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Case Report

Reversible nitrous oxide myelopathy and a polymorphism in the gene encoding 5,10-methylenetetrahydrofolate reductase

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We present a case of a patient who received nitrous oxide on two occasions within a period of 8 weeks and who subsequently developed a diffuse myelopathy, characterized by upper extremity paresis, lower extremity paraplegia and neurogenic bladder. Laboratory testing revealed hyperhomocysteinaemia and low levels of vitamin B_{12}. Because of this uncommon clinical presentation, we analysed the patient's DNA, and found a polymorphism in the MTHFR gene that is associated with the thermolabile isoform of the 5,10-methylenetetrahydrofolate reductase enzyme, which explained the myelopathy experienced by the patient after being exposed to nitrous oxide. Soon after initiating supplementary therapy with folic acid and vitamin B_{12}, the neurological symptoms subsided.

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The enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) (Enzyme commission 1.5.1.20) catalyses the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the predominant circulatory form of folate and carbon donor for the re-methylation of homocysteine to methionine.[1] Nitrous oxide (N_2O) irreversibly oxidizes the cobalt atom of vitamin B_{12}, thereby inhibiting the activity of the cobalamin-dependent enzyme methionine synthase, which catalyses the latter reaction (Fig. 1).[2] Methionine, by way of its activated form, *S*-adenosylmethionine (SAM), is the principal substrate for methylation in many biochemical reactions, including assembly of the myelin sheath, methyl substitutions in neurotransmitters, and DNA synthesis in rapidly proliferating tissues.[2]

We present a patient with a polymorphism in the gene coding for MTHFR, who presented with an acute myelopathy after being repeatedly exposed to N_2O during successive surgical procedures and recovered almost *ad integrum* after treatment with vitamin supplementation.

Case report

A 52-yr-old male, ASA I, developed symptomatic cervical intervertebral disc herniations and spinal stenosis at C4, C5 and C6, that produced bilateral distal sensory deficit in the C6 and C7 dermatomal distribution. This was further confirmed with electromyography, a computed tomography scan (CT scan) and magnetic resonance imaging (MRI) which showed C4–C5/C5–C6 intervertebral disc herniations and a 8 mm spinal stenosis at C6 level. The patient underwent surgery with general anaesthesia. The drugs used at induction of anaesthesia were etomidate, fentanyl and atracurium. The patient's trachea was intubated and anaesthesia was maintained with isoflurane and 50% N_2O in oxygen for an uneventful procedure that lasted 200 min. At the conclusion of the operation, the tracheal tube was removed, and the patient was transferred awake to the postoperative care unit, with no neurological deficit.

Two weeks after surgery, the patient complained of paraesthesia of the lower extremities associated with an ataxic gait, which got worse in the ensuing 8 weeks. At that time, the surgical team performed a laminectomy on the same area because of worsening of the symptoms. The presumptive diagnosis was spinal stenosis myelopathy. The anaesthetic technique included the use of thiopental, fentanyl and atracurium at induction, oral tracheal intubation and maintenance with isoflurane and 50% N_2O in oxygen. The procedure lasted 105 min. Soon after surgery,

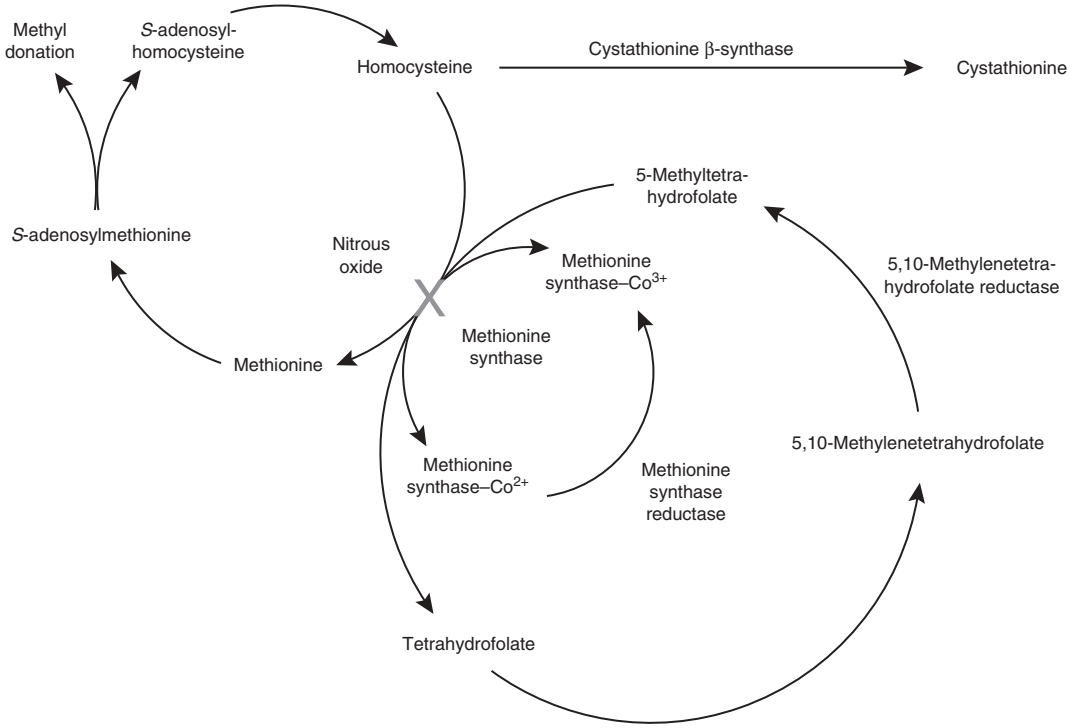

Fig 1 The folate and homocysteine metabolic cycles and the enzymatic site of N_2O toxicity. Co denotes cobalt.[2]

neurological examination showed mild quadraparesis, predominantly involving the lower extremities, associated with neurogenic bladder that required an indwelling bladder catheter.

Three weeks after the second operation, the patient was admitted to our institution because of left leg deep vein thrombosis and symptoms of bladder obstruction. The patient exhibited bilateral progressive paraparesis leading to paraplegia. There was a proprioceptive and vibration sensory deficit at T1 and below, hypo-aesthesia to all sensory modalities below T5, an absent patellar reflex, enhanced Achilles tendon reflex, bilateral Babinski's sign, and neurogenic bladder. Laboratory examination revealed macrocytic anaemia, hyperhomocysteinaemia: 113 μmol litre^{-1} (normal: 4.0–14.5 μmol litre^{-1} in men), low plasma vitamin B_{12} concentration (<60 pg ml^{-1}, normal: 200–900 pg ml^{-1}) and normal plasma folate concentration (9.5 ng ml^{-1}, normal 5.3–14.4 ng ml^{-1}). Imaging studies showed a normal thoraco-lumbar CT scan and a diffuse and extensive hyperintense cervico-thoraxic image on T2 weighted spinal MRI, suggesting a diffuse myelopathy.

Five cycles of methylprednisolone had been given since the initial presentation, for a presumptive diagnosis of an inflammatory demyelinating syndrome. After no obvious improvement, the neurologists began a trial with supplementary therapy with vitamin B_{12} and folic acid, on the basis that the low plasma vitamin B_{12} concentrations and the prior exposure to N_2O may have contributed to the injury. The patient had a slow but progressive motor recovery but with little change in the sensory deficit and the neurogenic bladder. The patient was discharged home with vitamin B_{12} and folic acid supplementation, as well as intermittent catheterization of the bladder and physical therapy.

Six months later, the patient had no motor deficit, normal bladder and sphincter functions; however, he still had proprioceptive deficits in both legs, with minimal ataxia and normal deep tendon and plantar reflexes. By this stage his daily activities were unimpaired. At 5 yr follow-up, the neurological exam was unchanged. His current treatment is a monthly injection of vitamin B_{12} and daily folic acid supplementation. His most recent laboratory results are: homocysteine: 5.7 μmol litre^{-1} (normal: 4.0–14.5 μmol litre^{-1} in men); plasma vitamin B_{12}: 1029 pg ml^{-1} (normal: 200–900 pg ml^{-1}); haematocrit: 40.6% with normal sized and shaped erythrocytes.

Because of this uncommon clinical presentation, we decided to analyse the patient's DNA for possible abnormalities in the gene coding for MTHFR.

Preparation and sequence analysis of genomic DNA

After Institutional Review Board approval, genomic DNA was isolated from the patient's blood using standard extraction techniques. Each of the 11 exons of the MTHFR gene located on chromosome 1p36.3, were amplified from genomic DNA by the polymerase chain reaction (PCR) with the use of pre-designed intronic primers that have