

Myelopathy Due to Copper Deficiency Following Gastrointestinal Surgery

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Background: Ataxic myelopathy due to copper deficiency has been described in ruminant animals and is called swayback. Neurological manifestations due to inherited copper deficiency secondary to the failure of intestinal copper absorption is well recognized as Menkes disease. The neurological consequences of acquired copper deficiency in humans are not well described.

Objective: To report 2 cases where patients developed a myelopathy with copper deficiency after gastrointestinal surgery.

Patients: Two patients developed a myelopathy many years after gastrointestinal surgery. Both had severe copper deficiency, which was the likely cause of the myelopathy.

Conclusions: Acquired copper deficiency may present as a myelopathy. Gastrointestinal surgery and resulting decreased copper absorption may be causative.

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COPPER IS an essential trace metal and is a component of many key metalloenzymes and proteins that are involved in the structure and function of the central nervous system. Owing to its ubiquitous distribution and low daily requirement, acquired copper deficiency in humans is rare. Anemia and neutropenia due to copper deficiency are well described,¹ but the literature on the neurological manifestations due to acquired copper deficiency in humans is very limited.²⁻⁴ We report 2 cases where patients developed a myelopathy in the setting of copper deficiency.

REPORT OF CASES

CASE 1

A 49-year-old woman had a 2-year history of progressively increasing imbalance that she attributed to lower limb stiffness and numbness. She reported an increase in her symptoms in the dark. An associated complaint was painful paresthesias involving the feet. The numbness involved the lower limbs and hands. The gait difficulty caused her to use a walker, and a fall and resultant right femur fracture caused her to be wheelchair bound for 6 weeks prior to her ex-

amination. She had undergone an intestinal bypass procedure for obesity 24 years ago. For the past 4 years, she had pain involving the small joints of the hands and was diagnosed as having bypass arthropathy. Since the onset of her gait difficulty, she had received vitamin B₁₂ injections on 2 occasions despite having normal serum vitamin B₁₂ levels. No improvement was noted in response to the injections.

Her neurological examination revealed increased lower limb tone with normal strength and symmetrically brisk reflexes and extensor plantars. Perception of vibration was absent at the toes and ankles, and tibial tuberosity and perception of position sense was reduced at the toes. There was decreased perception of pinprick and touch in the lower limbs with the distal lower limbs being most affected. She had a spastic ataxic gait with a positive Romberg sign.

Her laboratory investigation results were most notable for abnormalities in copper levels. Her serum copper level was reduced to 17 µg/dL (2.7 µmol/L) (normal range, 75-145 µg/dL [11.8-22.8 µmol/L]), her serum ceruloplasmin level was reduced to 2.8 mg/dL (normal range, 22.9-43.1 mg/dL), and her serum zinc level was nearly normal at 64 µg/dL (9.8 µmol/L) (normal range, 66-110 µg/dL [10.1-16.8

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Copper Metabolism in Cases 1 and 2*

	Serum Copper Level, $\mu\text{g/dL}$	Serum Ceruloplasmin Level, mg/dL	Serum Zinc Level, $\mu\text{g/dL}$	24-h Urine Copper Excretion Rate, μg	24-h Zinc Excretion Rate, μg
Case 1					
Initial	17	2.8	64	24	666
10 d after a 5-d course of IV cupric sulfate	61	NA	43	NA	NA
After 3 5-d courses of IV cupric sulfate across an 8-wk period	60	NA	NA	NA	NA
Case 2					
Initial	Undetectable	2.2	109	15	2875
After 5 d of IV cupric sulfate	28	5.0	111	20	2238
1 mo later	34	6.0	NA	12	2198
2 mo after oral cupric sulfate	16	NA	150	NA	NA
After second course of IV cupric sulfate	41	NA	156	NA	NA
After 8 wk of no cupric sulfate	34	6.1	142	NA	NA

Abbreviations: IV, intravenous; NA, not applicable.

SI conversion factors: To convert serum copper levels to micromoles per liter, multiply by 0.1574. To convert serum zinc levels to micromoles per liter, multiply by 0.153.

*Normal serum copper level range is 75 to 145 $\mu\text{g/dL}$; normal serum ceruloplasmin level, 22.9 to 43.1 mg/dL ; normal serum zinc level, 66-110 $\mu\text{g/dL}$; normal 24-hour urine copper excretion rate, 15 to 60 μg ; and normal 24-hour urine zinc excretion rate, 300 to 600 μg .

$\mu\text{mol/L}$). Twenty-four-hour urine studies revealed a normal copper excretion rate of 24 μg (normal range, 15-60 μg) and a near normal zinc excretion rate of 666 μg (normal range, 300-600 μg) (Table).

The other remarkable abnormalities in laboratory results included a reduced serum β -carotene level of 15 $\mu\text{g/dL}$ (0.3 $\mu\text{mol/L}$) (normal range, 48-200 $\mu\text{g/dL}$ [0.9-3.7 $\mu\text{mol/L}$]) and a reduced 25-hydroxyvitamin D level of 6 ng/mL (15 nmol/L) (normal range, 8-38 ng/mL [20-95 nmol/L]). Her hemoglobin level was at the lower limits of normal at 11.9 g/dL (normal range, 12.0-15.5 g/dL). Normal laboratory test findings included those for white blood cell count, a paraneoplastic panel, a very long chain fatty acid profile, Lyme disease titers, human T-lymphotropic virus 1 and human immunodeficiency virus serologies, and tests for sedimentation rate, serum vitamin A, vitamin B₆, and vitamin E level, and serum electrolyte, glucose, folate, angiotensin-converting enzyme, antinuclear antibody, and cryoglobulin levels. The patient's serum vitamin B₁₂ level was 228 pg/mL (168 pmol/L) (normal range, 200-1100 pg/mL [148-812 pmol/L]) and her methylmalonic acid level was elevated to 2172 nmol/L (normal range, 90-279 nmol/L). Genetic testing results for the spastin gene mutation and cerebrospinal fluid analysis were normal. A brain magnetic resonance image was remarkable for small nonspecific foci of increased T2 signal in the white matter, and spine magnetic resonance images revealed a mild disk bulge at the C4-5 and C6-7 interspaces with no intramedullary signal change. Nerve conduction studies were remarkable for slight reductions in the peroneal motor and medial plantar sensory amplitude that were felt to be consistent with a mild sensorimotor peripheral neuropathy.

She received 2 mg of cupric sulfate intravenously daily for 5 days on 3 occasions across an 8-week period. Each set of infusions was associated with a slight decrease in numbness and an increased perception of tingling sensation. The paresthesias were reported as being less painful. Her blood work done 10 days after the first 5 days of intravenous cupric sulfate revealed improvement in se-

rum copper levels to 61 $\mu\text{g/dL}$ (9.6 $\mu\text{mol/L}$), and levels close to this one have been maintained since (Table).

CASE 2

A 78-year-old woman had a 10-year history of progressive lower limb paresthesias. For the past 2 years, she had symptoms of gait difficulty with lower limb weakness and recurrent falls. Her medical history was remarkable for long-standing Crohn disease. A partial small-bowel resection was performed 30 years ago following an episode of small-bowel obstruction. She had undergone a Billroth II partial gastrectomy and vagotomy for refractory ulcers 15 years ago. The postoperative period was complicated by a gastric-outlet obstruction that required a revision gastrectomy a few months later. During the past decade, she was said to have malabsorption, iron and vitamin B₁₂ deficiencies, and anemia that did not respond to iron and vitamin B₁₂ replacement therapy. For the preceding 5 years, she had received 1000 μg of intramuscular vitamin B₁₂ every 3 weeks. Despite this and normal serum vitamin B₁₂ levels, her condition continued to worsen.

Our initial neurological examination revealed increased lower limb tone with weakness in an upper motor neuron pattern. She had brisk reflexes except the ankle jerk, which was normal. The plantar response was extensor. Position sense was impaired at the toes, and vibratory sense was diminished at the toes and malleoli. Perception of touch and pinprick was decreased distal to the ankles. She had a spastic gait with a positive Romberg sign and an inability to walk tandemly.

Laboratory study findings were remarkable for undetectable serum copper levels (normal range, 75-145 mg/dL [11.8-22.8 $\mu\text{mol/L}$]) and reduced serum ceruloplasmin levels of 2.2 mg/dL (normal range, 22.9-43.1 mg/dL). Her serum zinc level was normal at 109 $\mu\text{g/dL}$ (16.7 $\mu\text{mol/L}$) (normal range, 66-110 $\mu\text{g/dL}$ [10.1-16.8 $\mu\text{mol/L}$]). Twenty-four-hour urine studies showed a urine

copper excretion rate of 15 μg (normal range, 15-60 μg) and a urine zinc excretion rate of 2875 μg (normal range, 300-600 μg) (Table).

Laboratory study results revealed additional abnormalities. This included a macrocytic anemia and neutropenia. Her hemoglobin level was 9.4 g/dL (normal range, 12.0-15.5 g/dL), her mean corpuscular volume was 113.8 fL (normal range, 81.6-98.3 fL), and her neutrophil count was 1020/mm³ (normal range, 1700-7000/mm³). The folate level and the findings from the iron studies were normal. Her serum vitamin B₁₂ level was 631 pg/mL (466 pmol/L) (normal range, 200-650 pg/mL [148-480 pmol/L]) with a methylmalonic acid level of 0.18 $\mu\text{mol/L}$ (normal level, <0.4 $\mu\text{mol/L}$) and a serum homocysteine level of 13 $\mu\text{mol/L}$ (normal level, <13 $\mu\text{mol/L}$). Her serum urea nitrogen value was elevated to 59 mg/dL (21.1 mmol/L) (normal range, 6-21 mg/dL [2.1-7.5 mmol/L]), and her creatinine level was normal. Her total protein level was decreased to 5.4 g/dL (normal range, 6.3-7.9 g/dL), and her alkaline phosphatase level was elevated to 423 U/L (normal range, 119-309 U/L) with normal alanine aminotransferase and aspartate aminotransferase levels. The findings from the lipid profile, immunoelectrophoresis, thyroxine test, antinuclear antibody test, paraneoplastic panel, vitamin E level test, and the fatty acid profile were normal. Findings for Lyme disease titers, syphilis, human T-lymphotrophic virus 1, and hepatitis B and C serologies were also normal. The lumbosacral spine magnetic resonance imaging results showed incidental degenerative changes. No signal change was present in the lateral or dorsal columns. The nerve conduction studies were remarkable for an axonal sensorimotor polyneuropathy based on an absent sural sensory potential with slight reduction in the peroneal and tibial motor amplitude with normal lower limb motor-conduction velocities.

She received 2 mg of cupric sulfate intravenously daily for 5 days. Following the 5 days of parenteral copper administration, her serum copper and serum ceruloplasmin levels improved to 28 $\mu\text{g/dL}$ (4.4 $\mu\text{mol/L}$) and 5.0 mg/dL, respectively. Her serum zinc value was 111 $\mu\text{g/dL}$ (17.0 $\mu\text{mol/L}$), and the 24-hour urine studies showed excretion rates for copper and zinc at 20 μg and 2238 μg , respectively. Follow-up at 4 weeks revealed resolution of the paresthesias and some improvement in gait difficulty but no improvement in the lower limb weakness. Her serum copper and serum ceruloplasmin levels were 34 $\mu\text{g/dL}$ (5.4 $\mu\text{mol/L}$) and 6 mg/dL, respectively; her 24-hour urine copper excretion level was reduced to 12 μg ; and her 24-hour urine zinc excretion level remained elevated at 2198 μg . She was given oral cupric sulfate (2 mg daily) for 8 weeks. The initial gains in the increased serum copper level were not maintained, and her serum copper level decreased to 16 $\mu\text{g/dL}$ (2.5 $\mu\text{mol/L}$) and her serum zinc level increased to 150 $\mu\text{g/dL}$ (23.0 $\mu\text{mol/L}$). The patient's condition had clinically worsened. A 5-day course of intravenous cupric sulfate was again associated with clinical and biochemical improvement with the serum copper levels increasing to 41 $\mu\text{g/dL}$ (6.5 $\mu\text{mol/L}$). During the subsequent 8 weeks, her copper replacement administration ended, her serum copper level decreased to 34 $\mu\text{g/dL}$ (5.4 $\mu\text{mol/L}$) and painful paresthesias returned (Table).

Both patients described had a gait difficulty that was predominantly due to a severe sensory ataxia. Clinical and electrophysiologic evidence of a peripheral neuropathy was present but was not the predominant reason for the gait difficulty. They both had prominent upper motor neuron signs on examination. Evaluations for a cause of the myeloneuropathy were futile except for the copper deficiency state. In both patients, copper administration resulted in short-lived and mild improvement in the sensory symptoms. Both patients had surgery on their gastrointestinal tracts, and both had laboratory evidence of malabsorption. In our second patient, intravenous administration of copper was associated with an improvement in symptoms and copper levels, but the improvement was not sustained when she was given oral copper, which is consistent with copper malabsorption. Given the history of gastrointestinal surgery and clinical presentation, vitamin B₁₂ deficiency had been considered as a possible cause of myelopathy in both patients. We believe that both patients may have had vitamin B₁₂ deficiency at some point in time. The continued worsening of the patients' conditions despite vitamin B₁₂ administration and normal vitamin B₁₂ levels and the response to copper replacement suggest that copper deficiency was the likely cause of the patients' deteriorating conditions.

In humans, gastrointestinal absorption of copper appears to take place in the stomach and proximal duodenum,⁵ and copper deficiency can occur after gastrectomy or with prolonged enteral or parenteral feeding without copper supplementation.¹ The first report of copper deficiency-associated myelopathy in humans was in a patient who had undergone 2 gastrectomies and a segmental colon resection because of gastric ulcers and related complications.² The patient described had clinical symptoms very similar to our 2 cases. She showed normalization of serum copper and serum ceruloplasmin levels with 5 days of parenteral copper supplementation. As in our cases, the paresthesias improved, but the paresis did not. We recently reported a patient who developed a myelopathy in the setting of copper deficiency after having consumed 15 to 30 times the recommended daily allowance of zinc for more than 2 decades.⁴ He showed clinical, biochemical, and electrophysiologic improvement after cessation of zinc intake and copper supplementation. There have been only 2 other reports of patients who have had neurological manifestations due to acquired copper deficiency.^{3,6} These patients had gait difficulty and paresthesias with prominent upper motor neuron signs that were attributed to central nervous system demyelination. In both patients, the cause of the low copper levels was unclear, but the serum zinc levels were elevated. Our second patient had a sustained elevation of the 24-hour urine zinc excretion rate with serum zinc levels that at least initially were normal. Zinc is known to cause up-regulation of metallothionein production in the enterocyte, which effectively decreases intestinal absorption of copper.⁷ Elevated zinc levels have been described to be a heritable abnormality.⁸ Epidemiological studies have suggested that

zinc may be implicated in the pathogenesis of multiple sclerosis.^{9,10}

A progressive ataxic myelopathy due to nutritional copper deficiency is well documented in ruminant animals and is known as swayback.¹¹ Copper deficiency in rats is associated with axonal swelling that can be reversed by early copper administration.¹² Also well described are neurological manifestations due to the failure of intestinal copper absorption in Menkes disease. Menkes disease is an X-linked disorder caused by mutations in the *ATP7A* gene, which encodes a P-type adenosine triphosphatase (MNK) that has multiple copper-binding motifs near its amino terminus.¹³ Even though Wilson disease is a disorder of copper excess, the mutated gene (designated *ATP7B*) is a close homolog of MNK and encodes a P-type adenosine triphosphatase (WND) that is highly expressed in the liver.¹⁴

Potential causes of copper deficiency include malnutrition, prematurity, parenteral or enteral feeding without copper supplementation, gastrectomy, ingestion of copper-chelating agents, and excessive zinc therapy.^{1,15} Chemotherapy regimens using tetrathiomolybdate can result in copper deficiency.¹⁶ We should be vigilant to signs of myelopathy or myeloneuropathy in patients with a high risk of developing copper deficiency. Prompt recognition is essential, as early institution of therapy might prevent neurological deterioration.

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