Case Report

Recreational nitrous oxide abuse causing B12 deficiency with subacute combined degeneration of the spinal cord: A case report

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Abstract

The recreational use of nitrous oxide (N_2O) is a growing public health concern. Increasing numbers of young individuals are presenting to accident emergency departments complaining of adverse neurological symptoms as a result of N_2O induced vitamin B12 deficiency. Despite its increasing popularity, many are still not aware of its devastating potential to cause a myriad of severe longstanding neurological impairment. Herein we present a case that highlights the effects of N_2O abuse and the best way to investigate and manage such patients.

Keywords: Neurological impairment, nitrous oxide, subacute combined degeneration of the spinal cord, vitamin B12 deficiency

Case History

An 18-year-old male presented to accident and emergency with a 1-month history of pain and numbness in all four limbs, trunk, and back. The symptoms were most apparent in the palms of the hand and soles of the feet. He admitted to heavy recreational use of N_2O gas via inhalation of small cannisters (75–100 cannisters daily) commonly referred to as "whippets" preceding the symptoms.

Neurological examination revealed altered sensation in both hands accompanied with a weakness in the ability to grip. There was also marked hyporeflexia and impaired proprioception in both upper and lower limbs.

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Blood tests revealed a borderline low B12 of 186 ng/L (normal range 191–900 ng/L). Plasma methylmalonic acid (MMA) of 3.45 umol/L (>0.7 umol/L is consistent with overt B12 deficiency).

Magnetic resonance imaging (MRI) of the spine showed abnormal T2 hyperintensity within the dorsal aspect of the cord, extending from C2 to C5/C6 confirming a diagnosis of subacute combined degeneration of the spinal cord.

Treatment was commenced with intramuscular B12 injections and he was strongly advised to stop N_2O use. On discharge from hospital follow-up was arranged with the neurologist.

At outpatient review 7 months later, his symptoms had improved considerably. Neurological examination was grossly normal apart from a mild hyporeflexia of the lower limbs and slightly decreased sensation to light touch in the toes.

Unfortunately, he did not comply with the treatment course of B12 injections and follow-up in primary and secondary care was poor.

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It was therefore unsurprising that 16 months later he re-presented to hospital with symptoms of severe progressive paraesthesia and unsteadiness. He admitted to using 48 cannisters of N_2O daily for 2 weeks preceding his attendance. Clinical examination revealed altered sensation in all four limbs, pyramidal weakness, hyporeflexia, up going plantars, and a sensory ataxic gait for which he required a rollator frame to mobilize. Blood tests revealed lower serum B12 levels of 130 ng/L.

A course of B12 injections was recommenced and he was again strongly advised to stop use of N_2O. On discharge, follow-up was arranged with the neurologist, he was referred for specialist physiotherapy input and district nurse services for administration of B12 injections.

On review in neurology clinic 6 months later, he reported some improvement in his symptoms, however this time around he was left with residual symptoms of neuropathic pain and difficulty mobilizing. Although he was not reliant on a rollator frame to walk, he still needed the aid of a stick. In addition to this, he reported new symptoms of chronic constipation and difficulty passing urine.

Discussion

History of nitrous oxide (N_2O)

N_2O is a colorless, odorless, sweet tasting gas first isolated by Joseph Priestly in 1772. It was a few years later in 1799 that Sir Humphrey Davy a former president of the Royal Society began to self-experiment with the gas and discovered its euphoric and relaxant properties, this led him to coin the term "laughing gas."[1]

It was during the same era the popularity of the gas soared, mainly for recreational use as a source of entertainment in the British upper class. Many years later in 1844, N_2O was used for the first time as an anesthetic by dentist Horace Wells for a dental extraction.[2,3]

Modern day use

Today N_2O is sold legally all around the world. Its use ranges from the catering industry where it is available in small cannisters called "whippets" to act as a propellant in the production of cooking sprays and whipped cream, to the automotive industry where it enhances engine performance and most commonly the medical field where its use has been regulated for anesthetic and analgesic purposes.[4]

However, in the past few years medical use of N_2O has declined but its popularity as a recreational drug has seen a sharp rise globally.

The Global Drug survey of 2019 revealed N_2O was one of the 10 most used recreational drugs worldwide (excluding alcohol, tobacco, and caffeine products).[5]

The United Kingdom (UK) has one of the highest uses of recreational N_2O in the world. In the 2017/18 Crime Survey for England and Wales, 8.8% of young people aged 16–24 years admitted to N_2O use in the preceding year. This was higher than the number that had used cocaine, ecstasy, or ketamine.[6]

The rise in the illegal use of the gas brings with it numerous challenges and risks for both users and healthcare professionals.

Recreational use of N_2O

Recreational users of N_2O commonly use the gas neat, directly inhaling through a nozzle inserted into a small metal cannister or alternatively the gas is released into a balloon and then inhaled.

It remains a popular drug in teenagers and young adults attending concerts, clubs, music festivals, where it is commonly referred to as "noz" and "hippy crack." As it stands it is the second most used drug in England after cannabis in 16–24-year-olds.[7]

Its popularity is likely because of it being readily available legally and the rapid onset and offset of the desired effects which often gives the user a false sense of security over its safety.

Short- and long-term effects of N_2O

Depending on the amount and frequency of N_2O use, the effects can vary. The most common short-term effects include euphoria, behavioral disinhibition, hallucinations, and reduced pain sensation. Alongside these, users also commonly report unpleasurable side effects of dizziness, headaches, and nausea. In people who are inhaling high concentrations of pressurized gas, possibly with the aim of prolonging the desired effects, there has been reported cases of hypoxaemia, hypoxic brain injury, and in severe cases death by asphyxiation.[4,8]

Long-term intensive use of N_2O can lead to neurological deficits from peripheral neuropathy and subacute combined degeneration of the spinal cord as a result of a relative vitamin B12 deficiency. Patients can present with a myriad of symptoms and signs, including sensorimotor neuropathy, paraesthesia, ataxia, loss of proprioception, bladder and bowel disturbances and mood changes.[4,8]

Inhalation of N_2O has been shown to irreversibly oxidize the active cobalt ion in vitamin B12 known as cobalamin into an inactive form. This inactivation causes a deficiency of active cobalamin which in turn halts the production of methionine. Methionine is necessary for the methylation of myelin sheath phospholipids and a reduction in this process results in neuronal loss, leading to myelopathy and peripheral neuropathy.[9,10]

Blood results in such patients often reveal low or low normal B12 levels. The borderline low or low normal results may be misleading as laboratory measurements include both the active and inactive forms of B12. In order to get a more accurate measurement of functional B12 deficiency a more sensitive

test is to look for raised levels of methylmalonic acid and homocysteine (precursor for methionine).[10,11]

B12 deficiency can also cause megaloblastic changes of the bone marrow with or without anemia, however most patients with neurological symptoms present with normal MCV and hemoglobin levels.

In addition to the laboratory findings, radiological findings on MRI often demonstrate long segmental hyperintensity changes on T2 weighted images of the posterior columns, consistent with subacute combined degeneration of the spinal cord.[10,11]

Treatment

The treatment of N_2O related neurological impairment should involve complete cessation of the gas and prompt administration of parenteral high dose vitamin B12 and folate. Emphasis should be given to close follow-up and supportive treatment with a multidisciplinary team approach through primary and secondary care services as relapse rates are high in these patients. Regular support through specialist drug and alcohol teams in the community are vital to maintain prolonged abstinence just like other addictive drugs. Early involvement of physiotherapy and occupational therapy are essential to help in the recovery from the neurological impairments. Patients are often lost to follow-up and subsequently disengage with treatment. Therefore, response to treatment is variable: some patients report a full recovery after a course of high dose vitamin B12, while others are left with residual neurological deficits as a result of irreversible neuronal damage.[11,12]

Public health

Recreational N_2O use is a growing public health problem. The number of cases presenting to accident and emergency across the UK are steadily rising and there has been an increase in the number of associated fatalities.[7,11,12]

The use of N_2O has also been linked to antisocial behavior, low level crimes, and illegal activities.

Despite the introduction of the Psychoactive Substance Act 2016 in the UK which made it an "offence to supply, or offer to supply any substance intended for human consumption that is capable of producing a psychoactive effect," the authorities have found it difficult to control the ballooning use of N_2O in the UK. Investigative reports have shown how easy it has been to obtain N_2O cannisters from corner shops, the internet and through social media.[13] More recently local council campaigns in the UK such as the "no laughing matter" initiated by the London Borough of Tower Hamlets to tackle littering and antisocial behavior associated with recreational N_2O use has also failed to have an impact.[14] There have been calls to have the sale of N_2O licensed in the hope to make checks over sales more rigorous.

The role of primary care

This case is pertinent to primary care clinicians for several reasons. Firstly, patients may present early on to their primary care physician with non-specific neurological symptoms such as, tingling or paraesthesia. Recognizing these symptoms early should prompt primary care physicians to screen directly for N_2O use, as well as having a low threshold to check for B12 and methylmalonic acid levels.

Patients requiring long-term intramuscular B12 injections will often be referred back from secondary care to their primary care physician for treatment and follow-up. Managing such patients in primary care can be quite challenging as they can have very chaotic lifestyles and are generally unaware of the harmful effects of N_2O. This can result in failure to complete the treatment course and poorer outcomes long term. It is therefore important for these cases to be treated with the same level of care as for any other substance misuse. A multi-disciplinary integrated care approach is needed. Case management of these patients with discussion in multi-disciplinary team meetings getting input from nursing staff, administrative teams, and primary care physicians is essential to prevent these patients getting lost in the leviathan health services.

Conclusion

It is evident that more needs to be done to tackle the growing problems associated with N_2O abuse. Focus on increasing awareness among patients and healthcare professionals about the short- and long-term adverse effects of N_2O abuse is crucial. For patients, appropriate preventative information is key in tackling this ongoing issue as users are often unaware of the complications or just chose to ignore the risks of this seemingly "harmless" inhalant. For clinicians it is important to recognize the risk of severe irreversible neurological complications and fatal hypoxia associated with N_2O abuse and consider this an important differential diagnosis in patients presenting with atypical neurological signs and symptoms. Due to the perceived harmless nature of this habit, it is important for clinicians to directly question patients about its use in a sensitive manner. Finally, it is pertinent that clinicians are not falsely reassured by borderline low B12 levels when investigating.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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