteinemia and elevated methylmalonic acid levels, despite normal vitamin B12 levels. Treatment included intramuscular vitamin B12, folic acid, and neurotrophic agents, along with physical rehabilitation. Psychiatric symptoms, possibly exacerbated by nitrous oxide, and complicated adherence to therapy.

Conclusions. This case underscores the neurotoxic potential of nitrous oxide, particularly its disruption of cobalamin metabolism, and highlights the need for thorough patient histories to uncover substance use contributing to neurological symptoms. Despite treatment, some neurological deficits may persist, emphasizing the importance of early intervention and comprehensive care strategies.

Keywords: nitrous oxide, subacute combined degeneration of the spinal cord, vitamin B12 metabolism

Abbreviations (in alphabetical order):

B12 vitamin	– cobalamin
EMG	– electromyography
MRI	– Magnetic Resonance Imaging
N2O	– nitrous oxide
NMDA	– N-methyl-D-aspartate
SCD	– subacute combined degeneration
TOF	– time-of-flight

INTRODUCTION

Nitrous oxide is nonirritating gas used as an anesthetic agent, in the culinary industry and in the car fabrication industry [1]. It is also known as "laughing gas" for its euphoric effect nowadays being a widely used drug among teenagers and young adults, with seemingly harmless effects. What is less known to most users is that it presents neurological effects that vary in intensity and can sometimes be permanent. Identifying consumption, in accordance to the clinical and paraclinical findings is the key to correct diagnosis and treatment, as exemplified in the following clinical case.

Corresponding author:
Mihaela Aftinia Marian
E-mail: mihaela.marian@umfcd.ro

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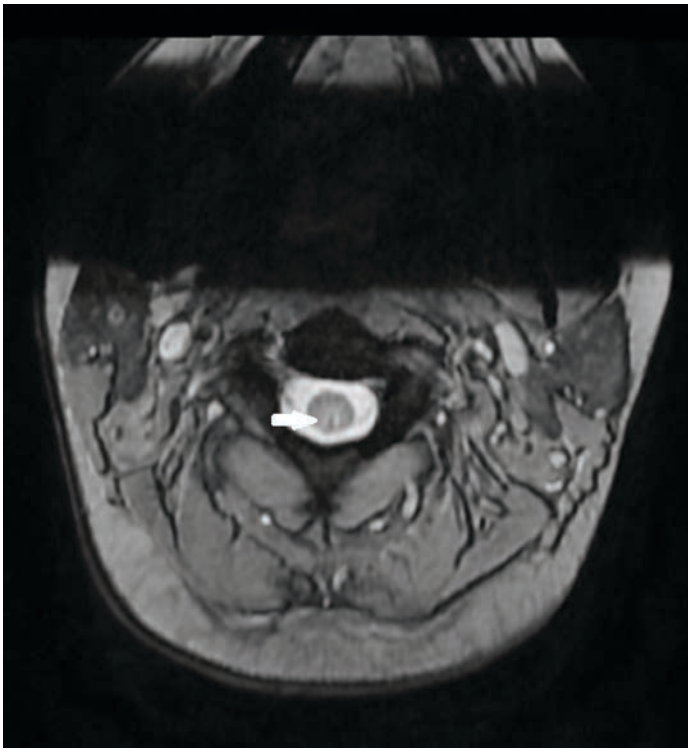

FIGURE 1. Axial T2/STIR MRI of the cervical region showing symmetrical hyperintense signals shaped like inverted "V" letters affecting the posterior columns

CASE REPORT

This is the case of a 27-year-old female patient admitted to the Neurology Department for tetrameric paresthesia, predominantly in the lower limbs, with ascending evolution over the last two weeks, associating walking difficulty with onset on the day of presentation. Following a thorough anamnesis, the patient admitted drug consumption, including cocaine, ecstasy, nitrous oxide (N2O) balloons last administration two weeks before being admitted to the hospital, weekly alcohol consumption and multiple unprotected sex contacts.

The medical history consisted of depression under treatment with Escitalopram 20 milligrams (mg) per day, Alprazolam 2-4 mg per day, insomnia under self-medication with 10-50 mg of Zolpidem per day and multiple cosmetic surgical interventions such as rhinoplasty, breast augmentation and liposuction, that were suggestive for a body dysmorphic condition.

Physical examination revealed an overweight, afebrile, hemodynamically and respiratory stable patient. Neurological examination revealed mild tetraparesis predominantly in the distal part of the limbs, lower limbs and right upper limb coordination disturbance, generalized hyporeflexia, tetrameric paresthesia extending to the knees and halfway up the forearms, tactile hypoesthesia with the sensitivity level at T4 and globally diminished mioartrokinetic sensitivity.

Electromyography (EMG) and nerve conduction studies revealed moderate to severe sensory neuropathy in the lower limbs. A cerebral magnetic resonance imaging (MRI) with time-of-flight (TOF) angiography was performed showing no abnormalities and normal cerebral vascular system. Nevertheless, the MRI with contrast of the cervical and thoracal spine regions revealed symmetrical hyperintense signals on T2/STIR sequences, without gadolinium enhancement, shaped like inverted "V" letters, affecting the posterior column of the cervical spinal cord from the first to the sixth cervical vertebrae (Figure 1).

The laboratory results showed a mild inflammatory syndrome consisting in leukocytosis and mild hyperfibrinogenemia, macrocytosis, low iron values, normal vitamin B12 (cobalamin) levels 312 pg/mL (reference range, 211-911 pg/mL), hyperhomocysteinemia >50 μmol/L (reference range, <12 μmol/L) and high levels of methylmalonic acid 97 9-32 μg/L (reference range, 9-32 μg/L). Apart from these modifications, the autoimmunity panel antinuclear antibodies, anticoagulant lupus, antineutrophil cytoplasmic antibodies, along with thyroid markers, serum copper level, Treponema pallidum antibodies, HIV test, hepatitis B and C test, antibodies for acute and chronic infection with Varicella Zoster Virus and Cytomegalovirus, tumoral markers and bacteriologic samples were all negative.

At the end of the investigations report, the patient's presentation was consistent with N2O use–induced toxicity with subacute combined degeneration (SCD) of the spinal cord.

The treatment was initiated consisting of intramuscular vitamin B12 administration as following: 1000 micrograms per day for the first three days succeeded by 1,000 micrograms every two days, 5 mg of folic acid per day, 1,600 mg of alpha lipoic acid per day, 1,200 mg of Palmitoylethanolamide per day and 400 mg of deproteinized hemoderivative of calf's blood, along with 0.6 ml of Enoxaparin for deep venous thrombosis prophylaxis and the chronic psychiatric treatment. Kinesiotherapy and physical rehabilitation was also started consisting in about two hours of daily active and passive exercise.

Total hospitalization duration was of three weeks during which the patient underwent the treatment, with slow amelioration of the symptoms. The evolution was hindered by decompensation of the psychiatric pathology: the patient became verbally aggressive, anxious, repeatedly requesting to be discharged and subsequently reversing the request, with episodes of tachycardia and tremors. A psychiatric evaluation was requested, raising the suspicion of drug withdrawal syndrome with further recommendation of evaluation within a detoxification facility. It also must be taken into consideration that the psychiatric manifestations could have also been caused by the direct effect of the

prolonged nitrous oxide on the opioid and NMDA receptors.

Due to the psychiatric pathology that led to lack of adherence to medical therapy, the patient asked to be discharged before the complete remission of the symptoms, therefore a recommendation to continue the intramuscular administration of vitamin B12 1000 mcg 3 days a week until the complete alleviation of the symptoms along with physical rehabilitation was made, followed by a neurological reassessment to assess the necessity of further oral administration of B12 vitamin.

The neurological examination previous discharge from the neurology compartment showed no motor deficit, amelioration of the ataxic syndrome, tactile hypoesthesia with the sensitivity level at T4, intermittent distal paresthesia extending to ankles and wrists and mild alleviation of the globally diminished mioartrokinetic sensitivity.

DISCUSSION

Nitrous oxide is a colorless, nonirritating gas with a sweetish smell that has initially been used as an inhalational anesthetic agent widely used in dentistry and obstetric practice [1]. N2O is also widely used in the culinary industry as a mixing and foaming agent for whipping cream preparation [2]. As a result of its hallucinogenic and relaxing properties and those of inducing euphoria it is also known as "laughing gas", becoming increasingly popular as a street drug [3]. In terms of methods of administration, it is usually inhaled through a balloon or bulb, manifesting almost instant effects within second after inhalation. The peak effects occur in about one minute and fade away within minutes without hangover effect. This, along with the fact that it is legal in most countries make it superior to other drugs and thus highly addictive [2,3]. Moreover, another mechanism of inducing dependence is based on the rewarding effects mediated through the blockade of the N-methyl-D-aspartate (NMDA) receptors and agonism of the opioid receptors by N2O [4].

The toxic impact of N2O usage can be divided into acute toxicity and chronic toxicity. Due to its pharmacokinetics, N2O is more water-soluble than oxygen. After being inhaled, it diffuses across the basement membrane of the alveoli directly into the bloodstream faster that oxygen, causing dilution of the alveolar oxygen. Consequently, the generalized hypoxia can potentially induce seizures, arrhythmias, even respiratory or cardiac arrest and can lead to asphyxia in closed spaces [2].

The chronic use of N2O has been associated with myelopathy, peripheral neuropathy, demyelizing diseases, thrombosis, anemia and skin changes. MRI studies revealed progressive degeneration of the spinal cord in the N2O users, the extent of N2O consumption being related to the degree of spinal degeneration. The vast majority of these, especially the neurological damage, are connected to vitamin B12 deficiency, but other factors might also be involved [2,5]. Furthermore, toxic usage has been associated with symptoms within the psychiatric area, such as anxiety, depression, delirium and neurocognitive impairments. Nevertheless, vitamin B12 deficiency did not appear to be the cause of these psychiatric symptoms [6].

The underlying molecular mechanism behind N2O neurological toxicity center around the B12 metabolism. Chronic nitrous oxide users do not always present decreased levels of cobalamin per se. In contrast, elevated serum levels of homocysteine and methylmaolnic acid are more relevant biomarkers related to neurological damage, having more often values outside the normal range compared to B12 vitamin, that can be normal [7].

Vitamin B12 exists in two active forms, methylcobalamin and adenosylcobalamin, which are produced through two separate metabolic pathways, thus serving two different purposes [8]. Nitrous oxide induces irreversible oxidation of the cobalt-ion in cobalamin, rendering it inactive and unusable in any of these pathways [5]. This causes neurological damage through intricate mechanisms that can be explained by knowing the compounds and the destination of each pathway.

The first pathway uses adenosylcobalamin as a co-factor for methylmalonyl-CoA mutase that transforms methylmalonyl-CoA, resulted from methylmalonic acid, to succinyl-CoA, which is a part of the carbohydrate metabolism. One of outcomes of the carbohydrate metabolism is the contribution to neuronal myelin synthesis [8]. In addition to the myelin synthesis disruption, the high levels of methylmalonic acid generated by N2O induce neurotoxicity through a direct effect [9] (Figure 2).

The other pathway utilizes methylcobalamin to regenerate methionine from homocysteine and to produce tetrahydrofolate, which subsequently plays a role in nucleic acid synthesis and amino acid metabolism [5]. Apart from the prothrombotic effect of increased homocysteine that accumulates under chronic N2O exposure, it also has a neurotoxic potential by overstimulation of N-methyl-D-aspartate (NMDA) receptors that increases the cytoplasmatic calcium ions and the reactive oxygen species, consequently causing apoptosis [10]. Moreover, nitrous acid acts as a noncompetitive antagonist of the NMDA receptor, potentially providing a neuroprotective effect in the short term. However, prolonged blockage by N2O could lead to neuronal vacuolation [11]. Summarizing everything, repeated N2O exposure inactivates cobalamin and produces high levels of homocysteine and methylmalonic acid, triggering multiple metabolic effects that contribute to neurotoxicity that takes on several forms observed in practice, such as spinal cord degeneration. This also explains why the vitamin B12 levels can be normal in

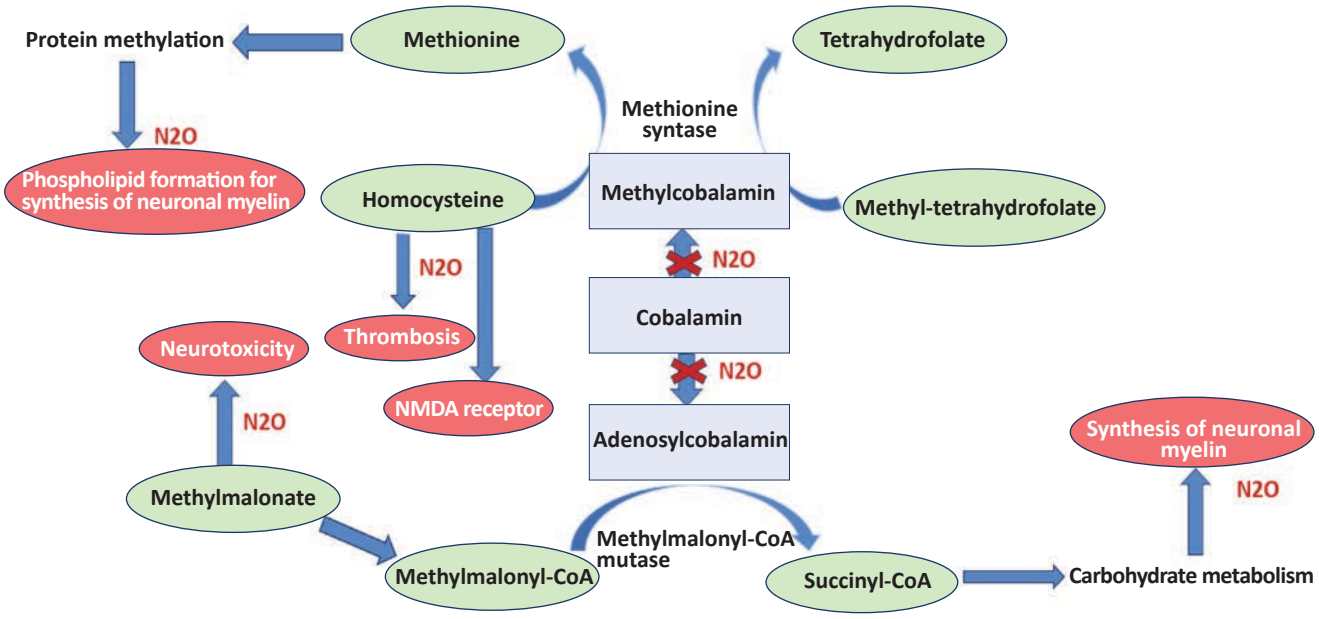

FIGURE 2. Cobalamin metabolic pathways disrupted by nitrous oxide leading to intricate mechanism of neurological toxicity

some cases, but metabolically inactive, making the homocysteine and methylmalonic acid more suitable laboratory tests.

The psychiatric effects of nitrous acid are mediated through different types of interaction with receptors. At subanesthetic concentrations it activates the opioid receptors in the brainstem that further inhibit the gamma-aminobutyric acid releasing neurons resulting in activation of the descending noradrenergic pathways that inhibit pain [12,13]. Another possible mechanism is the antagonism at the NMDA receptor, same as ketamine, enhancing the inhibition on dopamine neurons by GABA neurons and generating bursting spikes of dopamine [14]. These two effects may explain the anxiety, irritability, even hallucinations and psychosis, as well as the addictive effect of nitrous oxide.

Immediately after diagnosing chronic usage of N2O as the underlying cause of the subacute combine degeneration of the spinal cord, cessation of nitrous oxide exposure, as well as intramuscular treatment with 1000mcg of vitamin B12 should be started and continued for at least two weeks. Injections can initially be administered daily, then three times a week until there is no further neurological improvement or until the symptoms completely disappear. The supplementation therapy should not be continued past the acute phase if the patient had normal serum B12 level [15]. Other neurotrophic agents and physical rehabilitation also play an important part in the recovery process.

Another important aspect is that despite the personal history of nitrous oxide usage of the patient, other non-toxicologic etiologies could explain the symptoms and should not be ruled out. Among these can be mentioned vitamin B12 or copper deficiency resulting from pernicious anemia, malabsorption or nutritional deficiency. Syphilis leading to tabes dorsalis, HIV virus infection or autoimmune conditions such as Guillain-Barré syndrome and multiple sclerosis should also be taken into consideration [16].

CONCLUSION

Recreational use of nitrous oxide has become increasingly popular in light of its properties, being legal in most countries, easily accessible, with an effect that sets in within a few minutes. Its action on multiple metabolic pathways and different receptors leads to neurological and psychiatric symptoms. In this clinical case the patient developed subacute combined degeneration of the spinal cord and sensory neuropathy in the lower limbs, at the same time worsening the underling chronic psychiatric pathology that made the therapeutic compliance more difficult. Despite the correct treatment with intramuscular vitamin B12 symptoms may persist, as it was also described in this clinical case. Further follow-up and reevaluation could not be made as a result of the low adherence to medical advice.

This case illustrates the importance of a detailed medical history, which also focuses on aspects that are often overlooked, such as living conditions and harmful behaviors in young patients without an apparent cause of the symptoms.

Patient consent:
Written informed consent was obtained from the patient for the publication of this study and accompanying images.

Conflict of interest:
The authors declare no conflict of interest.

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