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Case Report

Subacute combined degeneration from nitrous oxide abuse ☆,☆☆

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ABSTRACT

Nitrous oxide is an anesthetic medication which can also be recreationally abused in the form of whippet canisters. Its prolonged abuse can interfere with Vitamin B12 metabolism and lead to its functional deficiency. We report a case of a 30-year-old male who presented with generalized weakness and was found to have subacute combined degeneration (SCD) of the spinal cord. His laboratory workup showed low Vitamin B12 with elevated homocysteine and methylmalonic Co-A levels, and further questioning revealed prolonged nitrous oxide abuse. Nitrous oxide causes functional inactivation of methylcobalamin by rendering it unable to function as a coenzyme for methionine synthase enzyme. This leads to the decreased production of methionine and subsequent production of myelin. This case describes nitrous oxide abuse as an important etiology to be considered in patients presenting with weakness and myeloneuropathy and describes important imaging findings.

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Introduction

Nitrous oxide is an anesthetic drug which can be misused for recreational purposes in the form of whippet canisters. It interferes with Vitamin B12 metabolism and causes its interference with methylation, leading to reduced formation of methylcobalamin. Methylcobalamin is an apoenzyme required for the conversion of homocysteine to methionine and the further formation of myelin. Myelin is a continuously regenerating tissue and continuous supply of methylcobalamin is essential for it [1]. Nitrous oxide's availability as a recreational agent is unregulated but has the ability to cause complications such as subacute combined degeneration (SCD) and potentially irreversible neurologic consequences. This case aims to shed light on the unregulated use of nitrous oxide, and the investigations needed to diagnose SCD.

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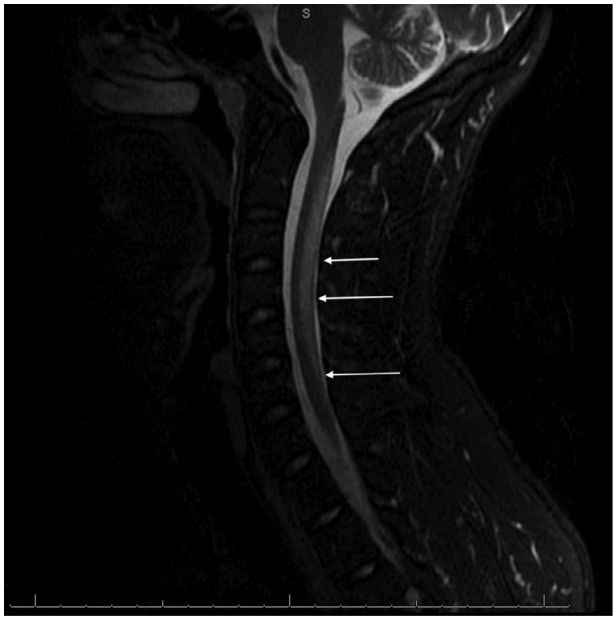

Fig. 1 – Mid sagittal plane view of T2-MRI sequence showing increased T2 signal intensity (arrows) in dorsal columns suggesting subacute combined degeneration.

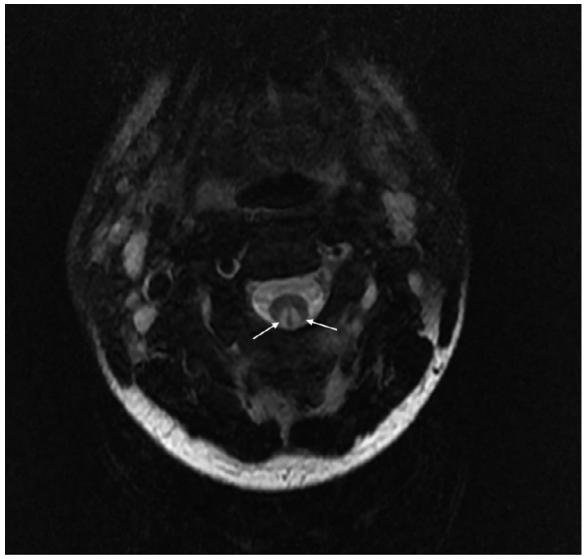

Fig. 2 – Cross-sectional plane view of T2-MRI sequence showing increased T2 signal intensity (arrows) in the region of dorsal columns resembling rabbit ears demonstrating "rabbit ear sign".

Case presentation

A 30-year-old male presented with a 2-week history of bilateral limb paraesthesias, generalized weakness, and inability to walk. His prior medical history constituted bipolar disorder and schizoaffective disorder, for which he was taking fluphenazine and lamotrigine. The patient was somnolent but alert and oriented to time, place, and person. His neurological examination revealed absent fine touch sensations in all distal extremities and decreased proprioception at the lower extremity joint movements bilaterally. He had motor strength of 5/5 in bilateral upper and lower extremities and an unremarkable cranial nerve examination. He had 1+ deep tendon reflexes in bilateral lower extremities, with extensor plantar reflexes bilaterally. There were no signs of meningismus, ataxia or dysmetria. The complete blood count was unremarkable, with hemoglobin of 14.6 g/dL (normal range 13.5-17.0 g/dL) and mean corpuscular volume (MCV) of 93.2 fL (normal range 80-100 fL). Magnetic Resonance Imaging (MRI) showed increased signal on short tau inversion recovery (STIR) and T2-weighted images involving the dorsal cord from C2 to C7 disc level, extending to upper thoracic discs consistent with subacute combined degeneration (Fig. 1). The vertebral bodies and intervertebral discs were maintained in height and signal throughout. Cross-sectional imaging at the cervical spine level showed an "inverted V sign" or "rabbit ear sign" highlighted by the increased signal intensity in the areas of demyelination of dorsal columns (Fig. 2).

Further blood work revealed undetectable Vitamin B12 levels of <150 pg/mL (normal 232-1245 pg/mL) and a workup for the underlying cause of Vitamin B12 deficiency was pursued to determine the inciting factor. He had a negative intrinsic factor antibody, elevated homocysteine level of >44 μmol/L (normal 3-14 μmol/L), and an elevated methylmalonic acid level of 1.22 μmol/L (normal <0.40 μmol/L). He did not have any history suggesting small bowel diseases such as Crohn's disease or celiac disease to account for a possible malabsorptive syndrome. On further review of possible causes of Vitamin B12 deficiency, the patient reported using around 10 nitrous oxide cartridges (whippets) a day for the last 6 months for recreational purposes.

Over the next few days in the hospital, he was found to have persistent urinary retention and constipation which was attributed to SCD associated autonomic disturbances. Cerebrospinal fluid testing (Table 1) was reassuring with mildly elevated protein to 64.8 mg/dL, and no evidence of pleocytosis. Given no pleocytosis, and no hyper intensities on MRI brain (Fig. 3) there were no concerns for demyelinating etiology or autoimmune encephalitis. Also, there was low evidence of bacterial or viral infection due to no pleocytosis.

The patient was started on daily intramuscular Vitamin B12 injections (1000 μg) for 1 week and then transitioned to weekly injections for 2 months. He was noted to have urinary retention for which foley catheter was placed. It was presumed to be from the interruption in the neural pathways from the extensive degeneration. Over the course of 10 days in the hospital, he did not have much improvement in his neurologic deficits and was discharged to an inpatient rehabilitation facility for regular physical therapy. A follow-up appointment with Neurology was arranged and the patient was counselled to abstain from further nitrous oxide use.

The patient was followed for one year as he received rehabilitation services at the inpatient facility and outpatient services. Despite aggressive physical and occupational therapy, the patient had little to no improvement in his neurological deficits. For urinary retention, the patient underwent

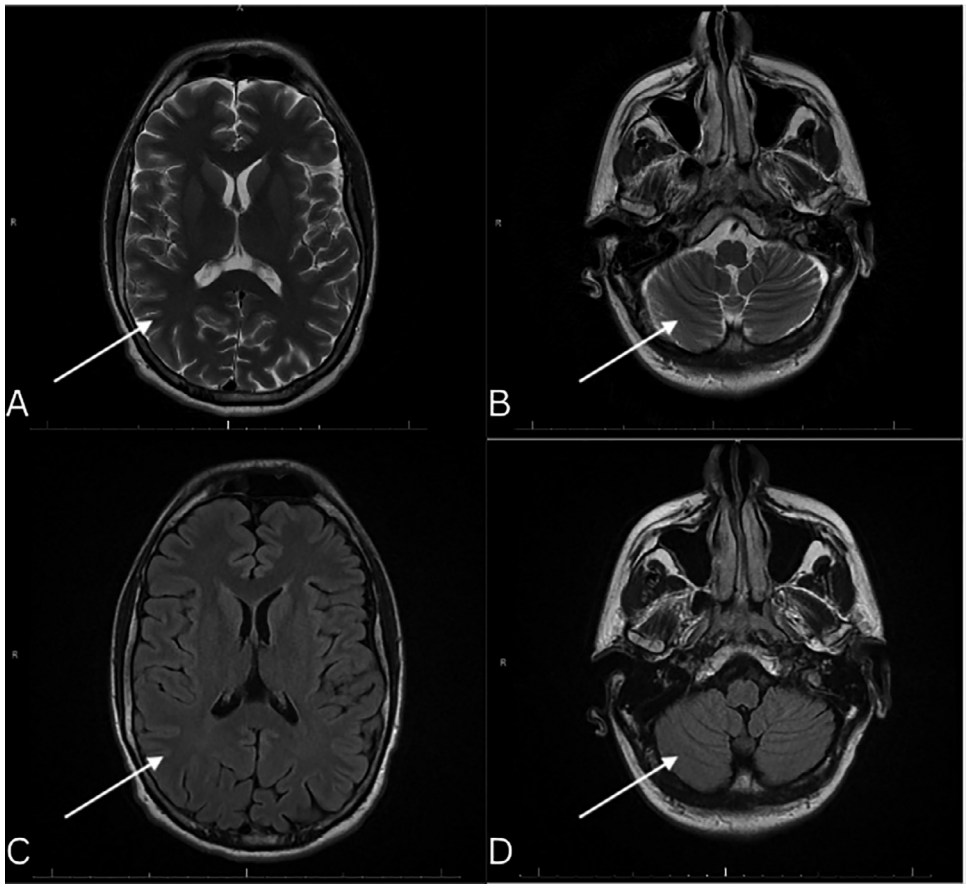

Fig. 3 – MRI Brain T2 (A, B) showing and T2 FLAIR (C, D) cross-sectional plane views show no evidence of acute infarct, hemorrhage, or hyper intense lesions. The arrows in A and C, and B and D show no signal abnormality in the cerebral cortex and cerebellum respectively to indicate any pathology.

a suprapubic catheterization procedure and undergoes close follow-up with Urology.

Discussion

Nitrous oxide was first discovered by Joseph Priestly in the late 1700s. Its ability to produce euphoria and render the user less sensitive to pain stimuli when inhaled was reported by Humphrey Davy in 1800 [2]. The recreational use of inhaled nitrous oxide gas is becoming increasingly popular as suggested by the 2014 Global Drug Survey. The findings showed 38.6% and 29.4% lifetime prevalence of N2O use in the UK and the US respectively. It is generally consumed via gas-filled balloons at festivals and clubs where the use of other recreational substances is common [3]. Its chronic use interferes with Vitamin B12 metabolism leading to neurological sequelae such as SCD which if not recognized or treated early can lead to long term permanent neurological deficits.

Vitamin B12 is a bound coenzyme of methionine synthase. The molecular structure of Vitamin B12 has a tetrapyrrole ring with a monovalent cobalt ion at the center which functions as a methyl carrier for the transmethylation reaction to convert homocysteine to methionine [1]. Nitrous oxide causes conversion of the cobalt ion contained in the structure of Vitamin B12 from monovalent to the bivalent form which can no longer function as a methyl carrier [4]. Decreased formation of methionine leads to decreased amounts of S-adenosyl methionine which is essential in the production of DNA, RNA, and myelin [1]. This dysregulation of myelin production within the spinal cord eventually results in demyelination of the spinocerebellar tracts, lateral corticospinal tracts, and dorsal columns, eventually leading to various neurologic manifestations.

Initial clinical features of chronic nitrous oxide abuse are due to the degeneration of dorsal column, a heavily myelinated tract and manifests as gait disturbance due to diminished proprioception and vibration sensation. This is usually followed by motor weakness due to the degeneration of lateral corticospinal tract which leads to spasticity, extensor plantar responses, and hyperreflexia [5]. Autonomic disturbances, dementia and psychosis have also been reported which is likely due to antagonism at the level of N-methyl D-aspartate receptors [6].

Nitrous oxide abuse is known to lead to functional Vitamin B12 deficiency which can be assessed by measuring levels of methylmalonic acid and homocysteine. These are the sub-

Table 1 – Cerebrospinal fluid analysis from the lumbar puncture.

Component, CSF	Ref Range and Units	Value
Color	Colorless	Colorless
Red Blood Cells	0 /cu mm	20
Total Nucleated Cell Count	0-5 /cu mm	1
Glucose	40-80 mg/dL	67
Protein	15-55 mg/dL	64.82
Lactic acid	1.2-2.4 mmol/L	1.8
HSV 1 DNA	Not detected	Not detected
HSV 2 DNA	Not detected	Not detected
B. burgdorferi Abs (EIA)	<0.99 LIV	0.08
West Nile IgG Abs	<1.30 IV	<1.30
West Nile IgM Abs	<0.90 IV	<0.90
VDRL, CSF	Nonreactive	Nonreactive
CMV, DNA, PCR	Not detected	Not detected
EBV DNA	Not detected	Not detected
IgG	0.8-6.1 mg/dL	6.5
Albumin	<35 mg/dL	46.3
IgG, serum	610.3-1616 mg/dL	777
Albumin, serum	3500–5200 mg/dL	4,399
IgG Index/CSF	0.3-0.7 Ratio	0.8
Toxoplasma gondii DNA (PCR)	Not detected	Not detected

CMV, Cytomegalovirus; CSF, Cerebrospinal fluid; DNA, Deoxyribose nucleic acid; EBV, Ebstein Barr Virus; EIA, Enzyme immunoassay; HSV, Herpes Simplex Virus; IgG, Immunoglobulin G, IgM: Immunoglobulin M; PCR, Polymerase chain reaction; VDRL, Venereal Disease Research Laboratory.

strates of reactions catalyzed by Vitamin B12 and are crucial clues for early diagnosis. Mean serum B12 concentrations in such cases have shown a cumulative normal Vitamin B12 result with abnormal serum homocysteine and methylmalonic acid, which serve as a marker of functional B12 deficiency. Macrocytosis and anemia are not prominent features in this cohort of patients [7]. Magnetic resonance imaging (MRI) imaging of the spine shows a characteristic feature of dorsal column hyperintensity on T2 weighted images. MRI findings include demyelination in the dorsal columns with a high proportion of cases showing cervical spinal cord involvement. Lower limb mixed axonal and demyelinating patterns are also noted. No change on MRI brain is reported in literature [8].

Withdrawal of exposure and prompt vitamin B 12 supplementation is recommended for effective treatment. The usual recommended dose is 1000 to 2000 μg daily [9]. After the diagnosis, close follow-up remains essential due to high risks of relapse. Multidisciplinary measures with involvement of addiction medicine, psychotherapy and physical therapy are needed to help with recovery [9]. Earlier age of presentation (less than 50 years), short duration of symptoms, absence of sensory deficits, absence of Romberg's sign, absence of Babinski sign, involvement of ≤ 7 spinal segments on MRI, presence of spinal cord edema, and contrast enhancement of the spine and absence of spinal cord atrophy are associated with better short term neurological outcomes [10,11]. Our patient had sensory symptoms, positive Babinski bilaterally, and involvement of >7 spinal segments on MRI spine, which is suggestive of slower recovery with prolonged neurological manifestations.

In a retrospective analysis of 57 patients with SCD, only 8 patients achieved complete clinical and neurological resolution as a response to B12 therapy [10]. Patients of SCD require prolonged duration of at least 3-12 months to recover [12]. This indicates low potential for prompt recovery after Vitamin B12 supplementation as myelin formation takes time. CNS myelination in rodents was found to have a rate of $5 \times 10^3 - 5 \times 10^4$ μm^2/cell/day [13]. Early diagnosis and prompt treatment with a multidisciplinary approach is essential to prevent irreversible spinal cord damage and chronic neurological sequelae such as paraplegia and quadriplegia [14].

Conclusion

Nitrous oxide is an unregulated substance with increasing prevalence. Its users and clinicians need to be aware of it causing functional vitamin B12 deficiency and future consequences such as subacute combined degeneration. In suspected cases, absence of anemia and macrocytosis should not prevent the clinicians from ordering further diagnostic tests. At the time of diagnosis, treatment with Vitamin B12 is recommended along with removal of exposure to nitrous oxide. The clinical recovery of the published cases remains poor which implies the importance of preventive management.

Patient consent

A written, informed consent was obtained from the patient's legal guardian (mother) regarding the publication of this case.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Prior presentation of abstract statement

No previous presentations.

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