Nitrous Oxide Anesthesia–Associated Myelopathy

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Background: The role of nitrous oxide exposure in neurologic complications of subclinical cobalamin deficiency has been reported, but few cases are well documented.

Observation: Two weeks after surgery for prosthetic adenoma, a 69-year-old man developed ascending paresthesia of the limbs, severe ataxia of gait, tactile sensory loss on the 4 limbs and trunk, and absent tendon reflexes. After a second surgical intervention, the patient became confused. Four months after onset, the patient had paraplegia, severe weakness of the upper limbs, cutaneous anesthesia sparing the head, and confusion. Moderate macrocytosis, low serum B12 levels, and a positive Schilling test result led to the diagnosis of pernicious anemia. Results of electrophysiologic examinations showed a diffuse demyelinating neuropathy. Magnetic resonance imaging of the spinal cord disclosed hyperintensities of the dorsal columns on T2-weighted images.

Conclusions: Pernicious anemia can result in severe neurologic symptoms with only mild hematologic changes. The role of nitrous oxide anesthesia in revealing subclinical B12 deficiency must be emphasized. Magnetic resonance imaging of the spinal cord might be helpful in making the diagnosis.

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Acute combined degeneration of the spinal cord caused by pernicious anemia (PA) is characterized by combined involvement of pyramidal tracts and posterior columns of the spinal cord, sometimes associated with peripheral neuropathy, optic atrophy, and encephalopathy. Diagnosis might be difficult when anemia or macrocytosis are lacking or in the presence of normal serum cobalamin (Cbl) levels. Nitrous oxide exposure may trigger development of neurologic complications in patients with subclinical Cbl deficiency (see Green and Kinsella and Schilling). We describe a patient with previously unrecognized PA who developed an extremely severe and long-lasting neurologic disease after 2 exposures to nitrous oxide during anesthesia.

REPORT OF A CASE

A 69-year-old retired butcher underwent surgery for benign prostate hypertrophy under 40% nitrous oxide anesthesia (3.2 L/min) for 1 hour. Two weeks later he started having distal paresthesias of the lower limbs that extended progressively to the trunk and upper limbs. Two months later he had severe gait ataxia, with loss of position sense and pallesthesia, and absent tendon reflexes. Paraparesis developed thereafter with a bilateral Babinski sign; sensory loss became complete in the lower limbs, and the upper limbs became ataxic. He again underwent surgery for cholecystitis and became confused. Four months after onset, the patient had complete flaccid paraplegia, urine retention, fecal incontinence, severe ataxia and moderate weakness of the upper limbs, and complete loss of all sensory modalities below the C2 level. He was also time and place disoriented, with impaired memory and visual hallucinations. Visual acuity was 12/20 in both eyes. Fundi and visual fields were normal.

Electrophysiologic testing 2 months after onset detected a generalized slowing of sensory conduction velocities (26 m/s; amplitude of the right superficial peroneal nerve potential, 10 µV), normal motor conduction, and no denervation on electromyography. Four months after onset, mild denervation and slowing of motor conduction velocities were found in the upper limbs (right median nerve, 40 m/s).
Sensory evoked potentials could not be recorded; visual evoked potentials were delayed on both sides (right, 134.4 milliseconds; left, 131.2 milliseconds).

Results of a complete blood cell count 1 month after onset were normal (patient being free from folic acid treatment) except for an increased mean corpuscular volume (101 fL); 3 months later the results were as follows: hemoglobin level, 10.7 g/dL; red blood cell count, 2.99 × 10^12/L; mean corpuscular volume, 103.6 fL; red blood cell distribution width, 19%; white blood cell count, 5.30 × 10^9/L; and platelet count, 2.72 × 10^9/L. Results of bone marrow aspiration were normal. The serum Cbl level was less than 37 pmol/L (reference range, 1.30-700 pmol/L), and the serum folic acid level was 30 nmol/L (reference range, 5-30 nmol/L).

Anti–intrinsic factor antibodies were detected (13 U/mL [reference range, <8 U/mL]), and intrinsic factor was absent in gastric fluid (3.7 U [reference range, 30-40 U]). Gastric mucosa appeared macroscopically normal, but fundic biopsy specimens disclosed atrophy and intestinal metaplasia. The Schilling test confirmed the diagnosis of PA: Cbl excretion after intrinsic factor, 12.7% (reference range, 14%-40%; PA >9); without intrinsic factor, 3.2% (reference range, 14%-40%; PA <10); ratio, 4.0 (reference range, 0.7-1.2; PA >1.7).

Spinal magnetic resonance imaging (Figure) revealed hyperintensity of the posterior two thirds of the spinal cord on sagittal T2-weighted images involving mainly the posterior and lateral columns on axial slices from the cervical level to T10 and only the posterior columns from T10 to the terminal cone. Use of gadolinium did not enhance the signal. Brain magnetic resonance images were normal.

Three months after the first symptoms appeared the patient received intramuscular cyanocobalamin, 1000 µg/d for 5 days, and then 5000 µg every other day for 6 months. A short course of intravenous hydroxocobalamin was given (5000 µg/d), which did not seem to hasten recovery. Improvement was delayed and slow, starting with the disappearance of disorientation and hallucinations. Six months after introduction of cobalamin supplementation, the patient was well oriented but still chairbound, with spastic paraparesis, proprioceptive sensory loss of the lower limbs, incomplete urinary retention, and mild ataxia of the upper limbs. Results of a complete blood cell count were normal. Magnetic resonance imaging showed persistent dorsal column hyperintensities but sparing of lateral columns. During the next 6 months he continued receiving 5000 µg of intramuscular cyanocobalamin weekly. After 1 year of treatment the patient could walk unaided for short distances with mild ataxia. He died of intestinal occlusion. An autopsy was not performed.

COMMENT

Untreated Cbl deficiency might result in neuropathy, subacute combined degeneration of the spinal cord, and encephalopathy, in isolation or in various combinations. Of 143 patients with Cbl deficiency reviewed by Heal ton et al, 41% had combined neuropathy and myelopathy. Our patient also had encephalopathy, a complication observed in only 8.1% of patients in other studies.6,7

Visual impairments are uncommon (0.5%). Although our patient had no visual complaints, he had bilateral alteration of visual evoked potentials. Severe peripheral and central nervous system damage might thus occur in Cbl deficiency despite relatively mild hematologic changes.8

Magnetic resonance imaging of the spinal cord demonstrated conspicuous changes in posterior and lateral columns, in accordance with the anatomical lesions of subacute combined degeneration of the spinal cord.9 Previous studies also reported T2 hyperintensities of the spinal cord, either diffuse10,11 or confined to the dorsal columns,12-14 or involving both lateral and dorsal columns. Even in the latter case, however, the dorsal columns are the first to be involved and the most altered. Most authors have reported axonal degeneration of peripheral nerves with or without associated demyelination. Healton et al9 observed decreased mean corpuscular volumes, absent or reduced sensory evoked potentials, and fibrillations in distal muscles, indicating a mixed sensorimotor axonal demyelinating pattern. McCombe and McLeod2 found axonal degeneration by electromyography and sural nerve biopsy examination in 3 patients. In our patient, findings of electrophysiologic examinations initially suggested a demyelinating sensory neuropathy that eventually progressed to a mixed axonal demyelinating pattern.

In most patients, the diagnosis of Cbl deficiency depends on serum Cbl measurements, as in our patient, who also had anti–intrinsic factor antibodies and fundic atrophy, which suggests PA rather than a hereditary defect.15,17 Our patient’s neurologic symptoms started shortly after nitrous oxide exposure and worsened after a second surgical procedure under nitrous oxide anesthesia. Kondo et al18 showed that exposure to nitrous oxide causes multiple defects in Cbl metabolism. Kinsella and Greer19 described 2 patients similar to ours with unsuspected Cbl deficiency who developed acute Cbl deficiency symptoms after a single exposure to nitrous oxide during a surgical procedure. Nitrous oxide is a potent oxidant that disrupts the methionine synthetase reaction by causing oxidation of Cob(I)alamin to Cob(II)alamin, which blocks regeneration of the cobalamin coenzyme methylcobalamin, produces a condition simulating Cbl deficiency, inhibits methylation of myelin phospholipids, and alters incorporation of fatty acids into the myelin sheaths.20 In patients with normal stores of Cbl, a sufficient quantity...
of unoxidized Cbl may be available to maintain enzyme function; in patients with borderline Cbl stores, even short exposures to nitrous oxide may be sufficient to precipitate a Cbl deficiency syndrome.

CONCLUSIONS

Pernicious anemia may lead to extremely severe neurologic complications despite few hematologic changes. It might also be more frequent than usually thought because using serum Cbl levels below 200 pmol/L as the indicator of deficiency, its prevalence ranges from 7% to 16%. Exposure to nitrous oxide during anesthesia is an underrecognized and potentially important factor in triggering and worsening the neurologic consequences of Cbl deficiency. The subacute onset of a sensory neuropathy, myelopathy, encephalopathy, or any combination of these in the days or weeks after undergoing a surgical procedure should raise the question of Cbl deficiency even in the absence of hematologic changes.

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