

Nitrous oxide and cervical myelopathy

A 25-year-old woman presented with progressive paraesthesia and numbness, both of which started from the left hand. Her symptoms progressed to the fingertips of her right hand and bilateral soles over a few days. There was associated confusion and altered mental status on admission. There was no weakness of the face and limbs, visual impairment, speech difficulty, swallowing impairment, or urinary and bowel incontinence. She had no significant medical history, though it was revealed that she had been inhaling nitrous oxide (N_2O) from 3–4 canisters of whipped cream charger daily for 2 months. N_2O , commonly known as “laughing gas”, is often used as a recreational inhalant. There was loss of proprioception and vibration senses over the bilateral thumbs and toes. Pain and temperature senses were intact. Deep tendon reflexes were normal and Babinski reflex was positive bilaterally. She had sensory ataxia and her gait was unsteady. Her clinical presentation pointed to a pathology at the posterior column of the spinal cord.

She had a borderline low vitamin B12 level of 131pmol/L (normal: 133–675pmol/L), with normal folate but elevated homocysteine of 101 μ mol/L (normal: 5–15 μ mol/L). Her serum copper level was normal. Other test results including those for full blood count, thyroid panel, HbA1C, syphilis and human immunodeficiency virus antibodies, erythrocyte sedimentation rate, and systemic autoimmune screen were normal. Anti-aquaporin-4 antibody, anti-intrinsic factor and anti-parietal cell antibodies were negative. The nerve conduction study results were normal.

Magnetic resonance imaging (MRI) of the brain was normal. MRI of the cervical spine was performed (Fig. 1). Her lumbar puncture was normal. Cerebrospinal fluid (CSF) infection screen was negative. CSF oligoclonal bands were absent.

What is your diagnosis?

- Subacute combined degeneration (SCD) of the spinal cord
- Syringomyelia
- Multiple sclerosis (MS)
- Neuromyelitis optica (NMO)
- Spinal cord infarction (SCI)

Our patient presented with clinical features suggestive of a pathology at the posterior column of the cervical

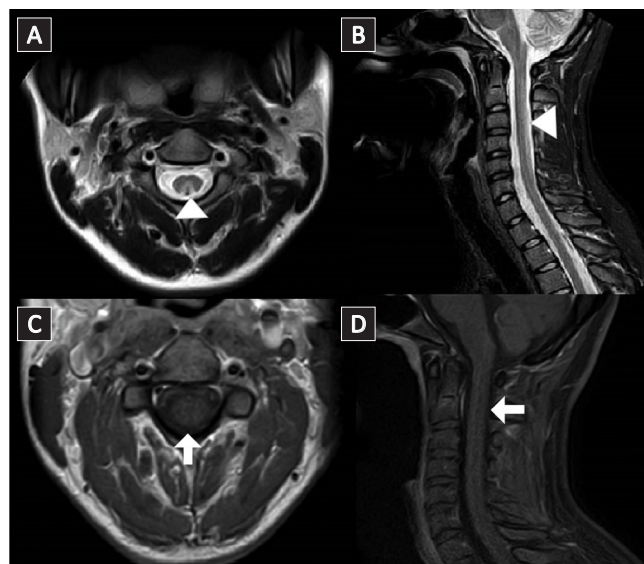


Fig. 1. Magnetic resonance imaging (MRI) of the cervical spine. (A) Axial T2 sequence at C3 level. (B) Sagittal T2 sequence. Arrowheads indicate T2 hyperintensity over the cervical spinal cord. (C) Axial post-contrast T1 sequence at C3 level. (D) Sagittal post-contrast sequence. Arrows indicate no contrast enhancement at cervical spinal cord.

cord. Her MRI demonstrated long segment symmetrical T2 hyperintensity over both the posterior column at C2–C5 levels (Fig. 1B) and an inverted V sign (Fig. 1A), suggestive of vitamin B12 deficiency myelopathy. No contrast enhancement was seen on post-contrast T1 sequence (Figs. 1C and 1D). These findings are typical of SCD. Given the history of N_2O inhalation, with presence of low vitamin B12 level and high homocysteine level, N_2O -induced SCD should be the top differential diagnosis.¹

N_2O , is commonly used as an anaesthetic agent for dental and medical procedures. However, its misuse and complications have been increasing in recent years.² The Global Drug Survey 2021 reported N_2O to be the 14th most abused drug globally.³ In Singapore, N_2O is not banned, and is available in the open market. In the baking industry, “whippet” chargers are used in propelling whipped cream in cans, with each canister priced affordably. Common clinical features of N_2O abuse include myeloneuropathy, paraesthesia, gait ataxia, amnesia, confusion, and bowel/bladder and sexual dysfunction.⁴

N_2O interferes with methionine synthesis by inactivating methylcobalamin, resulting in vitamin B12 deficiency.

Answer: A

Vitamin B12 level can be normal, with functional deficiency¹ that can be diagnosed based on high methylmalonic acid and/or homocysteine level.² The abnormal methylation of myelin protein results in demyelination within central and peripheral nervous systems. Interestingly, N₂O-mediated inactivation of vitamin B12 is not commonly associated with haematological disorders such as anaemia. Additionally, the prognosis of N₂O-mediated SCD is also not related to presence of anaemia, low serum B12 level or MRI abnormalities.⁵

SCD commonly involves the dorsal column. On the MRI, the inverted V sign in axial T2 sequence is a characteristic feature of SCD.^{1,2} Most patients have MRI lesions extending over 3–6 spinal segments, most commonly involving the cervical spine.^{1,2} Cervical cord is extremely vulnerable to N₂O neurotoxicity due to the high density of myelinated fibre in the fasciculus gracilis. Cord enhancement is anticipated in inflammation and neoplasms, a feature which is not seen in SCD. The minimal contrast enhancement in SCD is likely due to breakdown of the blood-brain barrier caused by perivascular demyelination and inflammation.⁶

Typically, syringomyelia causes cape-like loss of pain and temperature sensation along the back and arms. Furthermore, motor deficits in the upper limbs are disproportionately greater than the lower limbs. In our patient, her pain and temperature senses were intact. She had no motor deficits and she presented with altered mental status and confusion, which are atypical of syringomyelia. Syringomyelia has MRI features such as the presence of a cyst in the spinal cord parenchyma.⁷ The presence of fluid flow voids or cysts, which reflects the pulsatile movements of syrinx fluid, can be seen in

up to 40% of patients.⁸ Our patient's clinical and MRI findings were not consistent with that of syringomyelia.

To diagnose MS, clinical features and imaging findings that are consistent with lesions disseminated in space and time are required. MS was an important potential diagnosis to consider for our patient, but she did not have a history of recurrent episodes of neurological deficits and optic neuritis. Although MS has preferential involvement of the cervical cord and posterior column, it rarely exceeds 2 segments in length.⁹ This is different from our patient's MRI features, which showed long segment spinal cord involvement. Furthermore, the presence of oligoclonal bands in the cerebrospinal fluid (CSF), and/or an MRI of the brain demonstrating additional lesions at periventricular, juxtacortical/cortical and infratentorial are required for the diagnosis of MS. Our patient's brain MRI was normal and CSF oligoclonal bands was negative.

NMO usually presents with long segment, contrast-enhanced spinal cord lesions on the MRI, especially for the active lesions.¹⁰ Other common clinical features include optic neuritis, narcolepsy, area postrema and brainstem syndromes. The presence of anti-aquaporin-4 antibody is sensitive and specific to NMO. Our patient had no other clinical and radiological features suggestive of NMO, and her anti-aquaporin-4 antibody was negative.

The diagnosis of SCI is unlikely as her symptom onset was subacute. SCI typically has an abrupt onset to nadir within 12 hours. Although SCI can present with longitudinally extensive lesion on the MRI, posterior column infarcts are rare, and usually occur in older age.¹¹ Our patient is young and has no significant cardiovascular risk factors.

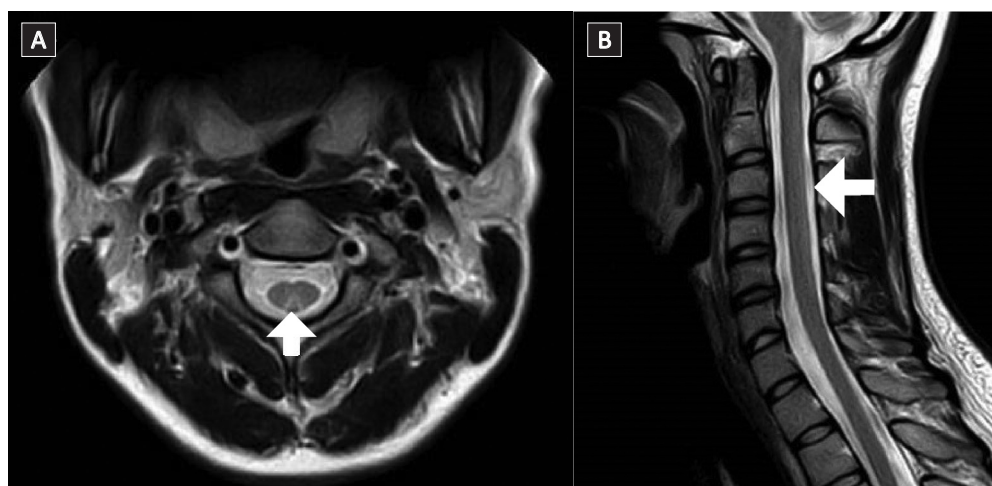


Fig. 2. Magnetic resonance imaging of the (A) axial T2 sequence and (B) sagittal sequence at C3 level showing improvement of T2 hyperintensities (arrows).

The final diagnosis was subacute combined degeneration of the spine from N₂O misuse. After treatment with high-dose methylcobalamin replacement, the patient's symptoms resolved with improvement of MRI findings (Fig. 2).

To the best of our knowledge, this is the second reported case of N₂O misuse from “whippets” in Singapore.¹² Literature has mostly reported incidents of SCD in controlled, anaesthetic environments, while our case highlights the phenomenon of SCD caused by recreational abuse of N₂O.¹³ Given the under-regulated N₂O market and potentially detrimental complications following its misuse, it is therefore important for physicians to be educated about this phenomenon.

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