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Laughing Gas: Does it Really Make us laugh? A **Case Report of Subacute Combined Degeneration** due to Nitrous Oxide Abuse

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Keywords: Vitamin B12 deficiency; Nitrous oxide; Subacute

combined degeneration; Recreational drugs.

Keywords: MMA: Methylmalonic Acid; SCD: Subacute Combined Degeneration; UDS: Urine Drug Screens; ED: Emergency Department; LDH: Lactate Dehydrogenase; IVIG: Intravenous Immunoglobulins; MRI: Magnetic Resonance Imaging; wwo: With and Without; OSH: Outside Hospital; CT: Computer Tomography; WBC: White Blood Cell.

Abstract

In recent years, the incidence of toxicity from nitrous oxide abuse, also known as "whippet" or "laughing gas", has increased significantly. Nitrous oxide use can lead to vitamin B12 deficiency resulting in disabling neurological complications. We are presenting the case of a young man and his wife who were hospitalized with progressive paresthesia and gait instability. Their evaluation revealed extensive T2 hyperintensity in the cervical spine, elevated Methylmalonic Acid (MMA) levels and normal vitamin B12 and homocysteine levels. Both patients were found to suffer from Subacute Combined Degeneration (SCD) due to inactivation of vitamin B12 by nitrous oxide as a result of "laughing gas" abuse. Both showed an improvement in their overall status with parenteral vitamin B12 administration.



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Introduction

Nitrous oxide is a colorless gas that is used for anesthetic purposes in dentistry and during surgical procedures. In recent years, it has been increasingly used as a recreational drug [1]. Nitrous oxide abuse is not without unwanted consequences. It can lead to vitamin B12 deficiency causing Subacute Combined Degeneration (SCD) involving the dorsal columns and lateral corticospinal tracts, which results in a corresponding clinical presentation [2]. Timely treatment with parenteral vitamin B12 is necessary and the degree of improvement depends on the degree of spinal cord damage [3].

Case presentation

We are presenting a case of a 32-year-old male who was independent with his activities of daily living at baseline. He had a known past medical history of chronic back pain, traumatic brain injury, Bell's palsy, and polysubstance (fentanyl and methamphetamine) abuse but his five most recent Urine Drug Screens (UDS) were negative. He presented to the Emergency Department (ED) with progressive difficulty walking, paresthesia's in his feet and hands, and gait instability for several days. On arrival at the ED, he reported a worsening sense of imbalance over the past several days and he was unable to stand without assistance. He denied any drug use within the past year, including IV, recreational and prescription drugs. He also denied any recent travels but was unsure of possible insect or tick bites. His neurological examination was notable for a flat affect but otherwise normal mental status. His patellar and Achilles reflexes were absent with down-going toes to plantar stimulation (absent Babinski sign). Proprioception was decreased up to the knees bilaterally and there was patchy loss of pinprick sensation on the arms, legs, and torso with normal sensation above the neck. He was also found to have dysmetria in both upper extremities worse on the left side. A Romberg sign was present. His gait was wide based. The rest of the exam was unremarkable. Blood work (Table 1) revealed a macrocytic anemia with low reticulocyte count and normal haptoglobin and Lactate Dehydrogenase (LDH) levels. UDS was negative. He was admitted for further evaluation.

Table 1: Complete blood work.

Test	Result/ Status	Flag	Units	Ref Range
White blood cell (WBC)	8.2	-	10*3/uL	3.6 - 11.2
Red blood cell (RBC)	3.22	L	10*6/uL	4.1 - 5.7
Hemoglobin (Hg)	11.3	L	g/dL	13.1 - 16.8
Hematocrit (Hct)	34.9	L	%	38.2 - 48.4
Mean corpuscular volume (MCV)	108.4	Н	fL	80.1 - 98.5
Mean corpuscular hemoglobin (MCH)	35.1	Н	pg	27.0 - 34.0
Mean corpuscular hemoglobin concentration (MCHC)	32.4	L	g/dL	33.0 - 36.0
Red cell distribution width (RDW)	22.2	Н	%	11.8 - 15.1
Platelet (PLT)	310	-	10*3/uL	150 - 400
Mean platelet volume (MPV)	9.1	-	fL	7.5 - 11.2

An extensive infectious and autoimmune workup was completely unremarkable. Metabolic and toxic workup revealed normal vitamin B12, folic acid, vitamin B1 and E, copper, ceruloplasmin, and thyroid stimulation hormone levels. Cerebrospinal fluid could not be studied as he refused the lumbar puncture. Patient was started on a five-day course of Intravenous Immunoglobulins (IVIG).

Over the next day, the patient's paresthesia had progressed to his upper thighs and elbows despite IVIG treatment. Magnetic Resonance Imaging (MRI) of brain With and Without (wwo) contrast was normal, while MRI cervical spine (c-spine) wwo contrast (**Figure 1**) showed increased T2 signal intensity throughout most of the length of the cervical spinal cord anteriorly and posteriorly. MRI of the thoracic spine (t-spine) was not diagnostic due to motion artifact.

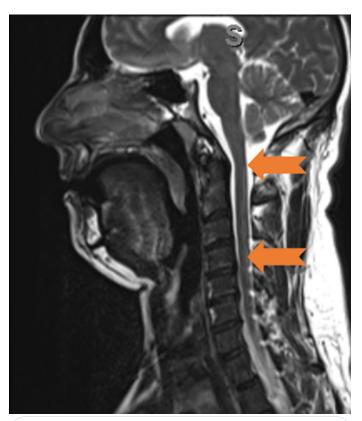


Figure 1: MRI of cervical spine showing increased T2 signal intensity of cervical spinal cord more prominent posteriorly than anteriorly.

His symptoms continued to worsen despite treatment with IVIG. On hospital day, three he ultimately admitted to using whippets with his wife for the past several months. The patient was started on intramuscular vitamin B12 injections. After initiation of parenteral vitamin B12 treatment, his gait and sensory deficits started improving. On hospital day five, he was discharged to a rehabilitation center and he reported continued improvement during a follow up telephone encounter. His homocysteine and Methylmalonic Acid (MMA) levels, drawn earlier, returned after he was discharged and revealed a normal homocysteine with increased MMA level. His only dietary restriction was an aversion to dairy products due to indigestion.

During his admission, he related that his wife, a 29-year-old female with history of alcohol use, was admitted to an Outside Hospital (OSH) three weeks before him with one week of altered mental status and progressive difficulty with walking. He gave consent to contact his wife and she gave consent to review her OSH records, which revealed the following: On admission,

she was noted to be oriented to self and time, but not to place. She had 3/5 weakness in the lower extremities, 3/4 biceps and patellar reflexes, and bilateral ankle clonus. UDS was positive for cannabinoids. Computer Tomography (CT) of the head was unremarkable. MRI brain without contrast demonstrated multiple T2 hyperintense lesions in the corpus callosum and in the periventricular and subcortical white matter. MRI c-spine wwo contrast (Figure 2) revealed a non-contrast enhancing, longitudinally extensive T2 hyperintense lesion from C2 to C7. MRI t-spine was poor quality and nondiagnostic.

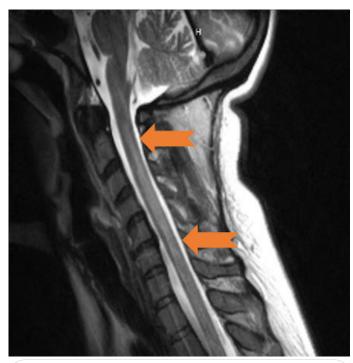


Figure 2: MRI of cervical spine showing increased T2 signal intensity of cervical spinal cord more prominent posteriorly than anteriorly.

Her CSF revealed increased protein at 90 with a normal White Blood Cell (WBC) count, and glucose level. CSF cytology was unremarkable as were the CSF autoimmune studies (oligoclonal bands, neuromyelitis aquaporin 4 antibodies, anti-myelin oligodendrocyte glycoprotein antibodies). MRI brain wwo contrast after LP showed pachymeningeal enhancement. Patient was started on intravenous solumedrol 500mg for 5 days. Her ESR, CRP, and thiamine levels were normal. Vitamin B12 levels were undetectable (<150) and her MMA was elevated. She was started on parenteral vitamin B12 supplementation with improvement in her lower extremity strength and was discharged to rehabilitation center.

These two patients were diagnosed with SCD due to vitamin B12 deficiency related to nitrous oxide abuse. In both cases, diagnosis was made based on their history, clinical presentation and workup notable for normal or decreased vitamin B12 with increased MMA levels associated with corresponding spinal cord findings on spinal MRI.

Discussion

Nitrous oxide is a colorless gas of which the first anesthetic usage was described in 1979. Since its introduction it has also been used as a recreational drug [1]. It may be legally obtained in the form of whipped-cream chargers, which are metal canisters, filled with nitrous oxide. Use of nitrous oxide in this form is called a "whippet." Widespread recreational use of nitrous oxide has not remained unnoticed as it can cause significant

health consequences. Nitrous oxide interferes with cobalamin metabolism by changing its active form to the inactive form. The active monovalent form of vitamin B12 participates in DNA, RNA, and myelin synthesis as a coenzyme [4]. As a result of inactivation of vitamin B12 by nitrous oxide myelin synthesis gets impaired, which leads to demyelination [3]. Vitamin B12 deficiency manifests itself with signs and symptoms consistent with dorsal column and lateral corticospinal tract involvement resulting in subacute combined degeneration. As a result of dorsal column involvement patients suffering from cobalamin deficiency develop impaired position and vibration sense, sensory ataxia, a present Romberg sign, paresthesia's and decreased reflexes due to peripheral neuropathy, optic nerve atrophy, and cognitive decline. Lateral corticospinal tract involvement causes weakness, increased tone and hyperreflexia [2,5].

In our case report, the husband presented with gait instability, impaired proprioception, and a Romberg sign suggesting progressive dorsal column involvement. In the case of his wife, her record suggested that she presented with progressive gait instability, symmetric weakness, hyperreflexia, and increased tone consistent with dorsal column and lateral corticospinal tract involvement.

The diagnosis of subacute combined degeneration secondary to cobalamin deficiency is made based on the history, clinical presentation and laboratory evaluation. MRI of the spine may reveal increased T2 signal intensity in the cervical and thoracic spinal cord involving the posterior columns alone, or also the lateral columns [6]. Prominent involvement of the dorsal columns at the level of the cervical and thoracic spinal cord is very characteristic of SCD [7,8].

Nitrous oxide abuse is likely an underrecognized cause of cobalamin deficiency in young adults, who may not disclose whippet usage during social history questioning. In our case, the patient did not disclose his whippet use in the initial hospital interview since whippets are legal to possess and use, so he did not perceive it as substance use. The diagnosis should be considered especially in patients with a prior history of substance use or an unexplained cause of longitudinally extensive myelopathy.

In both cases presented here, the diagnosis was made based on the clinical history of whippet abuse for the last several months associated with clinical presentation consistent with SCD. Workup was notable for increased MMA with normal vitamin B12 values in the husband and undetectable values in the wife. MRI of the cervical spine was notable for longitudinally extensive symmetric increased T2 signal intensities in both patients.

Management of vitamin B12 deficiency leading to SCD is with parenteral vitamin B12 supplementation. It is given as intramuscular injections, and the degree of recovery and ability to return to baseline depends on the severity of spinal cord damage [9]. Both patients discussed in this case report were started on intramuscular vitamin B12 supplementations and had some improvement in neurological deficits in short term follow up.

Conclusion

Vitamin B12 deficiency is becoming a more frequently encountered side effect of nitrous oxide, also known as "laughing gas", abuse. The clinical presentation is consistent with subacute combined degeneration and results in disabling complications in some cases. Timely diagnosis and treatment are es-

sential for better outcomes as it affects the level of recovery and ability to return to baseline.

Declarations

Consent for publication: Written consent from both patients was obtained.

Availability of data and material: The datasets used and/or analyzed during this case report are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: All authors read and approved the final manuscript. CW and UG interviewed and examined the patients and prepared the manuscript. CC has collected information on related work. IF has guided and reviewed the final manuscript.

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