

Subacute combined degeneration of the spinal cord following recreational nitrous oxide use

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Background and aim

Subacute combined degeneration of the spinal cord (SACD) is a well-documented complication of vitamin B12 deficiency. However, nitrous oxide (N₂O) toxicity as an etiology of the condition is not well known. Recreational N₂O use is prevalent among young people.

This case highlights a potential rare complication of N₂O toxicity and the importance of the consideration of N₂O toxicity induced SACD as a possible diagnosis of a young patient with undifferentiated neurological symptoms.

Method

Clinical information

A 22-year-old woman with no significant medical history presented with a gradual worsening of uncomfortable tingling sensation in her feet over eight weeks and a three-day history of poor balance.

Her social history was remarkable for recreational N₂O bulb use. She had been abusing N₂O intermittently for a year until approximately two months ago when she regularly used N₂O approximately three times weekly with 60 bulbs per session. The patient reports good dietary intake and social alcohol use of no more than two standard drinks a day on average. There was no history of illicit drug use.

On examination, the patient was alert and oriented. Repeated voluntary movements of lower limbs were noted which patient reported improved paraesthesia. Cranial nerve and upper limb neurological examinations were unremarkable. Lower limb neurological examination revealed mild weakness (4-/5) and hyperreflexia. Proprioception and vibration sensations were absent over the lower limbs. Pinprick and light touch sensations were reduced below the sixth thoracic dermatome. A broad based gait, positive Romberg and Lhermitte sign were noted. Fundoscopy revealed no optic atrophy.

Discussion

Investigations

Blood tests showed a low serum vitamin B12 level of 76 pmol/L [140-770 pmol/L]. Anaemia was not detected and mean corpuscular volume was within normal range. Methylmalonic acid level was raised at 0.92 [< 0.35 $\mu\text{mol/L}$]. Blood sugar level, thyroid function test, serum folate, copper and ceruloplasmin levels were normal.

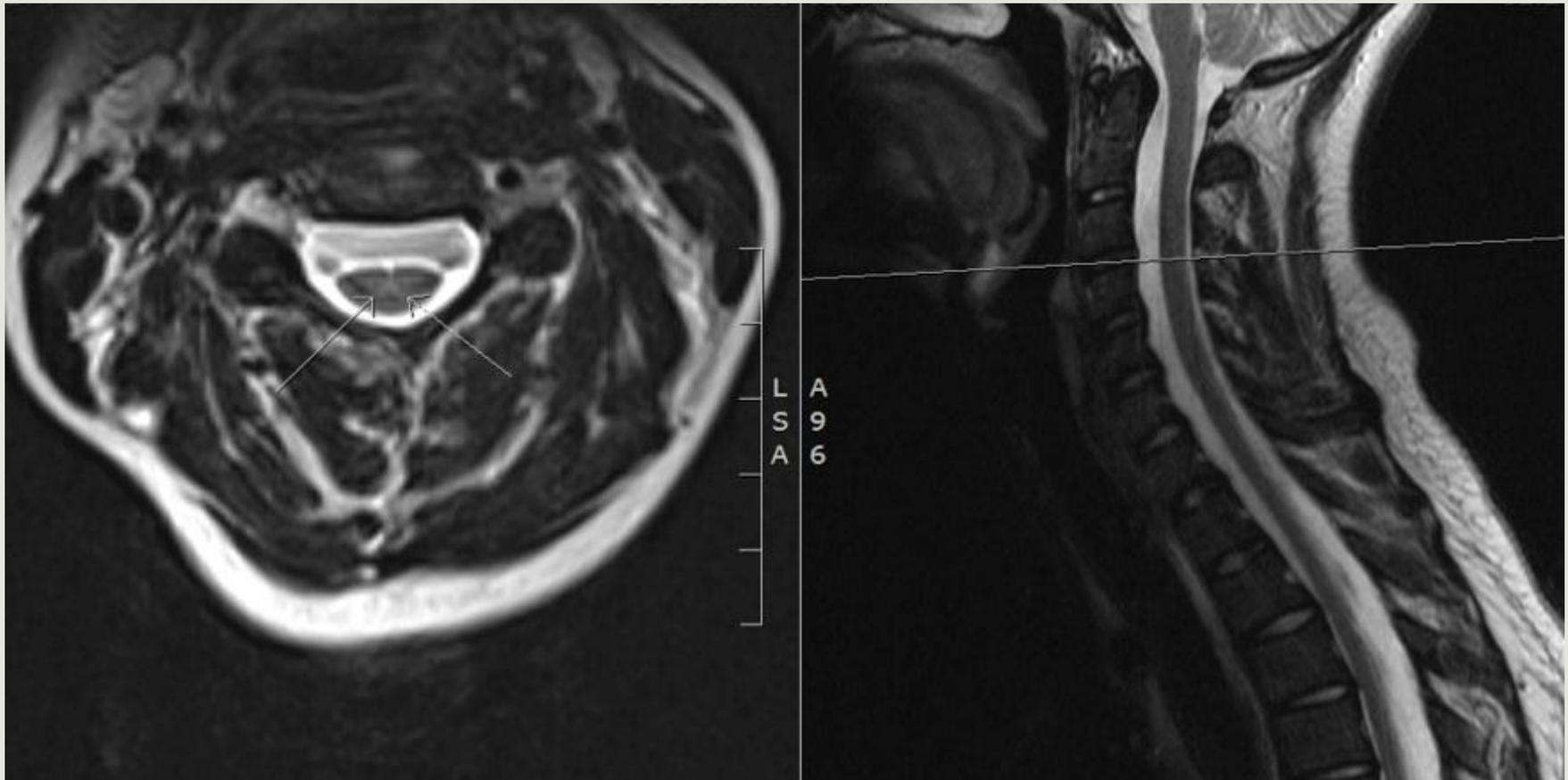
Antibodies to syphilis, Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus were negative. Intrinsic factor and parietal cell autoantibodies were absent. Swabs taken for gonorrhoea and Chlamydia were all negative.

T2-weighted MRI scans of the spinal cord showed hyperintensity changes at the posterior column from the second to the fourth cervical vertebrae.

Cerebrospinal fluid analysis was not performed in this case due to the subacute presentation and a lack of risk factors for infectious causes.

Discussion

T2-weighted axial MR imaging showing hyperintensity changes at the posterior column.



Discussion

Differential diagnosis and outcome

The clinical presentation is of symmetric subacute paresthesias, loss of proprioception, and progressive ataxic weakness which indicates posterior and lateral column involvement. Differential diagnoses such as infectious (HIV-1 associated myelopathy, neurosyphilis), autoimmune (autoimmune myelopathy, Guillain-Barre syndrome), demyelinating (multiple sclerosis), nutritional (vitamin B12, copper deficiency) and neoplastic (paraneoplastic syndrome) disorders should be considered.

With investigations showing vitamin B12 deficiency and posterior column changes on MRI, subacute combined degeneration of the spinal cord was most likely. Common causes of vitamin B12 deficiency including pernicious anaemia, acquired malabsorption and malnutrition were ruled out with patient history and blood tests. The diagnosis of SACD as a complication of N2O toxicity was made.

The patient was admitted to the hospital under neurology for daily vitamin B12 injections (1000 µg/day) and physiotherapy. She gradually improved and was discharged on day 13 with weekly injections of vitamin B12 (1000 µg/week) for 4 weeks. She was reviewed at 18 months post discharge and noted to be well and free of any disabling neurological symptoms.

Discussion

N₂O is an inhalational anaesthetic agent commonly used in dentistry. Industrial applications include its uses as a food aerosol propellant and an engine accelerant.

N₂O exerts its harmful effects by irreversibly oxidizing the cobalt ion of cobalamin (vitamin B₁₂). Oxidation of the cobalt ion by N₂O inhibits methylcobalamin as a cofactor of methionine synthase in the production of methionine and subsequently S-adenosylmethionine, which is necessary for methylation of myelin sheath phospholipids. The result is demyelination of the nervous system involving the spinal cord and sometimes peripheral neuropathy and optic atrophy. Thus, nitrous oxide induces SADC through inactivation of the vitamin B₁₂ metabolism. Pathologic changes occur initially in the lower cervical and upper thoracic segments of the spinal cord which appear as high signal lesions on T₂-weighted MRI scans due to increased water content secondary to edema.

Clinically, patients with subacute combined degeneration may present with a subacute onset of paraparesis and impaired sensation and proprioception. The clinical diagnosis could be confirmed by an abnormal signal on MRI of the spinal cord, low serum vitamin B₁₂ levels and peripheral nerve conduction study. However, the findings of these tests could sometimes be normal. Measurement of methylmalonic acid levels can be employed to make the diagnosis in the presence of normal or low normal vitamin B₁₂ level.

Abuse of N₂O has been previously reported in the literature amongst healthcare workers, such as dentists, as well as young adults who use the drug more frequently. Despite its purportedly high rate of usage, serious side effects as a result of its abuse remain uncommon, with less than 20 cases reported in the literature. The usual amount of N₂O bulbs inhaled in a session is usually <5, but the average of bulbs inhaled amongst reported cases ranges from 10-20 to >100. This suggests that N₂O use alone is unlikely to result in serious neurology amongst most young, healthy adults, but when used in excess of 10 bulbs/day, the risk of permanent neurologic deficits, including ataxic paraplegia, increases exponentially. Amongst the reported cases, there appears to be correlation between amount of use and extent of symptoms although significant symptoms can occur with moderate use.

Removal of the offending agent and vitamin B₁₂ replacement appear to be effective treatment. Whether the patient makes a partial or full recovery depends on the degree of the neuropathological damage to the spinal cord. The absence of sensory deficits and Romberg and Babinski signs were associated with a higher full recovery rate. In cases where symptoms persist methionine treatment has been successful where B₁₂ treatment alone has failed. The incidence of N₂O induced neurotoxicity is underestimated and should be recognized as an important cause of subacute combined degeneration of the spinal cord especially in young patients presenting with undifferentiated neurological symptoms considering serious complications such as irreversible paralysis and cardiac arrest can occur if not detected early.

Conclusion and acknowledgements

Nitrous oxide abuse is common amongst young people.

N₂O toxicity induced subacute combined degeneration of the spinal cord should be considered as a possible diagnosis in a young patient with undifferentiated neurological symptoms.

Usage of more than 10 N₂O bulbs/day has a potential to result in significant neurological complications.

Measurement of methylmalonic acid levels can be employed to make the diagnosis in the presence of normal or low normal vitamin B12 level.