Postoperative myeloneuropathy: a preventable complication in patients with B₁₂ deficiency

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Two cases of postoperative neurological deterioration following routine neurosurgical procedures are presented. In each instance, the patient was found to have hematological abnormalities present preoperatively consistent with vitamin B₁₂ deficiency and to have undergone general anesthesia involving N₂O. This caused inactivation of the remaining marginal stores of B₁₂ with resultant neurological decompensation. The frequent use of N₂O in general anesthesia and the significant incidence of B₁₂ deficiency make it imperative that the surgeon be aware of this complication and its easy prevention. The preoperative recognition of B₁₂ deficiency and N₂O-induced neurological deterioration in patients with B₁₂ deficiency is reviewed.

KEY WORDS: vitamin B₁₂ deficiency, anesthesia, nitrous oxide, anemia, spinal cord degeneration, neuropathy

Since the article by Lassen, et al., in 1956, a gradual understanding of N₂O toxicity and its relationship to vitamin B₁₂ deficiency has emerged. Nitrous oxide inactivates vitamin B₁₂, and in the B₁₂-deficient patient normally nontoxic doses of N₂O can cause neurological deterioration. This provides the rationale for the recommendation that N₂O is contraindicated in the B₁₂-deficient patient. However, this has been reported only recently in the literature and remains poorly recognized. It would seem that neurosurgeons in particular should be aware of this effect, as they daily evaluate and operate on patients with neurological deficit. Neurological deficits in a neurological practice are most often due to structural lesions such as a herniated disc, spondylosis, trauma, or tumor. Vitamin B₁₂ deficiency can mimic these lesions or be totally asymptomatic. Therefore, it is important that the neurosurgeon be familiar with the symptoms and laboratory abnormalities seen in B₁₂ deficiency. To this end we review the clinical course of this disease.

Clinical Features of B₁₂ Deficiency

Vitamin B₁₂ deficiency can occur as a result of pernicious anemia, gastrectomy, resection or disease of the ileum, bacterial overgrowth, fish tapeworm, blind-loop syndrome, or defective binding by tissue, liver, and serum proteins. Of these, pernicious anemia is the most common cause in temperate climates. Its incidence in the general population is 0.1% to 0.2% but this rises to 10% in the over 60-year-old group. This condition is most common in people of northern European descent, with an equal male to female ratio, and an average presenting age in the sixth decade of life. It is thought to be an autoimmune process directed against the gastric parietal cells which produce the intrinsic factor necessary for absorption of B₁₂ in the distal ileum.

The effects of B₁₂ deficiency can be divided into gastrointestinal (GI), hematological, and neurological dysfunction. Briefly, GI disease is manifested by a sore beefy red tongue, anorexia, weight loss, and diarrhea. The hematological picture can vary. The hemoglobin can be within normal levels or be so low as to cause symptoms of angina and congestive heart failure. There is, of course, an elevated mean corpuscular volume, mean corpuscular hemoglobin, and decreased B₁₂ levels. There may be abnormal red cell formation, moderate eosinophilia, and hypersegmented polymorphonuclear cells seen in the peripheral smear. The presence of hypersegmented polymorphonuclear cells can precede red cell abnormalities. There can be leukopenia (4000 to 5000 leukocytes cu/mm) and thrombocytopenia. The bone marrow can show megaloblastic and erythroid hyperplasia, as well as abnormal myeloid and megakaryocytic elements.

Neurological changes can occur in the face of a normal hematocrit. The neurological dysfunction is due to progressive demyelination, sometimes followed by axonal loss. In subacute combined degeneration of the spinal cord this begins in the lower cervical and
Deterioration from $B_12$ deficiency and $N_2O$ use

upper thoracic cord, starting in the posterior columns and spreading anteriorly to involve the lateral and anterior cord. The process spreads up and down the cord as well. This same process can also affect the peripheral nerves and, more rarely, the brain.33

The progression of pathological change in the spinal cord is reflected in the course of the disease.6 This results in a clinical picture of a myelopathy combined with a polyneuropathy. The condition begins with numbness and paresthesias in the extremities, which are generally symmetrical and start distally. The legs are generally affected earlier and more severely. Rarely, the patient can even develop a sensory level. This is followed by unsteadiness of gait, poor finger coordination, and stiffness and weakness of the limbs. Bowel and bladder dysfunction can also occur.

The physical examination reflects the march of the disease process from the dorsal columns anteriorly into the cord.6 Early in the disease, the physical examination can be normal. Loss of vibratory sense in the legs is generally the first sign and progresses to involve the trunk and arms as well. Proprioception becomes impaired. Weakness and spasticity then develop. Reflexes can be increased, decreased, or normal as the effects of the myelopathy and the neuropathy are balanced. The toe reflexes are upgoing.

In addition, the disease process may affect the brain and optic pathways.6 A wide range of change in mentation can occur, including irritability, apathy, somnolence, suspiciousness, confusion, intellectual deterioration, and even psychosis. There can be visual changes, which can occasionally be the first or sole manifestation of $B_12$ deficiency. This ranges from an asymptomatic abnormality in the visual evoked potentials (VEP's) to a symmetrical centrocecal scotoma and optic atrophy.

Electrophysiological studies also reflect the progression of disease. Each test may be normal but, as the demyelination and axonal loss proceed, each becomes abnormal. Limited testing has been reported in the literature, but the somatosensory evoked potentials may represent an early and sensitive indicator. The $N_1$ component, which measures the integrity of the dorsal columns, is delayed. The lower extremities are more severely affected. The electromyogram (EMG) and nerve conduction velocity studies show an axonal degeneration peripheral polyneuropathy.12 The VEP's can be abnormal in pattern with a mild delay even in the asymptomatic patient.12,21 The brain-stem auditory evoked potentials are involved more rarely and only in the more severely affected patients.21 There is a delay of V wave latency and a prolonged I-V wave interval. In a small series, these abnormalities were seen to improve with treatment.21

We present the cases of two patients who had presumably symptomatic structural lesions and coexisting undiagnosed $B_12$ deficiency. Each underwent spinal surgery and suffered neurological deterioration as a result of the use of $N_2O$ during general anesthesia.

Case Reports

Case 1

This 54-year-old woman presented with an 8-month history of progressive painful paresthesias which started in her neck and traveled down both arms, more on the right than the left, to her thumb and index finger. Over the month prior to admission, she developed numbness in her legs and loss of balance. She denied weakness or loss of bladder control.

Her medical history is significant for an 8-year history of diabetes, and for a cholecystectomy, appendectomy, tonsillectomy, and nephrectomy for renal lithiasis. Her only medication was tolazimide. She denied alcohol or tobacco abuse.

Examination. The patient's general examination was unremarkable except for pain on palpation of the lower cervical spine and decreased range of motion. Her neurological examination revealed a normal mental status and intact cranial nerve function. She had 5/5 motor strength throughout, and sensation was intact to light touch and pinprick. Her reflexes were 2+ in the upper extremities and 3+ in the lower extremities. There was no clonus but the toes were upgoing and she had a Hoffmann’s reflex bilaterally. A cervical magnetic resonance (MR) image demonstrated a large ventral extradural defect located centrally and to the right at C5–6, causing cord compression. This was believed to correspond to the radicular numbness and explain the myelopathy. The patient was therefore scheduled for surgery.

Operation. The patient underwent a C5–6 anterior cervical decompression and fusion lasting 2 hours 15 minutes under general anesthesia with 50% $N_2O$, fentanyl, morphine, forane, and vecuronium. The intraoperative course was uneventful with stable blood pressure and oxygen saturation levels of 100%. A calcified ligament was found to be responsible for the thecal sac compression which was relieved with removal of the mass. A postoperative film revealed the bone plug to be in good position. The patient noted in the recovery room that her upper extremity symptoms had resolved. She was discharged on postoperative Day 1 with no significant change in her neurological examination.

Postoperative Course. Sixteen days later, the patient was readmitted with marked worsening of her myelopathy. Her weakness and spasticity had progressed so that she was unable to walk and had developed urinary retention. Her upper extremity symptoms had not returned. Upon further questioning, she recalled that for the past 4 months she had noted blurred vision and difficulty in concentrating. Her examination was now markedly abnormal. Upper extremity strength remained at 5/5 but hip flexion and dorsiflexion were now 4/5 and plantar flexion was 3/5. She had abdominal fasciculations and increased tone in her legs. Sensation in the upper extremities was intact but she had decreased light touch, pinprick, vibratory sense, tem-
perature sense, and position sense in her legs. Reflexes were 3+ in the arms and 4+ in the legs. Her toes were upgoing. She could stand but could not walk. Her mental status and cranial nerve function were intact.

An extensive re-evaluation was performed. Dislocation of the bone plug or a new herniated disc was ruled out with plain films and a cervical MR image. An EMG was unrevealing. The VEP's showed an abnormal pattern bilaterally with a mild delay. Laboratory studies showed a hemoglobin of 10.1 gm/100 ml with a mean corpuscular volume of 127 cu um and 3+ macrocytosis. The preoperative laboratory results were reviewed and it was found that, although she had a normal hemoglobin of 12.2 gm/100 ml, her mean corpuscular volume was elevated at 122 cu um (normal 82 to 97 cu um). The B12 level was less than 50 pg/ml (normal 200 to 950 pg/ml) and the folate level was less than 24 ng/ml (normal 2 to 17 pg/ml). A Schilling test revealed pernicious anemia.

The patient was begun on a course of B12 injections and was started in a rehabilitative program. The examination and laboratory study abnormalities improved slowly with replacement therapy. She was discharged ambulatory with a walker but still requiring intermittent catheterization.

Case 2

This 46-year-old woman presented to an outside neurosurgeon with a 3-month history of low-back pain and a right S-1 radiculopathy. She denied a history of trauma, bowel or bladder incontinence, or other neurological symptoms. She had failed a trial of conservative treatment. Her examination revealed a positive straight-leg raising test on the right at 60° and a dropped right ankle jerk. Her radiological evaluation revealed a right L5-S1 herniated disc.

She underwent an L5-S1 discectomy under general anesthesia for 2 hours using 50% nitrous oxide. Postoperatively, she had resolution of her back pain and radiculopathy but developed numbness of the upper right thigh and perianal and perivaginal regions, difficulty in walking, dizziness, blurred vision, mild cognitive impairment, and headaches. Her examination revealed sensory loss involving the upper right thigh, buttock, and perianal region. She also had mild diffuse right leg weakness. Her reflexes were 2/4 except for a dropped right ankle jerk. The rest of her examination was normal.

The patient was referred to several neurologists for diagnosis of this problem. Her workup included a lumbar MR image showing postoperative changes, an EMG consistent with a right S-1 radiculopathy, and a vestibular function test which showed left beating nystagmus. She also underwent the following studies, with normal results: computerized tomography and MR imaging of the head, electroencephalography, echocardiography, carotid Doppler ultrasonography, and thyroid function tests. A variety of diagnoses were entertained including arachnoiditis, viral syndrome, positional nystagmus, and a migraine variant. She was treated for 6 months with a variety of medicine including Antivert (meclizine hydrochloride), scopolamine, nortriptyline, verapamil, and diltiazem — all without lasting benefit. Because of worsening dizziness, blurred vision, and difficulty with concentrating, a second workup was initiated. This workup included a B12 level which revealed a value of 106 pg/ml (normal 200 to 1000 pg/ml). Hematocrit was normal at 41.8% but mean corpuscular volume was elevated at 104.5 cu um (normal 80 to 100 cu um). On review, her preoperative laboratory findings revealed these same abnormalities. She was started on a course of B12 injections with improvement in all of her symptoms.

Discussion

The two patients reported here had undiagnosed B12 deficiency and were given N2O during spinal surgery with subsequent neurological deterioration. The first patient had elements of subacute combined degeneration of the spinal cord preoperatively. She was myelopathic but had a gait disorder out of proportion to her spasticity. This was due to her posterior column disease. Postoperatively, she had worsening of her myelopathy, but also developed evidence of lower motor neuron disease with abdominal fasciculations. She had no worsening of cortical dysfunction but VEP's confirmed involvement of the visual system. The second patient was asymptomatic preoperatively but developed numbness, blurred vision, difficulty with walking, and headaches postoperatively.

The interaction of B12 deficiency and N2O is easily explained on a biochemical level. B12 is known to be involved in only two reactions:

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\begin{align*}
\text{methionine + methyltetrahydrofolate} & \rightarrow \text{homocysteine + tetrahydrofolate} \\
\text{methylmalonyl coenzyme A} & \rightarrow \text{succinyl coenzyme A.}
\end{align*}
\]

The products of these reactions are used in deoxyribonucleic acid (DNA) synthesis and the methylation of myelin basic protein. Nitrous oxide oxidizes the cobalamin of vitamin B12 from Co I to Co III, which results in the permanent inactivation of the enzyme vitamin complex. Recovery from N2O requires synthesis of new methionine synthase.

The similarity of N2O toxicity and B12 deficiency was discovered in 1956, when N2O was used on a chronic basis for the sedation of ventilated patients with tetanus.22 These patients developed a hematological picture identical to the megaloblastic anemia produced by B12 deficiency. This discovery led to the use of N2O in the rat as an animal model for the study of pernicious anemia.25,36 Many animals are very tolerant of B12-deficient diets, thus it has been difficult for physiologists...
Deterioration from $\text{B}_12$ deficiency and $\text{N}_2\text{O}$ use
to study pernicious anemia and other $\text{B}_12$ deficient states. This problem was eliminated with the use of $\text{N}_2\text{O}$ which proved to be far more powerful in inducing disease than dietary control. Rats, however, only suffer from the hematological effects and do not develop subacute combined degeneration of the spinal cord, due to species variability. It was not until 1978 that the effects on the nervous system of chronic $\text{N}_2\text{O}$ use were discovered.

Nitrous oxide was introduced to the public in the early 1980’s as laughing gas for the purpose of entertainment and general merriment. Unfortunately, the effects of prolonged repetitive use are quite serious. The neurological symptoms of chronic $\text{N}_2\text{O}$ exposure were first demonstrated in several dentists who used the gas for recreational purposes. A syndrome identical to $\text{B}_12$ deficiency develops. Again, the initial symptoms are paresthesias of the hands and legs, followed by ataxia, Lhermitte’s sign, weakness and spasticity of the legs, bowel and bladder dysfunction, personality change, and intellectual dysfunction. The EMG and nerve conduction velocity studies show an axonal sensorimotor polyneuropathy with denervation of the distal leg muscles. Monkeys exposed for 2 months to 50% $\text{N}_2\text{O}$ developed these symptoms and at sacrifice showed pathological changes in the cord identical to those of subacute combined degeneration of the spinal cord.

The effect of prolonged $\text{N}_2\text{O}$ use in inducing megaloblastic anemia and subacute combined degeneration of the spinal cord is well reported in the anesthesia literature. Methionine synthase activity has been shown to decrease during routine anesthesia in a dose-related fashion and this can be expressed as the percentage of $\text{N}_2\text{O}$ used $\times$ the number of hours of exposure ($\%$-hours). Our patients, for example, underwent approximately 2 hours of exposure to 50% $\text{N}_2\text{O}$ or 100%-hours (50% $\times$ 2). In humans, methionine synthase is depressed by 20% at 100%-hours and 70% depressed at 200%-hours. In the normal individual, this is well compensated for by stores in the marrow. The general anesthesia texts make note of this phenomenon but as Coleman states, “for routine use as a general anesthetic, $\text{N}_2\text{O}$ can be regarded as nontoxic and there need be no restriction on its use. When $\text{N}_2\text{O}$ is given for periods in excess of 6 hours, neurological and hematological defects may occur, which, however, are readily and rapidly reversible after discontinuation of inhalation.” However, it is critical to realize that in patients with $\text{B}_12$ deficiency, no such compensation is possible. Nitrous oxide inactivation of remaining stores may push the patient over the edge, resulting in serious consequences.

A recent report by O’Leary, et al., has shown a synergistic effect on pyrimidine synthesis by the combination of $\text{N}_2\text{O}$ and $\text{B}_12$ deficiency. They looked at the deoxyuridine suppression test (an indirect measure of methionine synthase activity) in bone marrow cells of $\text{B}_12$-deficient rats exposed to $\text{N}_2\text{O}$ and compared them to similar tests in rats which were $\text{B}_12$-deficient only or exposed to $\text{N}_2\text{O}$ only. They found that the effects of the combination of $\text{N}_2\text{O}$ and $\text{B}_12$ deficiency were greater than the sum of either variable alone. Other papers have supported this finding.

In 1986, Schilling reported on two patients with subclinical $\text{B}_12$ deficiency who underwent general anesthesia in which $\text{N}_2\text{O}$ was used and who subsequently developed neurological dysfunction consistent with subacute combined degeneration of the spinal cord. One patient with Crohn’s disease who had had an ileal resection underwent a colectomy with 90 minutes of $\text{N}_2\text{O}$ exposure. The other patient twice received general anesthesia with $\text{N}_2\text{O}$ for drainage of an abscess and was later found to have pernicious anemia. Preoperatively, these patients had normal neurological examinations and normal laboratory values, but within 8 weeks they had developed numbness, weakness, ataxia, poor finger coordination, and a Lhermitte’s sign. At that time, they were found to have anemia with macrocytosis, hypersegmented polymorphonuclear cells, and deficient $\text{B}_12$ levels. Each responded to $\text{B}_12$ injections.

Fortunately, $\text{B}_12$ deficiency is easy to detect. Elevation of the mean corpuscular volume and mean corpuscular hemoglobin should alert the clinician to the problem. However, the surgical and anesthetic preoperative checklist often do not extend past the hemoglobin and hematocrit; assurance that these two factors are normal can mislead the clinician into a false sense of security. Neurological deterioration in the $\text{B}_12$-deficient patient can certainly occur following administration of $\text{N}_2\text{O}$ in the face of a normal hemoglobin, as evidenced by our two cases. The mean corpuscular volume and mean corpuscular hemoglobin should always be checked (this becomes increasingly more important in the age group over 60 years old). If these are abnormally high the $\text{B}_12$ level must be checked. Surgery can proceed with an anesthetic other than $\text{N}_2\text{O}$. If it is suspected that all of the patient’s symptoms are due to $\text{B}_12$ deficiency, surgery can be delayed while further evaluation is undertaken. It is tempting to speculate on how many unexpected new postoperative neurological deficits in surgical patients may have actually been due to $\text{B}_12$ deficiency and $\text{N}_2\text{O}$ administration.

In summary, $\text{N}_2\text{O}$ is very dangerous in the $\text{B}_12$-deficient patient. Because $\text{B}_12$ deficiency is not uncommon and $\text{N}_2\text{O}$ use is ubiquitous, the potential exists in every neurosurgical practice for this complication to occur. Prevention is the key. The surgeon should be aware of this contraindication and should look for evidence of $\text{B}_12$ deficiency in every patient.

References


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