Case report

Encephalitis secondary to nitrous oxide and vitamin B_{12} deficiency

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SUMMARY

A 27-year-old woman presented with confusion, agitation and fever. Having initially been treated as an infective encephalitis case her initial and subsequent lumbar punctures revealed cerebrospinal fluid with a worsening pleocytosis and elevated protein. It was initially felt she had been suffering from tuberculous meningitis and started on treatment it later became apparent that she had a severe vitamin B_{12} deficiency related to recreational nitrous oxide use. She also was noted to have a peripheral neuropathy. After replacing her vitamin B_{12} and later stopping her tuberculous medication once cultures were negative her cognition and peripheral neuropathy continued to improve.

BACKGROUND

Nitrous oxide is becoming a more common legal high with widespread use particularly among younger populations. It is often viewed as less harmful than some other illicit drugs but this case demonstrates that it can cause severe neurological illness. Clinicians need to be vigilant and take a detailed drug history from their patients. This case demonstrates that fever and abnormal cerebrospinal fluid can be explained by nitrous oxide use and vitamin B_{12} deficiency.

CASE PRESENTATION

A 27-year-old Muslim woman of Ethiopian origin presented to the emergency department in a confused, agitated state. Her initial neurological examination was normal but she was feverish at 38°C, tachycardic at 106 beats per minute and hypotensive at 93/75 millimetres of mercury. There was evidence of cognitive impairment with a Montreal Cognitive Assessment (MOCA) score of 20/30.[1]

A collateral history was obtained early in the admission from the patient's family that revealed she had a 2-week history of lethargy, altered personality, memory loss and altered sleeping pattern. This worsened around 4 days before the admission with fevers, sweating, odd behaviour and inappropriate conversation. Immediately before the admission, she complained of a headache and then collapsed but did not lose consciousness and no seizure like activity was reported. She had not attended her usual workplace as a care assistant in the preceding week due to her illness. It was also reported that she had been using 'balloons' (figure 1) (a method of transferring nitrous oxide from a container for inhalation) more frequently recently with up to 24 canisters of nitrous oxide used each time. No other illicit drug use was reported. She was born in the UK and had last travelled to Ethiopia in October 2017 to visit relatives in Addis Ababa only.

Investigations

Urine beta HCG was negative and blood sugar was normal at 5.7 mmol/L. She was started on ceftriaxone 2 g once daily and aciclovir 750 mg three times per day and a lumbar puncture was performed which revealed a white cell count (WCC) of 10/μL (8 polymorphs: 2 lymphocytes) but normal protein and glucose concentrations. The CSF tested negative for the following infections: *herpes simplex 1 and 2, varicella zoster, cytomegalovirus, adenovirus, enterovirus, Epstein-Barr virus, JC virus, human herpes virus 6, parechovirus, pneumococcus* and *meningococcus* via PCR assays along with *cryptococcal* antigen that was also negative.

Initial bloods revealed a normal C-reactive protein 1 mg/L, WCC of 3.6×10^9/L and Erythrocyte sedimentation rate 8 mm/hour. However, they did show a microcytic anaemia with a haemoglobin of 81 g/L (110–147) and mean corpuscular volume of 75 fL along with a mild neutropenia of 1.34×10^9/L and normal platelet count. Urea and electrolytes, liver function tests, bone profile and clotting were all normal. Malaria antigen screen and blood film were negative. A negative urine toxicology screen for drugs of abuse included morphine, codeine, dihydrocodeine, 6-monoacetyl morphine, methadone, buprenorphine, amphetamine, methamphetamine, 3,4-methylenedioxyamphetamine, 3,4-methylenedioxyethamphetamine, 3,4-Methylenedioxymethamphetamine, diazepam, oxazepam, temazapam, lorazepam, nitrazepam, midazolam, 1-Benzylpiperazine, Methylenedioxypyrovalerone, 4-Methylethcathinone, mephedrone, cocaine, ketamine and cannabis. Serology for HIV, syphilis, hepatitis B surface antigen and hepatitis C antibody was also negative.

Given the marked anaemia she went on to be tested for vitamin B_{12}, folate and ferritin which revealed a severely deficient vitamin B_{12} level of <83 ng/L (187–883). Her ferritin was low at 11 ng/mL (15–204) which also suggested iron deficiency anaemia.

Imaging revealed a normal chest radiograph and CT head scan. MRI of head with contrast was also reported as normal. Given the likely diagnosis of encephalitis she went on to have an electroencephalogram that revealed features of a mild encephalopathy.

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Figure 1 Multiple nitrous oxide canisters and balloons found on a street close to our hospital.

An autoimmune encephalitis screen was negative for the following: *anti-Hu, anti-Yo and anti-Ri neuronal antibodies (blood), Gamma-aminobutyric acid B1, N-methyl-D-aspartate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 1 and 2, Leucine-rich glioma inactivated II and Contactin-associated protein 2 antibodies (CSF), voltage-gated Ca channel antibodies (blood). Her voltage-gated K channel antibody was equivocal 75 pmol/L (0–69).*

Further results later came to light during her outpatient follow-up including a negative interferon gamma release assay (QuantiFERON—QIAGEN) along with PCR, smear and culture for Tuberculosis (TB) on CSF that were all negative.

Differential diagnosis

It was initially felt that she was suffering from a infective encephalitis of bacterial or viral origin. Later when her bacterial culture was negative along with pneumococcal and meningococcal PCR her ceftriaxone was stopped. The CSF picture was also not in keeping with a bacterial picture. Her CSF was also negative for HSV and VZV on two occasions along with an extended viral screen. With this information along with an MRI and EEG out of keeping with a viral encephalitis her aciclovir was stopped. As there was little improvement and her CSF pleocytosis was worsening with a rising protein (table 1), we felt TB was more likely particularly in view of her demographic background and she was switched to empiric TB treatment while we awaited further results. When these came back negative and her peripheral neuropathy improved with B_{12} replacement, we were left with a nitrous oxide-induced B_{12} deficiency as our most likely diagnosis and TB treatment was discontinued.

Table 1 Comparison of CSF findings for patient

Date	20 June 2018	3 July 2018
WCC	10/µL	53/µL
Polymorphs	8/µL	<1/µL
Lymphocytes	2/µL	53/µL
Culture	No growth	No growth
CSF protein	0.3 g/L (0.15–0.40)	5.7 g/L (0.15–0.40)
CSF glucose	2.2 mmol/L (2.2–3.9)	3.0 mmol/L (2.2–3.9)
Serum glucose	Not done	4.5 mmol/L (3.9–5.8)
Opening pressure	22 cm H_2O	Not performed as sat upright

CSF, cerebrospinal fluid; WCC, white cell count.

Treatment

She was initially started on ceftriaxone and aciclovir on admission due to concerns about an infective encephalitis. Given the lack of improvement on ceftriaxone (3 days) and aciclovir (7 days), the negative results, the high protein and increased CSF WCC (table 1) it was decided to treat her empirically for tuberculous meningitis and she was started on standard treatment with voractiv (rifampicin, isoniazid, pyrazinamide and ethambutol) and pyridoxine. Her severely deficient vitamin B_{12} was replaced initially with intramuscular hydroxocobalamin 1 mg three times weekly for 2 weeks. There was steady but slow improvement over 2–3 weeks. While she regained insight relatively quickly there were still concerns about her ability to cope independently at home. Before being discharged home her MOCA was repeated and had improved to 29/30 and she was also re-examined and found to have a bilateral peripheral neuropathy to light touch from her patella down but with intact proprioception. Reflexes were absent at the knee and ankle and a 3/5 power was noted bilaterally in dorsiflexion. This may have been present earlier but missed as she was agitated and not fully compliant with examination on initial presentation.

OUTCOME AND FOLLOW-UP

Her peripheral neuropathy had significantly improved with B_{12} replacement with a repeat level of 255 ng/L 4 months after hospital discharge.

Given the above information, it was felt that her symptoms were most likely to be explained by nitrous oxide abuse causing a severe vitamin B_{12} deficiency and encephalitis that settled following replacement of B_{12} and abstinence from further nitrous oxide. Her antituberculous medication was therefore discontinued after 5 months. At follow-up 2 months after stopping her antituberculous medication, she remained well and was discharged from the clinic.

Discussion

Nitrous oxide was first synthesised in the 18th century and later developed as an anaesthetic agent in the late 19th century becoming popular for use in childbirth.[2] It is still used today as an analgesic in the modern healthcare setting, for example, in obstetrics with childbirth or trauma when relocating a joint. More recently, it has become increasingly popular as a 'legal high'.[3] The active form of vitamin B_{12} contains cobalt in a reduced form (Co^{+}). Nitrous oxide can cause irreversible oxidation to the Co^{++} and Co^{+++} forms that results in vitamin B_{12} being inactive. While there are several case reports documenting its ability to cause a peripheral neuropathy due to the interaction with hydroxycobalamin, encephalitis is less common.[3–6]

The initial impression that this patient's symptoms were due to an infectious aetiology became less likely as investigation results and additional history became available.

The persistent fever and abnormal CSF findings made it difficult to discount infection entirely. While there are a few case reports of the association of fever with severe B_{12} deficiency, this is not widely appreciated by clinicians or in the literature.[7 8] The mechanism is unclear though it has been proposed that fever in megaloblastic anaemia could be a result of hyperplasia leading to increased activity within the bone marrow and systemic fever.[7] It is possible that having a period in hospital without any nitrous oxide allowed her to recover along with replacement of her

vitamin B_{12}. Few case reports have documented serial lumbar punctures on the same patient and extensive encephalitis workup for these patients making this case novel.

While mildly elevated CSF protein has been described before in patients suffering from subacute degeneration of the spinal cord secondary to nitrous oxide-induced vitamin B_{12} deficiency our patient developed a significantly higher protein level than has been described before.[4] The other striking abnormality was a worsening pleocytosis on repeat CSF testing (table 1). Again other reports of neurological complications from nitrous oxide-induced B_{12} deficiency have observed acellular CSF.[3 4 9] While it is possible that both these abnormalities were related to a different cause an extensive screen for alternative diagnosis did not yield anything else. Furthermore, she significantly improved after cessation of nitrous oxide and replacement of her vitamin B_{12} lending further weight to the diagnosis.

With regards to her vitamin B_{12} level of <83 ng/L (187–883) reported the vitamin B_{12} levels of 12 patients in a case series the majority of whom had low levels but none as low as our patient's.[4] It is possible that this exceptionally low level resulted in a slightly different clinical and CSF picture than has been described before. The rise in CSF protein and cell count on the repeat lumbar puncture may be reflective of a lag phase between the pathological process and inflammatory response.

It is worth mentioning that her cultural background may have led to a false assumption that she would not have abused any recreational drugs and had it not been for family members providing this additional information it could have been missed here particularly as the standard drugs of abuse screen would not have picked up the nitrous oxide use. Others have highlighted this cultural issue such as one study that describes significant use in the Bangladeshi population of East London and postulated whether genetic, metabolic or nutritional differences could influence functional vitamin B_{12} metabolism and predispose to neurological damage.[4]

In conclusion, our case demonstrates the ongoing concern between excessive nitrous oxide use and neurological abnormalities secondary to the effect on B_{12} metabolism in young patients. The novel features of this case were the serial lumbar punctures showing a changing picture with worsening pleocytosis and elevated protein and the altered mental state with fever giving a diagnosis of encephalitis. While it was initially felt her symptoms and CSF findings could fit with TB this was disproved on lab testing. TB treatment was continued until the final results of CSF culture were available and reported negative which took several weeks. This result along with negative radiology and immunology investigations for TB made it more unlikely that any improvement was as a consequence of the TB treatment.

Patient's perspective

'I feel a lot better now compared to how I was when I was on the ward. The feeling in my feet and legs has got much better and I'm back at work now. I definitely won't be taking any more laughing gas—I'm staying away from that now'.

Learning points

- Nitrous oxide is a recognised cause of vitamin B_{12} deficiency.
- Vitamin B_{12} deficiency can cause fever in some patients.
- Abnormal cerebrospinal fluid findings can be due to non-infective aetiology such as nitrous oxide and vitamin B_{12} deficiency.
- A detailed drug history needs to be taken from all patients regardless of demographic background.

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