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Understanding nitrous oxide induced subacute combined degeneration of the cord: Two case reports with a review of the pathophysiology and MRI features

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Abstract

Introduction

There has been an increase in reports of N2O gas misuse with subsequent increase in neurological presentations.

Cases

Case 1: 21-year-old female with gradual lower limb weakness and loss of sensation.

Case 2: 19-year-old male with ataxia and lower limbs proprioception abnormalities.

Outcome

Both cases showed laboratory results of anaemia and functional vit B12 deficiency in addition to radiological evidence of spinal, mainly cervical, demyelination consistent with subacute combined degeneration of the cord (SCD).

Discussion

N2O induced SCD is a rising problem, the gas causes vitamin B12 dysfunction leading to demyelination which, with long term misuse, may result in permanent neurological damage. Laboratory results and MRI are helpful in diagnosing SCD. It is treatable if early detected and gas misuse stopped. Further investigation and multidisciplinary collaboration are recommended to properly outline and maybe control this problem.

Introduction

Nitrous oxide is a gas known historically for its use in the medical field as an anaesthetic. It was also introduced in the food industry because of its antibacterial properties [1]. However, recently it is reported that there has been an increase in recreational use among young population in many parts of the world, and a survey conducted by the Global Drug Survey (GDS) displayed the pattern of use and harms associated with misusing the gas [2–4]. In Ireland,

according to the European Monitoring Centre for Drug and Drug Addiction, it is believed that the number of nitrous oxide misuse increased at the pre Covid -19 lockdown as a result of young people congregations [5]. The gas is known for its anaesthetic and anxiolytic effects, however, its ability to produce euphoria, dissociated feeling and change in perception in body image were some of the reasons that led to its abuse [2]. It affects the immune, haematology, reproductive and nervous systems [6]. Neurotoxicity is the most concerning as the damage could be permanent[5]. Subacute combined degeneration of the cord (SCD) is a condition caused by prolonged nitrous oxide inhalation which alter vitamin B12 synthesis and as a result affecting myelination [7]. We present two cases of SCD secondary to nitrous oxide (N_2O) inhalation.

Case 1

The first patient was an 18-year-old young female who presented to the emergency department with an ataxic gait, intermittent loss of power and impaired sensation in the lower limbs. She admitted using nitrous oxide frequently. Symptoms started 3 weeks prior with decreased lower limb sensation and lower respiratory tract infection. The symptoms started gradually distally ascending proximally with symptoms more prominent on the Rt side. The patient denied limb weakness, altered bowel or bladder dysfunction. On examination power was intact bilaterally at all levels with dampened reflexes on her Lt lower limbs and intact right reflexes. Poor coordination also reported in the lower limbs and the gait was mildly ataxic. The patient had distal and for a lesser degree proximal lower limb weakness.

Her blood was investigated targeting vit B12, Folate, Homocysteine and Methylmalonic Acid (MMA) with the results showing normal vit B12 levels, increased homocystinuria and decreased serum folate.

The patient also performed nerve conduction studies which showed demyelination and some block predominantly in the lower limbs with slowing of sensory conduction velocities. Magnetic resonant imaging (MRI) scan was ordered and reported high T2 Weighted Image (T2WI) signal in the dorsal column extending from the craniocervical junction down to the level of C7, with inverted V shape configuration. Associated patchy high signals also seen within the thoracic spine confirming the diagnosis of SCD. Vit B12 injection protocol was initiated (immediately then alternating days for 2 weeks, follow up very 2 weeks). The patient reported improvement after treatment mainly with sensation in his first follow up.

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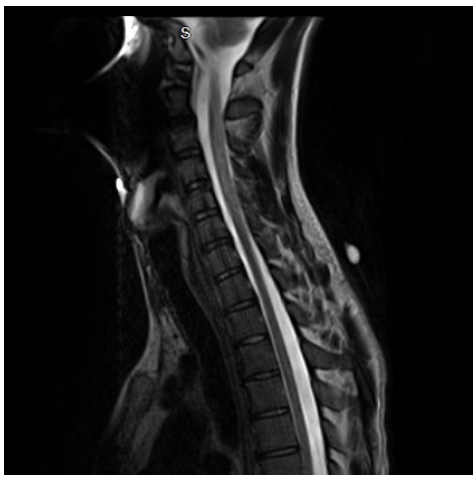


Figure 1a

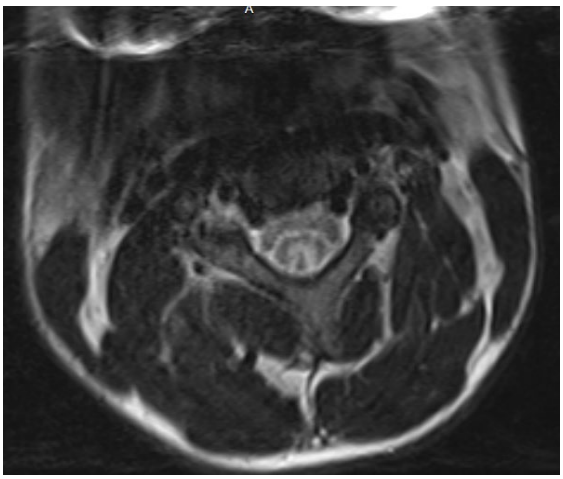


Figure 1b

Figure 1. Cervical MRI, Sagittal T2WI demonstrates abnormal signal within the posterior aspect of the cervical cord (a), while the second image shows characteristic inverted V shape of the posterior column in axial views (b).

Case 2

The second patient was another 21-year-old young man who was admitted due to ataxia and proprioception abnormalities of the lower limbs and showed neurological signs reflecting that. Upon questioning, the patient admitted recent nitrous oxide inhalation in the past 3 weeks.

Laboratory results showed normal levels of vit B12. It also showed decreased Red Blood Count (RBC), Mean corpuscular Haemoglobin (MCH) and Mean Corpuscular Volume (MCV) levels suggesting microcytic anaemia. In addition, an increased homocysteine and decreased serum folate levels were also noted in favour of functional deficiency.

Computed tomography (CT) and MRI brain scans showed no abnormalities, however cervical and thoracic spine MRI reported diffuse posterior column high signal seen as low as T11 level again consistent with N_2O induced SCD. Figure 2.

Standard treatment protocol with vit B12 was initiated with additional folate supplements with neurological follow up and reassessment recommended in the next 2 weeks.

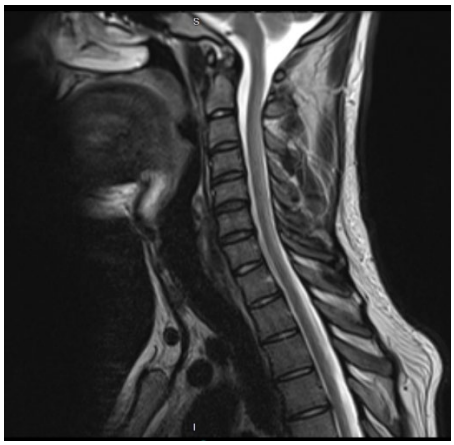


Figure 2a

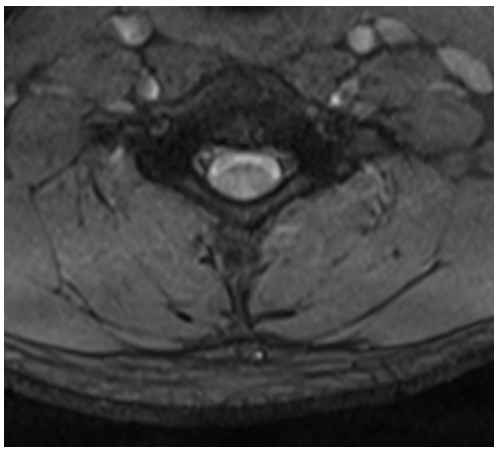
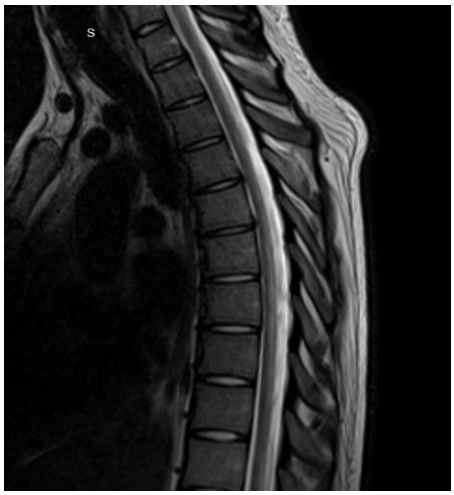


Figure 2b.



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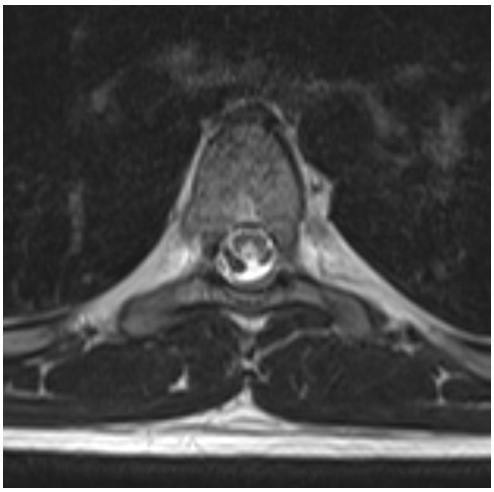

Figure 2d.

Figure 2. Cervical MRI sagittal images with diffuse posterior cord high signal (a) and posterior column high signal with less distinct inverted V shape (b), Thoracic MRI sagittal image posterior cord signal as low as T11(c) and posterior column pyramid shape high signal in axial images (d).

Discussion

Nitrous oxide affects the nervous system peripherally by causing polyneuropathy and centrally by causing demyelination of the cord. Neurological symptoms are mostly reported with heavy users inhaling the gas in a period of time ranging from weeks to years [5]. The main mechanism for neural damage is altering vit B12 synthesis which has a vital role in myelin formation [8]. There are two active forms of vit B12 in the body, and myelin dysfunction seems

to result from altering both forms which are Methyl- vit B12 (Met B12) and 5-deoxy-5-adenosylcobalmin (Ado B12).

Both forms, Met and Ado, act as a co-enzyme or a co-factor to a specific enzyme. In the case of Ado B12, the enzyme is Methylmalonyl -CoA Mutase (MMCoAM) which convert Methylmalonyl-coenzyme A (MMCoA) into Succinyl-coenzyme A. Deficiency of Ado B12 results in accumulation of MMCoA , therefor the formation of abnormal fatty acids affecting normal myelin formation[6,8], explained in Diagram 1.

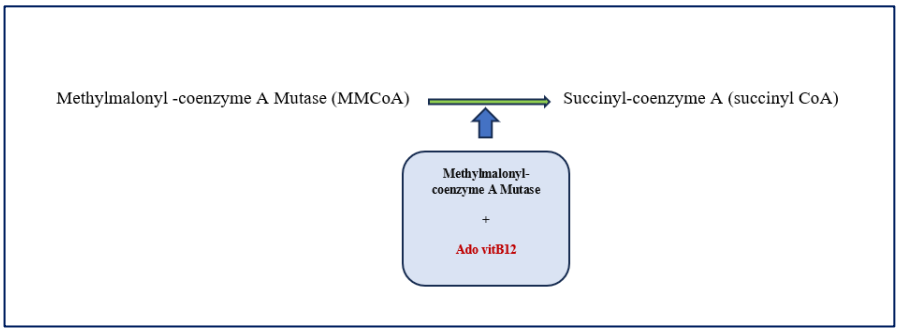

Diagram1. Ado vit B12 pathway.

This is one way of forming abnormal myelin due to vit B12 deficiency. The other method as mentioned earlier is affecting the other active form of the vitamin which is the Met B12. This mechanism is believed to be the primary cause of SCD due to N_2O inhalation in which the gas oxidises the cobalt ions of vitamin B12 causing irreversible deactivation of its active form, explained in Table 2. As with Ado B12, in Met B12 dysfunction, the affected enzyme is Methyl-Tetrahydrofolate-homocysteine Methyltransferase (MTR) which transforms homocysteine into methionine, the primary element of myelin sheath stability, and transforms methyl-tetrahydrofolate into tetrafolate and that is responsible for DNA synthesis, cell turnover [8] , oligodendrocyte growth and thus myelin synthesis [9].

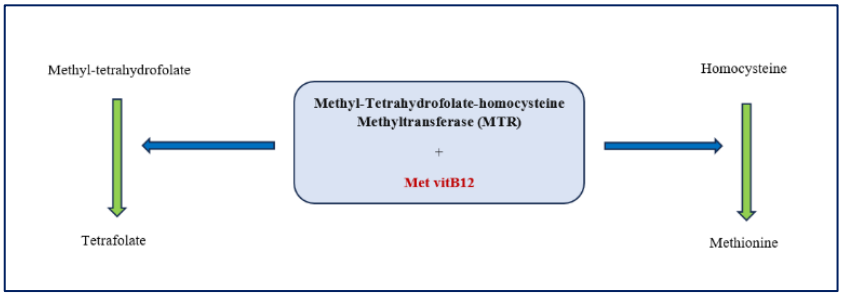

Diagram 2. Met vit B12 Pathway.

The gas is rapid and short acting with peak results in seconds after inhalation, lasting for few minutes afterwords. The adverse effects are related to using large amount of gas in a single session. Chronic abuse can cause neurotoxicity, acute poisoning is uncommon but acute presentation secondary to barotrauma and pneumomediastinum was observed[1]. Deaths due to N_2O inhalation is rare. Enhancing the gas effect is reported by a adding other substances such as alcohol[5].

The demyelination process can present as isolated peripheral, isolated central namely SCD or as a combination of both [1,4]. Peripherally, axonal neuropathy and mainly sensory neuropathy was reported [7,9]

Centrally, it affects primarily the cord. A study reported possible cortical abnormalities but mainly in the form of delayed response [9].

Subacute combined degeneration of the cord (SCD) is a clinical condition resulting from vit B12 deficiency, therefore any abnormality in the synthesis of this vitamin will result in demyelination and the accumulation of abnormal fatty acids as explained earlier. When the posterior column is affected, the main presenting symptoms would be loss of proprioception, unsteadiness and numbness which is typical in many cases including ours[7,10]. Patients may present with symptoms of hypo or hyperreflexia, in addition to weakness[4]. This symptom indicates lateral column involvement.

In terms of blood testing, vit B12 status in the body is always investigated by testing plasma vit B12, homocysteine and methylmalonic acids (MMA). The homocysteine and MMA were usually tested if vit B12 results were normal, suggesting functional abnormality. Other tests include blood count, electrolytes and other routine investigations. Folate is also included[4].

MRI of the spine is a very valuable tool to diagnose SCD, it is frequently reported that demyelination usually involves multiple continuous segments especially in the cervical cord with characteristic inverted V sign [3,4,6,8,9].

The posterior column of the cervical cord is the most affected followed by the lateral column and rarely the brain stem [3,6,8,9]. In a study, in addition to spinal involvement, abnormal hyperintense signal surrounding the 4th ventricle was reported, which then disappeared in post treatment follow ups [9].

MRI protocol of the spinal cord universally include sagittal and axial T2 weighted images, the latter is particularly appropriate in showing the inverted V signal of demyelination[4]. In some centres, T1 weighted images with contrast is added to the protocol, but no enhancement appreciated in the affected segments [9].

In a case series, MRI of the brain was either normal or showing hyperintense white matter in T2 fluid attenuated inversion recovery (FLAIR) sequence in the frontal, periventricular and centrum semiovale areas[4].

Regardless of MRI's usefulness in diagnosing SCD, it is thought that without collateral laboratory abnormalities, it would be less helpful in differentiating N_2O SCD from other myelopathic disorders. It is important to highlight that normal results of vitamin B12 does not exclude SCD as functional deficiency can occur with normal serum B12 levels[3]. This functional deficiency can be diagnosed by the high levels of serum homocysteine and methylmalonic acid[1].

Differentiating the classical SCD (resulting from vit B12 deficiency) from nitrous oxide induced- SCD could be challenging as well, however, it is found that N_2O induced SCD tends to involve the thoracic segments less, has wider involvement in sagittal views with fewer spinal segments with lesions and a higher rate of inverted V sign[4].

It is worth mentioning that N_2O induced neurological damage could be reversable with improved and even resolved associated MRI findings[6,8–10].

According to European Monitoring Centre for Drug and Drug Addiction, there are no established guidelines for treatment nitrous oxide toxicity. Managing such patient is a multidisciplinary task and involves medical treatment in the form of supplemental vit B12, physiotherapy and psychological support.

The main playing factor is the cessation of the gas inhalation and early treatment[1,5,6,8].

Management of SCD include medical treatment with vit B12 supplements. Folic acid was introduced to patients with anaemia. Management also incorporated physiotherapy in patients with permanent or semi-permanent disabilities[1]. Counselling and education were provided and patients were informed and understood that their condition was a result of N_2O abuse. The length of treatment differ between cases depending on the severity of the disease and abstinence from the gas, this is why follow up is important[4].

The journey of a patient with N_2O induced SCD in the health system starts with the general practice or the emergency department which involves investigations and scans, it also incorporates neurology evaluation in addition to physiotherapy, depending on the disability caused by the disease. Psychologic intervention offered for cases struggling with the abuse[1]. After discharge the patient is expected to engage with local drug and alcohol services along with outpatient appointments and injections. Paris et al. elicits a good example for N_2O SCD pathway where neurology consultation and weekly multidisciplinary meetings are performed.

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Larger scale research around the incidence and epidemiology of N_2O toxicity is highly recommended, this requires collaboration of multiple teams, allowing the opportunity to assess the influence of the N_2O abuse on the health system and community.

N_2O induced SCD is a preventable condition, sadly affecting an important sector of the society, the productive age group. Public health awareness and community recognition of this problem is crucial as health facilities receives more frequent cases in recent years.

In conclusion, N_2O induced SCD is a rising problem. It is the result of long-term gas abuse. The main mechanism is altering normal vit B12 synthesis which is responsible for normal myelination. The disease is diagnosed by investigating serum vit B12, in addition to homocysteine and methylmalonic acid (MMA), which indicates functional deficiency, in other word, inactivated vit B12. MRI is an excellent means to assess the spine in symptomatic cases and to exclude other pathologies. Patients diagnosed with SCD are treated medically by vit B12 supplements in addition to physiotherapy and psychological support in difficult cases. Although no recent data or statistics available to confidently act against nitrous oxide public availability, seeing more recent cases in young age groups encourages more investigation in this matter thus more research and multiple disciplines should engage.

Declaration of Conflicts of Interest:

None declared.

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