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•CASE REPORT•

Neuropsychiatric Symptoms Induced by Large Doses of Nitrous Oxide Inhalation: A Case Report

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Summary: Nitrous Oxide, which is also called laughing gas, now ranks as the 7th most popular drug in the world. Nitrous oxide mainly disturbs B12 metabolism and damages nerves, followed by apparent neuropsychiatric symptoms. It's beneficial to the prognosis of patients if we identify and treat their symptoms early. This case report describes a 19-year-old male who presented with auditory hallucination, persecutory delusions and unstable emotions after abuse of nitrous oxide over the course of half a year. Moreover, neurological signs such as weakness and hyperesthesia also appeared. After supplementation of vitamin B12, the neuropsychiatric symptoms improved, while the lower extremities achieved partial recovery. Therapeutically, we should pay attention to nerve repair, motivation enhancement and reinforce interventions that prevent relapse.

Key words: nitrous oxide; vitamin B12; neurologic impairment; mental disorders

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1. Case history, diagnosis and treatment

A 19-year-old male undergraduate who was referred to our hospital in a wheelchair on March 31, 2017 because of inhaling nitrous oxide ("laughing gas"), presented with auditory hallucinations, emotional instability and progressive weakness in limbs for the past half a year. Since October 2016, the patient had started to use nitrous oxide (N_2O) at parties with his friends. He felt excited and happy after using 48 branches of nitrous oxide (8 g/branch). After that, he would inhale intermittently 4-5 times a day. Since November 2016, the patient had started using nitrous oxide 2-3 times a day, 120-150 branches at a time. He experienced heavenly pleasure after inhalation, accompanied with fragmentation in his listening comprehension, suspicion and feelings that his family and friends were against him as well as feeling someone was talking about him when he was walking up the stairs. He had more nightmares and couldn't distinguish between dreams and reality. Recently, the patient developed weakness, tenderness when walking and numbness in both feet. Afterwards, he had symptoms of progressive weakness, numbness in both hands and upper limbs, as well as difficulty in movement and writing. In February 2017, the patient's use of nitrous oxide significantly increased to about 1000 branches per day. With the use of nitrous oxide from morning to night, the patient became careless and lazy, with progressive emotional instability, erectile dysfunction, urinary frequency and urgency. At the beginning of March 2017, the family discovered the patient's abnormalities and brought him back to live in the parents home. After moving in with his parents, the patient no longer used nirous oxide, but the symptoms of irritability, suspicion, idleness and weakness in his limbs still were present. On March 28, 2017, the patient was examined using cranial Magnetic Resonance Imaging (MRI) and electroencephalogram (EEG) at other hospitals but the results did not show any abnormalities. The patient was admitted to our hospital for further diagnosis and treatment. Since the onset of disease, the patient had irregular sleep but normal appetite. He had been mostly drug free in the past, although he reported taking ecstasy pills 2 or 3 times a few years ago (specific time period unknown) and occasionally using marijuana for half a year before June 2015.

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The patient's examination upon admission revealed poor mental status, however he was alert and cooperative during the exam and his vital signs were all normal. His proximal and distal limb muscle strength was grade 4 and 3, respectively, with extensor muscle tension being greater. He could not complete the finger-to-nose test, rapid alternating movement test and heel-knee-tibia test. He had systemic hyperalgesia in a glove and stocking pattern, slightly diminished perception of rough touch below T12 plane and diminished perception of position and fine touch. He had diminished bilateral tendon reflexes and lower abdominal reflexes, as well as bilateral Babinski sign (+). The patient's psychiatric examination revealed that he was conscious, had inappropriate deportment and normal orientation. His answers to questions were on point. Perceptual disorders including hallucinations were not present. He had illogical thinking, presented with suspicion, relational persecutory delusions, stable emotions, occasional negative ideation, diminished consciousness, as well as partial insight loss. Laboratory tests revealed RBC count: $4.94X10^{12}$/L [$(4.09-5.74)X10^{12}$/L], HB: 157 g/L (131-172 g/L), WBC count: $10.37X10^{9}$/L, ALT: 164 U/L (0-50U/L) and B12: 602.1 pmol/L. The rest of his blood routine, biochemical, ECG and EEG results were normal. Spinal cord MRI examination revealed an inverted V-shaped long T2 signal shadow in the posterior segment of the cervical spinal cord C2-C6. Neurologists were called in for consultation. Given the medical history and examination results, according to the diagnosis standard of ICD-10, the patient was diagnosed with psychoactive substances (nitrous oxide) dependence syndrome; psychotic disorders secondary to psychoactive substances (nitrous oxide); and subacute combined degeneration of spinal cord.

Considering the problems of spinal cord degeneration and substance dependence of the patient, spinal cord degeneration was mainly due to vitamin B12 metabolic disorder caused by nitrous oxide abuse. The following therapeutic strategies were adopted: Large dose of vitamin intramuscular injection, neurotrophic treatment, combined with exercise training were used for spinal cord degeneration. Small doses of antipsychotic drugs were used to control psychotic symptoms. Cognitive behavioral therapy and family therapy were used to increase motivation and maintain long-term rehabilitation. Process of diagnosis and treatment: The patient was started on daily 1000 mg B12 intramuscular injection, 100 mg B1 intramuscular injection, 15 mg folic acid oral administration, 5 mg olanzapine, combined with symptomatic treatments including liver protection and sleep treatment for 14 days. Exercise training was given 3 times/week to guide muscle training and fine motor movements. Cognitive behavior therapy was used 2 times/week to identify high-risk situations, to train skills for rejecting substance use, and to enhance motivation. The patient was from a good family, but he did not receive a lot of support for this issue, however family therapy improved this situation. After 5 days of treatment, the patient's psychotic symptoms improved, mood became euthymic and his circadian rhythm normalized. His proximal limb muscle strength partially recovered, but he was still unable to sit up independently. After 14 days of treatment, the patient's psychotic symptoms disappeared completely. He was in a stable mood and cooperated with the treatment. His distal muscle strength also improved significantly, allowing him to stand and walk for short distances. His finger dexterity improved, allowing him to perform simple and delicate movements. His symptoms of distal limb hyperalgesia disappeared. After 2 months, the patient was in a good mental state and was able to walk for short distances without assistance. Physical examination revealed that his dorsiflexion of two feet decreased and the muscle tension at the extensor side of his legs was higher.

2. Discussion

Nitrous oxide has been used as an anesthetic for a long time. In recent decades, due to its exact properties of bacteriostasis, colorless and sweet taste, nitrous oxide is also used in the food industry as a mixture and foaming agent. The use of nitrous oxide as a recreational substance can be traced back to the 19th century, when it was mainly used for entertainment in gentlemen's parties.[1] With an increasing number of case reports of nervous system damage caused by nitrous oxide, its abuse has received more attention. The World Drug Report 2016 showed that nitrous oxide has become the world's seventh most used drug, and its use is increasing.[2] A literature search shows that there is no epidemiological investigation on the use of nitrous oxide in China, but sometimes there are reports in the news and other publications. Nitrous oxide abuse occurs mainly in entertainment venues. People inhale nitrous oxide by blowing it into balloon and this accounts for 80.6% of all ways of inhalation.[3] Food-grade nitrous oxide in the form of cartridges (8 g/branch), also called whipped cream canisters, is the main source of recreational nitrous oxide use. In this case, the patient also got nitrous oxide by inhaling whipped cream canisters used as food additives. At present, there is a lack of effective control measures to separate reasonable applications in medical, automobile and industrial areas from recreational inhalation both at home and abroad. Nitrous oxide is easy to acquire and is sold at a low price. This may be one of the important reasons for the popularity of nitrous oxide. The average age of people who use nitrous oxide is 24.3 years old. This suggests that it is necessary to carry out publicity and education in schools on substances that have been clearly listed as illegal drugs. For harmful recreational substances, it is also necessary to strengthen publicity and education work for teenagers. At present, the Chinese Association of Drug Abuse Prevention and Treatment (CADAPT), an important academic group in the field of drug dependence in China, is appealing to the departments concerned to pay closer attention to the problem of nitrous oxide abuse. In the near future, relevant content will be published in the journal of this association.

Nitrous oxide abuse can produce a series of symptoms. Among them are personality changes, emotional disorders (e.g. anxiety, depression, mania), impulsive and aggressive behaviors, hallucination, delusions and other psychotic symptoms that have been mentioned in the literature.[4] Neurological symptoms include symptoms of central and peripheral nervous impairments, and the major symptoms include muscle strength weakness, numbness, deep sensory impairment, ataxia, optic nerve impairment and deep reflex hyperfunction, etc.[5,6] A systematic review suggested that many cases of death due to closed inhalation methods using a mask or plastic bag have been reported.[6] But the symptoms mentioned above can occur either alone or at the same time. The pathogenic mechanism of nitrous oxide is largely unknown. Studies have found that it is mainly associated with interference of nitrous oxide on vitamin B12 metabolism. Normally, the in vivo form of vitamin B12 is involved in the process of transition from methyltetrahydrofolate to tetrahydrofolic acid and is an important cofactor for the conversion of homocysteine to methionine.[5] These two processes are closely related to the formation of DNA, and to the repair and formation of myelin sheath in vivo. Nitrous oxide irreversibly oxidizes and inactivates vitamin B12, which in turn leads to demyelination, megaloblastic anemia, etc. In addition, the accumulation of homocysteine is closely related to vascular endothelial injury and thrombosis.[7] Studies also show that the occurrence of psychiatric symptoms may be related to a noncompetitive antagonism of NMDA receptor of nitrous oxide.[4] Nitrous oxide can also activate the nitric oxide synthase of the presynaptic membrane, and then increased nitric oxide reacts with oxygen free radicals to produce neurotoxic peroxynitrite.[8]

The patient had obvious symptoms of neurological impairment and mental symptoms at the same time. His psychiatric symptoms were manifested as paranoid delusion, hallucination and emotional instability. His neural symptoms were manifested as significantly decreased muscle strength, limb numbness and hyperalgesia in a glove and stocking pattern. Physical examination revealed deep sensory disorders (e.g. position and vibration sensation) and positive pathological signs. MRI of the spinal cord revealed a typical V-shaped T2 long signal shadow. These met the neurologic impairments of common vitamin B12 deficiency that was subacute combined with degeneration of the spinal cord. A low level of serum vitamin B12 was also important diagnostic evidence. However, this patient had voluntarily taken a small dose of vitamin B12 supplements before admission, which may have inteterfered with the diagnosis. A literature review by Garakani et al. showed that the level of vitamin B12 may be in the normal range even in patients without vitamin B12 supplementation,[6] and such patients' symptoms may be associated with functional vitamin B12 deficiency.[9] More sensitive indicators such as homocysteine and methyl malonic acid can be further measured.[10] One of the important reasons we report this case is that inhaling a high dose of nitrous oxide, such as up to 1000 branches/day (8 g/branch) in a short time is rare in previous literature, which allows us to learn more about this kind of patient and take appropriate therapeutic measures.

In this case, the most urgent thing is to treat the mental symptoms and physical symptoms of the patient. The patient was mainly treated with a high dose of vitamin B12 (1000 mg/d) and a small dose of olanzapine (25 mg/d). Vitamin B12 was initially given as an intramuscular injection, and later was taken orally. The patient was treated with other drugs including folate acid and methionine, and immediately stopped the use of nitrous oxide. At the same time, the patient underwent exercise rehabilitation 3 times a week to help restore motor function and reduce the risk of muscular atrophy due to prolonged bed rest. After 2 months of treatment, the patient was in a good mental state and was able to walk for a short distance independently. It should be noted that strategies of individual treatment are particularly important for different patients. Most case reports, including this case, support the effectiveness of large doses of vitamin B12 supplementation, but some reports suggest that vitamin B12 alone does not improve or may even exacerbate the disease. Morris et al. reported the occurrence of symptoms of lower motor neuron impairments in a case after correcting vitamin B12 levels, suggesting other pathogenic mechanisms of nitrous oxide should not be ignored.[11] Lin et al. found that for patients treated with vitamin B12 alone and with poor effect, supplementing vitamin B12 supplementation after plasma exchange may have a "magical" effect.[12] Besides the short-term rehabilitation of psychiatric symptoms and neurological symptoms, for dependent substances, comprehensive interventions in terms of physiology, behavior and social environment should also be considered for addiction. In this case, the patient previously took addictive substances, had a strong psychological dependence, lacked motivation, suffered from family conflicts and lacked family support. These are risk factors for relapse after discharge from hospital.[13] Therefore, corresponding motivational therapy and family therapy should be given to strengthen the motivation to abstain and restore family relationships, so as to reduce the risk of relapse.

In conclusion, this case suggests that (1) In patients with psychiatric symptoms and clear signs and symptoms of nerve damage the possibility of contact with toxic substances such as nitrous oxide should be considered. (2) Nitrous oxide mainly affects the metabolism of vitamin B12 in vivo. So adequate vitamin B12 should be given and individualized treatment plans should be implemented. (3) In addition to focusing on the improvement of short-term neuropsychiatric symptoms, the use of integrated therapy strategies for addictive substance should be considered to optimize the long-term outcome of patients.

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Conflicts of interest statement

The authors declare that they have no conflict of interest related to this manuscript.

Informed consent

The patient provided written informed consent and agreed to the publication of this case report.

Authors' contributions

CTZ drafted the manuscript. ZM, SHM and ZN critically reviewed the manuscript. SHM, ZN, JHF and CZK carried out the clinical diagnosis and treatments.

大剂量“笑气”吸食致神经精神症状 1 例病例报告

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概述：一氧化二氮，俗称“笑气”，已经成为全球第七大滥用药物。“笑气”吸食后影响维生素 B12 代谢，造成神经损伤，产生显著的精神神经症状。对于这类患者，及时的识别和治疗有助于改善预后。本文报告 1 例 19 岁的青年男性，在近半年时间内大剂量吸食“笑气”，出现幻听、被害妄想、关系妄想和情绪不稳。同时存在肢体无力，全身“手套 - 袜套”样痛觉过敏等神经症状。予大剂量维生素 B12 补充为主的治疗后，患者精神症状改善，神经损害好转，但下肢远端未完全恢复。治疗上，应遵循成瘾综合干预措施，除了及时修复神经损害外，还应增强患者治疗动机，针对复吸诱发因素加强干预，这对患者长期预后及回归社会非常有益。

关键词：一氧化二氮；维生素 B12；神经损害；精神障碍

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