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Letter to the Editor: New Observation

Laughing Ceased, Nitrous Oxide-Induced Myelopathy Evolved

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Recreational use of nitrous oxide is increasing among the younger population. There is a great concern about its associated neuropsychological complications with the increase in its accessibility. It is estimated that nearly one-third of the UK and US population has lifetime exposure to this recreational drug.[1] Subacute combined degeneration (SCD) due to functional vitamin B_{12} deficiency is the most common known neurological disorder due to nitrous oxide abuse. Movement disorder associated with cobalamin deficiency and/or nitrous oxide abuse is a recent issue with limited data in adults.[2]

A 19-year-old previously healthy man presented with progressive gait disturbance, numbness, and tingling in his feet and urinary retention from 1 week before admission. He needed bilateral aid for standing on his feet. He declared a history of "laughing gas" inhalation in the recent year and each time he had the same tingling sensation in his feet spontaneously improved in 2–3 days. His medical history was otherwise unremarkable.

On examination, he was alert and oriented. He had scanning speech and bidirectional horizontal nystagmus. Tendon reflexes were decreased in both upper extremities but hyperreflexia, spasticity, sustained ankle clonus, and Babinski's sign were seen in his lower limbs. He had asynchronous multifocal jerk-like movements in all his limbs and trunk but not face, which was exaggerated by tactile and auditory stimuli and intentional movements and persisted in sleep but was less severe. There was dysmetria on both sides in finger-to-nose and heel-to-shin examinations. (Videos 1 and 2). His proprioception was diminished in his feet and pinprick sensation was decreased in his trunk and limbs, with sensory level at C8-T1. The Romberg test was positive. He had a wide-based gait with impaired tandem walking.

Routine lab test revealed no abnormality. Mean corpuscular volume was 93.2 fl (Normal range:77–97 fl). Cerebrospinal fluid analysis was unremarkable and no oligoclonal bands were detected. Serum anti-HIV and anti-HCV antibodies were negative. The serum B_{12} level was low, 101 pg/ml (normal value: 211–946pg/ml). Although serum methylmalonic acid and homocysteine levels were normal, hyper-segmented neutrophils were seen in peripheral blood smear. Electroencephalography revealed no abnormality. Brain MRI was done using an "1.5 T Ingenia Philips" machine. Brain and spinal MRI was done using these sequences: T1, T2, FLAIR (only for brain), DWI and ADC (only for brain), STIR (only for spine), and gadolinium-enhanced T1 sequences. The T2/STIR sequence of the cervical spine MRI showed an inverted V-shaped lesion, preferentially affecting the posterior column, elongated from C2 to C6 segments without enhancement in post-gadolinium sequence (Figure 1).

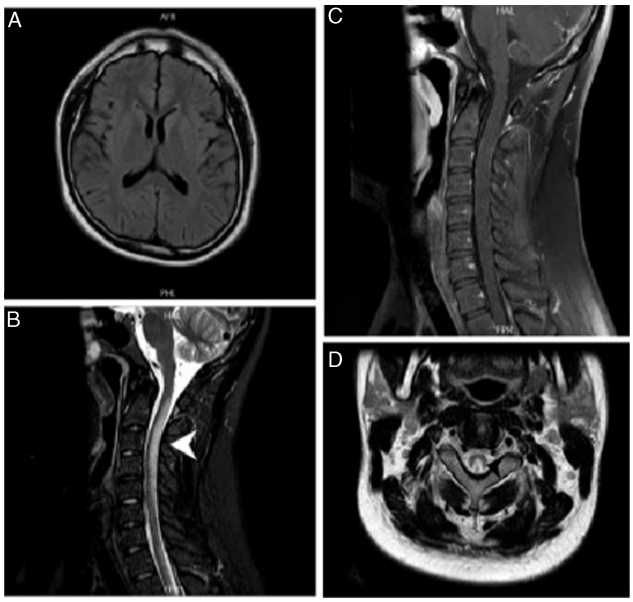

Figure 1: (A) T2/FLAIR transverse image of the brain. (B) T2/STIR sagittal image of the cervical cord, showing a longitudinal lesion extending from C2 to C6 segments without enhancement (C) in the post-gadolinium sequence. (D) T2-weighted axial image of the cervical spinal cord revealed an "inverted V-sign".

Considering the above findings and a history of frequent use of laughing gas, he was diagnosed with SCD caused by cobalamin deficiency. His symptoms improved partially after 7 days of intramuscular 1000 μg cyanocobalamin supplementation and continued weekly. A 2-month follow-up examination revealed a dramatic improvement in sensory and ataxia as well as myoclonus (Video.3).

Nitrous oxide has been used as an inhalant, short-acting anesthetic agent for many years. It can cause euphoria and sometimes hallucinations along with enhancing the effect of other illicit drugs and is being abused as a recreational drug called "laughing gas". Chronic inhalation of nitrous oxide, oxidate cobalt ion, the core

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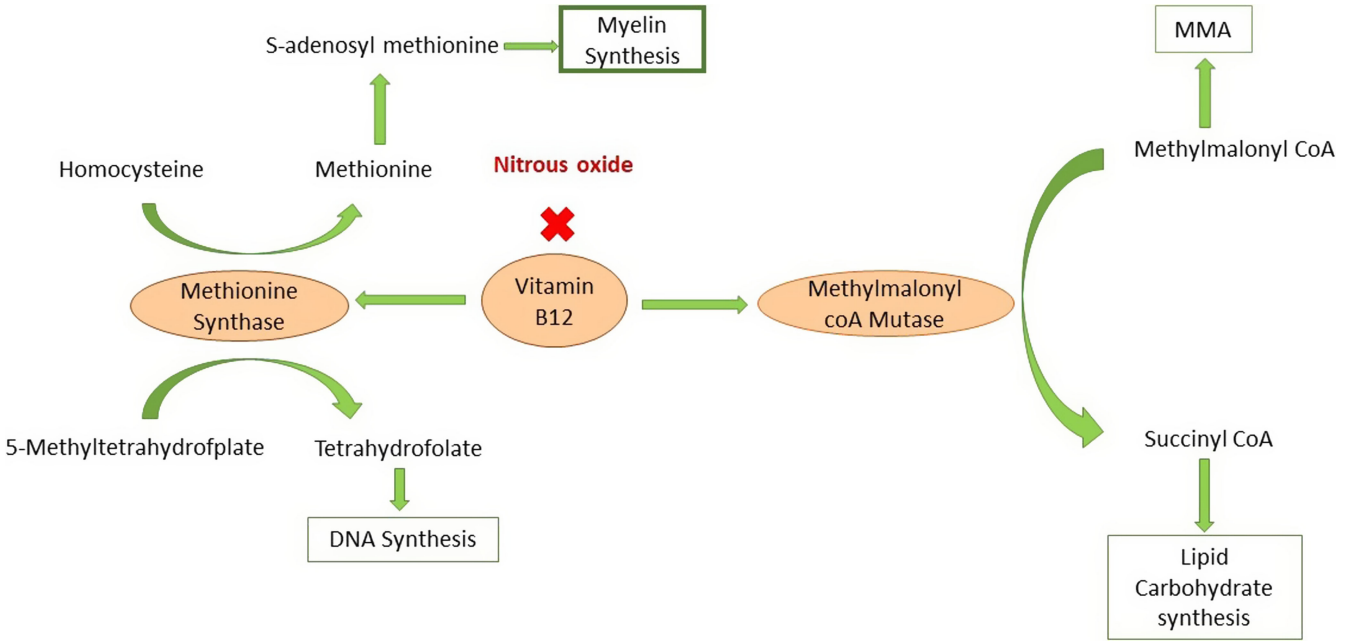

Figure 2: Schematic representation of how nitrous oxide causes functional vitamin B_{12} deficiency and impairs myelin protein synthesis. MMA: methylmalonic acid.

structure of the cobalamin, which inactivate vitamin B_{12} and cause functional cobalamin deficiency.[3] Vitamin B_{12} deficiency can cause megaloblastic anemia along with various neuropsychiatric symptoms. Demyelination of the posterior and lateral columns of the spinal cord causes the most common neurological finding, SCD.[4] S-adenosyl methionine, a crucial methyl donor for methylation of myelin protein, is produced by the methionine synthetase from homocysteine by the cofactor of vitamin B_{12} (Figure 2).

Our patient's neurological signs, except for his stimulus-sensitive generalized myoclonus, are explained by the diagnosis of SCD, which responded to vitamin B_{12} replacement.

A special feature of our patient was generalized stimulus-sensitive myoclonus with an intentional component. Previously, abnormal movements due to cobalamin deficiency, including tremors, myoclonus, and twitches, were reported in childhood and mostly after initiation of cobalamin replacement.[5] Spinal myoclonus has been reported due to cobalamin deficiency.[6,7] Reflex-sensitive spinal myoclonus can be due to the injury of the myelin in the dorsal and lateral columns and enhanced by the neuronal excitability caused by cobalamin deficiency.[8]

As it is widely accepted, the exact localization for the anatomic origin of the myoclonus needs electrophysiological study which was not available for our patient and this disadvantage complicates the determination of the anatomic origin. We presume that the clinical phenomenology of our patient was most compatible with a cortical origin of myoclonus. First, the myoclonus was mainly in the form of multifocal and distal polyminimyoclonus superimposed by generalized, stimulus-sensitive, and action-induced myoclonus. These features are mainly observed in cortical myoclonus rather than subcortical or spinal myoclonus. One may try to associate the myoclonus with the cervical spinal cord lesion, but the caution should be advised as the myoclonus with a spinal cord origin is either clinically in the form of "spinal segmental myoclonus" or "propriospinal myoclonus" neither of which is applicable to the phenomenology in our case.[9,10]

In a similar previous report, serum vitamin B_{12} levels were normal and there was an increased level of homocysteine and methylmalonic acid. However, our patient's serum analysis showed low vitamin B_{12} levels without megaloblastic anemia or a rise in methylmalonic acid and homocysteine levels. But his blood smear showed hyper-segmented neutrophils. It should be considered that hyper-segmented neutrophils in the peripheral blood smear often precede anemia and may be the sole finding of the cobalamin deficiency in a nonanemic patient (as was in our patient with normal MCV value, besides low serum cobalamin level).[11]

He responded well to cobalamin replacement, his myoclonus diminished, and other symptoms improved dramatically. He was encouraged to abandon laughing gas abuse.

Laughing gas-induced cobalamin deficiency has been reported in the previous decades. The unique point of our case was the combination of SCD and myoclonus. Whether his myoclonus was due to nitrous oxide poisoning and/or cobalamin deficiency is unresolved in our opinion and needs further investigations in similar cases.

This low cost, easily accessible recreational nitrous oxide has become a great concern around the world.[1] No blood testing, no definite dosing along with consumers lack of information, increase the associated harms and side effects.[12] It is crucial that clinicians be familiar with this increasingly encountered condition especially in youngsters using nitrous oxide as a recreational substance and be aware of its diverse associated symptoms.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2023.44.

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All authors contributed to the study conception and design. The first draft of the manuscript was written by MS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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