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A Case Report of Subacute Combined Spinal Cord Degeneration Caused by Nitrous Oxide ('Laughing Gas') Abuse

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Summary. Although nitrous oxide (N_2O) has long been used as an anesthetic, it's use as a recreational drug has recently increased. As N_2O abuse is associated with a number of adverse health effects, it has become a significant public health issue. Chronic abuse can lead to a number of neurological complications, most commonly related to functional vitamin B12 deficiency. One of the most encountered forms of N_2O neurotoxicity is a subacute combined degeneration, which can cause permanent neurological damage. The medical community should therefore be aware of the increasing scale of recreational N_2O exposure and the possible complications of this drug abuse. Early recognition and treatment of N_2O toxicity are crucial. We present the case of an 18-year-old male who was diagnosed with subacute combined spinal cord degeneration related to N_2O abuse.

Keywords: nitrous oxide, N_2O, neurotoxicity, vitamin B12 deficiency, subacute combined degeneration.

INTRODUCTION

Nitrous oxide (N_2O), known as 'laughing gas', is a colorless inhalant gas that has long been used for medical and recreational purposes. N_2O is currently used for medical purposes as an inhalational anesthetic, analgesic, and anxiolytic. It is also used in the food industry for whipped cream dispensers. Recently, it has gained popularity as a recreational drug due to its euphoric effect and is often inhaled using whipped cream dispensers or balloons [1–3]. In recent years, the scale of N_2O use for recreational purposes has increased, particularly among young adults [3, 4]. N_2O has become one of the 10 most popular psychotropic substances [5]. In the UK, for example, N_2O is the second most commonly used recreational drug among young people [6, 7]. According to the Global Drug Survey 2019 (GDS2019) data from 30 countries, up to 11.9% of the respondents have used N_2O in the last 12 months [8]. According to the General Population Survey (GPS), nitrous oxide usage is not that widespread in Lithuania. However, in the period from 2016 to 2021, there was an increase in the inhalant use from 2.2% to 5% [9]. The ease of access and the low cost may have contributed to the high prevalence of this drug [3, 10].

N_2O abuse is associated with a range of adverse health effects, but the most commonly observed toxicities are hematologic and neurologic [1, 11]. Either or both were observed in 96% of patients with N_2O toxicity in a systematic review and meta-analysis by Oussalah A. et al [1]. The mechanism underlying N_2O-induced toxicity is vitamin B12 inactivation. N_2O causes oxidation of the cobalt ion, which is located at the center of the vitamin B12 molecule. This process results in a functional deficiency of vitamin B12 [6, 12, 13]. Vitamin B12 is a cofactor for methylmalonyl coenzyme A mutase (MMCoAM), which is responsible for the conversion of methylmalonyl-CoA to succinyl-CoA, which is essential for the metabolism of fatty acids and carbohydrates. Thus, the lack of MMCoAM activity can lead to the accumulation of methylmalonyl-CoA, which is a neurotoxic metabolite, and the subsequent decrease in succinyl-CoA disturbs the processes of

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the citric acid cycle. In addition, vitamin B12 also plays a role as a cofactor for methionine synthetase (MTR), which is responsible for the methylation of homocysteine to methionine and the simultaneous conversion of 5-methyltetrahydrofolate to tetrahydrofolate. These processes are necessary for deoxyribonucleic acid (DNA) synthesis, repair, and myelin production. As a consequence, functional vitamin B12 deficiency can lead to a decreased level of methionine and tetrahydrofolate, which may lead to demyelination processes and impaired DNA synthesis [2, 13–15]. At the same time, hyperhomocysteinemia due to the lack of MTR activity can lead to oxidative stress and endothelial dysfunction [16]. Thus, the disruption of B12 metabolism plays a key role in N_2O-induced toxicity, the most common of which are neurological manifestations [1].

We present the case of an 18-year-old male who was diagnosed with subacute combined spinal cord degeneration related to the neurological toxicity of N_2O.

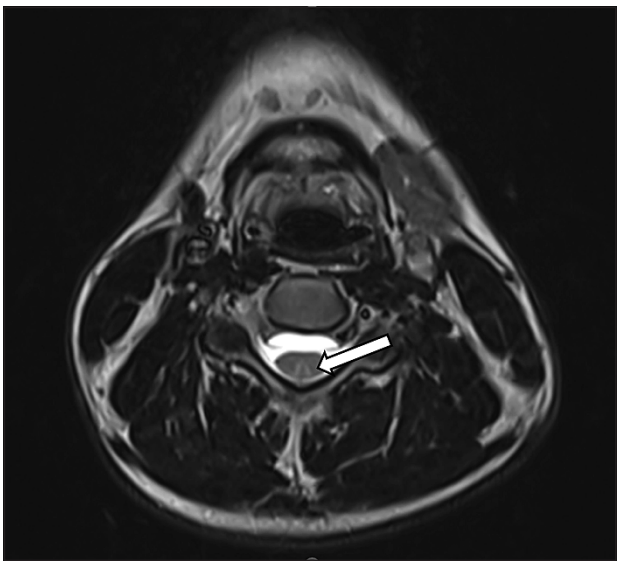

Fig. **Axial T2-weighted MRI image of the cervical spinal cord demonstrating T2 hyperintensity in the dorsal spinal cord extending from C2 to C6**

CASE PRESENTATION

An 18-year-old otherwise healthy male presented to the Neurology Department of Vilnius University Hospital (VUH) Santaros Clinics in October 2022 due to leg weakness, walking difficulties, and instability. He had sprained his right leg and developed ankle swelling while in the United Kingdom in July 2022. His local general practitioner recommended rest and he spent a month mostly confined to bed with minimal mobility and a diet consisting mainly of junk food. After a month, he noticed weakness in his left foot. When asked directly, the patient admitted to using N_2O gas several times before the illness. During his time abroad, several tests were performed, including brain computed tomography (CT) and magnetic resonance imaging (MRI), which revealed no significant changes. A decreased concentration of vitamin B12 was found, and he was prescribed Hydroxicobalamine 1000 mcg by intramuscular injection every other day for 10 days. After returning to Lithuania, he underwent a nerve conduction study and electromyography in another healthcare facility, which revealed severe distal sensorimotor axonal polyneuropathy in his legs with signs of active denervation on electromyography. Motor nerves were more affected than sensory. MRI of the lumbar spine revealed primary osteochondrosis and mediolateral protrusion of the L4-5 disc without radicular compression.

Neurological examination showed intact cerebrobulbar nerves, impaired proprioception in the legs with diminished vibration sensation in the feet (tested with a turning fork), and impaired joint position sensation. Examination of muscle strength showed weakness in both feet, with 1 point on the Medical Research Council (MRC) scale for dorsiflexion and 3 points for plantar flexion. Muscle strength was normal in the arms and proximal legs. The ataxic gait of moderate severity was noted when walking. The patient also had hyporeflexia in the arms and areflexia in the legs. Blood tests revealed a borderline low B12 level of 124.46 pmol/L and slightly elevated creatine kinase levels (CK 867 U/L). Other blood parameters including complete blood count, renal function, electrolytes, serum protein electrophoresis, thyrotropin, ANA, ANCA, rheumatoid factor (RF), cerebrospinal fluid protein, and cell counts were within normal range. Liver enzymes were slightly elevated, so viral hepatitis was excluded after performing hepatitis B and C markers. The patient tested negative for HIV and T.pallidum infections. Fibrogastroduodenoscopy was performed to determine the cause of vitamin B12 deficiency, but no abnormalities were found.

A nerve conduction study and electromyography were repeated in our clinic and showed a distal subacute axonal sensorimotor polyneuropathy with predominantly motor nerve damage. Signs of acute denervation were present (fibrillations and positive sharp waves), and ongoing reinnervation was also noted. The parameters of the sensory nerves were slightly improved compared to the previous examination. No changes were noted in the nerve conduction studies in the arms. MRI of the cervical spine showed increased signal on T2-weighted imaging in the posterior cervical cord extending from C2 to C6, consistent with subacute combined spinal cord degeneration (Fig.).

Based on the findings, the patient was diagnosed with vitamin B12 deficiency with severe neurological complications: subacute distal sensorimotor axonal polyneuropathy with predominantly motor damage in the legs, severe paresis of both feet, and subacute combined spinal cord degeneration. In this case, there was no other explanation for the vitamin B12 deficiency other than N_2O abuse. The patient was advised to continue vitamin B12 substitution, undergo rehabilitation, and was strongly encouraged to stop using N_2O.

DISCUSSION

Neurological complications due to N_2O abuse are increasingly encountered by neurologists due to the exponential growth in recreational N_2O use. According to the Global Drug Survey 2016 (GDS2016) data of 100.000 respondents from 50 countries, 4% of N_2O users have experienced neurotoxicity [1, 5]. Although our patient was the first case of N_2O-induced neurotoxicity diagnosed in the VUH Santaros Clinics and the first case report described in Lithuania, the trends are different in other countries. For example, nitrous oxide-induced subacute combined degeneration is diagnosed approximately every 9 days at the Royal London Hospital [6]. In the systematic review and meta-analysis by Oussalah A. et al., the majority of patients (57.0%) who experienced N_2O toxicity were recreational users and were regularly exposed to N_2O (76.0%) [1]. It should also be noted that patients with pre-existing subclinical B12 deficiency are more susceptible to the toxic effects of N_2O. [6]. The most common neurological manifestations of N_2O toxicity were subacute combined degeneration (28%), myelopathy (26%), and generalized demyelinating polyneuropathy (23%), while the most common neurological symptoms were paresthesia in the extremities (80%), unsteady gait or walking difficulties (58%), and weakness (43%) [1]. It is worth mentioning that N_2O abuse can lead to complications potentially related to the hypercoagulable state caused by N_2O-induced hyperhomocysteinemia. These complications may include ischemic stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis, and cortical vein thrombosis [6, 16–20]. There are also some toxicities related to N_2O use that are most likely caused by mechanisms other than B12 functional deficiency [3].

Detecting N_2O toxicity can be difficult due to various reasons. First, some patients may not disclose their N_2O abuse, as was observed in the case of our patient. Second, N_2O neurotoxicity may be underdiagnosed, as many physicians are unaware of this condition [6]. Since there is no specific test to confirm N_2O abuse, indirect tests are used to determine N_2O toxicity, such as B12 metabolism disturbance. Laboratory tests may reveal an increase in mean corpuscular volume (MCV), a decrease in serum cobalamin, and an increase in homocysteine and methylmalonic acid levels [3, 21]. It is important to note that B12 deficiency may still be suspected despite the serum cobalamin level being within the normal range. In this case, elevated methylmalonic acid or homocysteine levels indicate cellular vitamin B12 deficiency [2, 21]. In patients with suspected N_2O toxicity, a plasma B12 level of less than 150 pmol/L was observed in 70.7% of cases, while elevated homocysteine and methylmalonic acid levels were found in 90.3% and 93.8% of patients, respectively, according to a systematic review and meta-analysis conducted by Oussalah et al. [1].

N_2O toxicity can be detected indirectly by radiological tests, particularly MRI of the spinal cord. The longer the exposure to N_2O, the more obvious the changes become on MRI images [22]. The lesions are typically hyperintense on T2 sequences and show no contrast enhancement. The shape of the lesions is usually in the form of an inverted "V", "triangle", or "oval" on the axial MRI [23]. Lesions typically involve more than 3 segments in the posterior columns of the spinal cord, with changes more prominent in the cervical and less often in the thoracic part of the spine [3].

The effects of N_2O toxicity on peripheral nerves are generally similar to those of B12 deficiency caused by other factors, although there are some differences [24]. In cases of N_2O abuse, motor axons are affected more often, as in the case we described. The lesions are typically mixed, consisting of both demyelinating and axonal damage, although our patient was diagnosed with axonal nerve damage. The damage is more pronounced in the lower extremities and depends on the dose of N_2O [24, 25].

The optimal treatment for the consequences of N_2O neurotoxicity remains uncertain, as there are no agreed recommendations. First, patient education plays a vital role, emphasizing the importance of complete abstinence from N_2O [3]. Correcting vitamin B12 deficiency, which is strongly linked with N_2O neurotoxicity, is crucial [26]. While there is no standard dosing regimen, the recommended approach involves 1 mg of hydroxocobalamin administered as an intramuscular injection daily or every other day for at least two weeks, and then continued until a plateau is reached. Patients who were B12 deficient at the onset of symptoms should receive B12 injections or oral supplementation every 3-6 months [6]. However, it should be noted that follow-up of patients may be complicated by non-adherence to treatment, as this group of patients commonly suffers from substance abuse [6]. The pathophysiological mechanisms of N_2O neurotoxicity are not entirely clear, and it is believed that N_2O may cause harm through other pathways besides B12 deficiency, which have not yet been established [3]. As a result, B12 supplementation does not usually result in complete symptom recovery. There are rare case reports of significant improvement after treatment with methylprednisolone or plasmapheresis [3].

In conclusion, as the prevalence of N_2O abuse increases worldwide, physicians should remain vigilant about possible complications related to N_2O abuse. There is a risk of N_2O neurotoxicity being underdiagnosed, as most physicians are unaware of this previously unrecognized condition. Although this drug is not widely used in Lithuania, considering the tendencies of increasing prevalence in the world, a rise in cases could be expected in the future. Also, further research is needed to elucidate the precise mechanisms of N_2O toxicity, to identify the potential therapeutic targets, and to develop treatment guidelines.

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J. Guk, J. Valančienė, A. Klimašauskienė

POŪMĖS KOMBINUOTOS NUGAROS SMEGENŲ DEGENERACIJOS, SUKELTOS DIAZOTO MONOKSIDO („*LINKSMINANČIŲ DUJŲ*“) VARTOJIMO, KLINIKINIO ATVEJO APRAŠYMAS

Santrauka

Diazoto monoksidas (N_2O) yra inhaliuojamos dujos, jau ilgą laiką naudojamos anestezijai, tačiau pastaraisiais metais šios medžiagos vartojimas rekreaciniais tikslais tapo ypač populiarus. Piktnaudžiavimas N_2O dujomis yra susijęs su įvairiais nepageidaujamais reiškiniais, todėl tai tampa reikšminga visuomenės sveikatos problema. Lėtinis piktnaudžiavimas šia medžiaga gali sukelti įvairių neurologinių komplikacijų, dažniausiai susijusių su funkcine vitamino B12 stoka. Viena iš dažniausių N_2O neurotoksiškumo formų – poūmė kombinuota degeneracija, kuri gali lemti permanentinį neurologinį pažeidimą. Taigi, medicinos bendruomenė turėtų žinoti apie augantį rekreacinio N_2O vartojimo mastą ir galimas to komplikacijas. Tinkamas N_2O toksiškumo išraiškų atpažinimas ir gydymas yra būtini. Šiame straipsnyje pristatomas 18 metų vyro, kuriam buvo diagnozuota poūmė kombinuota nugaros smegenų degeneracija, susijusi su piktnaudžiavimu N_2O, atvejis.

Raktažodžiai: diazoto monoksidas, N_2O, neurotoksiškumas, vitamino B12 stoka, poūmė kombinuota degeneracija.

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