Copper Deficiency Myelopathy

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Background: In humans, Menkes disease is the well-recognized neurological disorder due to inherited copper deficiency. Myelopathy due to acquired copper deficiency is not a well-recognized entity in humans, although myelopathy due to copper deficiency is well documented in some animal species.

Patients: We describe 3 patients who developed a progressive spastic-ataxic gait with proprioceptive deficits. All patients had a severe reduction in serum ceruloplasmin and copper levels.

Results: All patients had evidence of posterior column dysfunction clinically and on somatosensory evoked potential studies. Two had a signal change in the posterior column on magnetic resonance imaging of the spinal cord.

Conclusion: Patients presenting with otherwise unexplained myelopathies should have their serum ceruloplasmin level measured.

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Copper Deficiency in Ruminants is known to cause a progressive ataxic myelopathy (“swayback”). In humans, Menkes disease is the well-recognized childhood neurological disorder due to inherited copper malabsorption. The literature on the neurological manifestations of acquired copper deficiency in human adults is limited, although the hematologic manifestations are well described.

Copper is a key constituent of various metalloenzymes, has an important role in mitochondrial metabolism, and is important for the structure and function of the nervous system. We describe 3 patients with a myelopathy related to copper deficiency.

REPORT OF CASES

PATIENT 1

A 72-year-old man was referred for an 8-month history of gait ataxia. His illness started with foot numbness, ascending over 4 months to involve the lower limbs. Hand numbness developed a few weeks after the foot numbness. Increasing gait unsteadiness paralleled these symptoms. A mildly reduced vitamin B12 level of 181 pg/mL (134 pmol/L) was treated with vitamin B12 injections. Despite subsequent vitamin B12 normalization, his neurological illness progressed. At the age of 26 years, he had undergone partial gastric resection for peptic ulcer disease.

His neurological examination results revealed lower limb spasticity, generalized hyperreflexia, ankle clonus, and extensor plantar responses. There was decreased perception of touch, pinprick, and position over the toes and fingers; his vibratory sense was reduced at the knees and distally. He required assistance to ambulate.

His vitamin B12 level was elevated, and there was a slight decrease in the hemoglobin level (Table). Normal investigation results were found for electrolytes, creatinine, homocysteine, methylmalonic acid, folate, antinuclear antibody, and thyroid-stimulating hormone levels; immuno-electrophoresis; the paraneoplastic panel; and human immunodeficiency virus and human T-lymphotropic virus I serological tests. Nerve conduction studies showed a mild sensorimotor axonal polyneuropathy. Tibial and median somatosensory evoked potentials were markedly abnormal, with evidence of impaired conduction in central proprioceptive pathways. Spine magnetic resonance imaging (MRI) showed an increased T2 signal in the dorsal aspect of the cord from verte-
A 49-year-old woman was examined for an 18-month history of gait difficulty and lower limb stiffness. At the onset of her illness, she had foot and distal hand paresthesias that progressed to involve the hands and lower limbs. Coordination difficulty with her hands was particularly evident if she did not look at what she was doing. She had stopped driving because she was unsure where her feet were in relation to the accelerator and brake. A short course of intravenous corticosteroids was of no benefit. Three months before the onset of her neurological symptoms, she had a hemoglobin level of 9.2 g/dL. Her vitamin B₁₂ level and mean corpuscular volume were normal, and the anemia responded to iron supplementation.

The results of her physical examination were remarkable for mild weakness of the hand muscles, hyperreflexia, ankle clonus, and extensor plantar responses. Pinprick and touch sensation were reduced in the feet. Joint position sense at the toes was severely impaired, and there was graded decreased perception of vibration in the lower limbs. She had a spastic-ataxic gait and a positive Romberg sign.

Normal test results were noted for the hematologic group, electrolytes, creatinine, thyroid-stimulating hormone, antinuclear antibody, lactate, creatine phosphokinase, vitamins B₁₂ and E, homocysteine, methylmalonic acid, folate, ferritin, and anti–gliadin antibody levels; immunoelectrophoresis; and cerebrospinal fluid analysis. Molecular analysis results for the fragile X mutation and the spinocerebellar ataxia panel were negative. Her arylsulfatase level and very-long-chain fatty acid profile were normal. The results of serological studies for Lyme disease, syphilis, the human immunodeficiency virus, and the human T-lymphotropic virus 1 were negative. A moderately severe axonal sensorimotor neuropathy was noted on nerve conduction studies. There was evidence of slowing in the central and peripheral somatosensory pathways on the evoked potential studies. The results of a surgical nerve biopsy showed an increased rate of axonal degeneration with empty nerve strands and a moderate collection of perivascular epineurial inflammatory cells. Spine MRI performed soon after illness onset showed a hyperintense T₂ signal in the paramedian dorsal spinal cord extending from vertebrae C₂ to C₆ (Figure 2A–C). Serum ceruloplasmin and copper levels were markedly reduced to 1.6 µg/dL and 11 µg/dL (1.7 µmol/L), respectively, and her serum zinc level was elevated to 147 µg/dL (22.5 µmol/L) (normal level, 66-110 µg/dL [10.1-16.8 µmol/L]) (Table). Urine 24-hour copper excretion was reduced to 6 µg (normal level, 15-60 µg).
µg), and 24-hour urine zinc excretion was elevated to 2060 µg (normal level, 300-600 µg). Oral copper therapy, 2 mg/d, for 3 months failed to increase her serum copper levels, and her upper limb symptoms worsened.

PATIENT 3

A 46-year-old woman presented with a 6-month history of ascending lower limb numbness and gait difficulty. Her gait difficulty was worse in the dark and on uneven ground. For 1 year before the onset of her symptoms, she had been treated with ferrous sulfate, 325 mg 3 times a day, for anemia of unclear cause. Four weeks after the onset of her neurological symptoms, a vitamin B12 level of 261 pg/mL (193 pmol/L) (normal level, 301-1100 pg/mL [222-812 pmol/L]) led to the administration of periodic vitamin B12 injections. The results of a methylmalonic acid level determination performed at that time and subsequent vitamin B12 level determinations were normal. Her gait deterioration continued.

The results of a neurological examination revealed mild distal lower limb weakness, generalized hyperreflexia except for depressed ankle jerks, absent vibratory sense to the level of the anterior superior iliac spine, decreased proprioception at the ankles and toes, an ataxic gait, and a positive Romberg sign. Superficial pain sensation was preserved.

Normal test results were noted for the hemetologic group, thyroid-stimulating hormone, creatine phosphokinase, antinuclear antibody, vitamins B12 and E, and methylmalonic acid levels; paraneoplastic antibody studies; and syphilis serological tests. The serum ferritin level was reduced to 7 ng/mL (normal level, 20-2000 ng/mL), although the serum iron level, the iron binding capacity, and saturation were normal. The results of brain and spine MRI were normal. Nerve conduction stud-
ies showed evidence of a mild sensory neuropathy. Tibial and median somatosensory evoked potential studies demonstrated significant slowing in central pathways with preserved peripheral latencies. Serum copper, ceruloplasmin, and zinc levels were reduced to 24 µg/dL (3.8 µmol/L), 3.5 mg/dL, and 43 µg/dL (6.6 µmol/L), respectively (Table). Urinary 24-hour copper excretion was reduced (8 µg), and zinc excretion was normal. Her iron supplementation was discontinued; she was given intravenous cupric sulfate, 2 mg/d, for 5 days, followed by oral copper supplementation. Five days after intravenous copper supplementation, she had significant biochemical and slight clinical improvement. On physical examination, her gait and proximal vibration sensation were improved. Three months after starting copper supplementation, she reported no further deterioration and a continued improvement in gait; her serum copper and ceruloplasmin levels normalized.

**COMMENT**

All 3 patients presented with a myelopathy and peripheral neuropathy (mild in 2 by electromyographic criteria). All 3 had markedly reduced serum copper and ceruloplasmin levels without other relevant abnormalities. Of the 3 patients, 2 (patients 1 and 2) had a hyperintense T2 signal within the posterior columns on spine MRI (Figures 1 and 2). Electrophysiological evidence of impaired central conduction, as demonstrated by abnormalities on the somatosensory evoked potential studies, was seen in each patient. Intravenous and oral copper supplementation normalized the serum copper and ceruloplasmin levels in one patient (patient 3), with stabilization of the neurological syndrome and mild improvement. Oral copper administration failed to improve the serum copper levels in patient 2.

Copper is a component of numerous metalloenzymes and proteins that have a key role in maintaining the structure and function of the nervous system. It is a constituent of cytochrome oxidase (oxidative phosphorylation), superoxide dismutase (antioxidant defense), ceruloplasmin (iron metabolism), tyrosinase (melanin synthesis), and dopamine β-monooxygenase (catecholamine synthesis). Because of its wide distribution in foods and low daily requirement, a copper deficiency due to an inadequate diet is rare. An acquired copper deficiency can occur in premature and malnourished infants, with parental nutrition without copper supplementation, in patients with malabsorption and nephrotic syndrome, and as a complication of zinc, penicillamine, and alkali therapy. An acquired copper deficiency can occur in premature and malnourished infants, with parental nutrition without copper supplementation, in patients with malabsorption and nephrotic syndrome, and as a complication of zinc, penicillamine, and alkali therapy.8

The literature on the neurological manifestations of acquired copper deficiency in humans is limited.2,6,12 and copper deficiency myelopathy has only limited precedents.2,4,6 To our knowledge, the first reported case of copper deficiency myelopathy was in a 46-year-old woman who developed spastic tetraparesis and sensory ataxia with hypocupremia and a hyperintense T2 signal on cervical spine MRI.2 A patient who developed a myelopathy after 20 years of high-dose zinc gluconate self-administration to prevent colds was recently described.4 Following discontinuation of zinc and oral copper administration, the biochemical findings and electrophysiologic results (somatosensory evoked potentials) normalized, and the clinical variables improved. Two other patients previously described developed a copper deficiency myelopathy many years after gastrointestinal surgery.5

Copper absorption in humans is believed to take place in the stomach and proximal duodenum.9 The first described patient with copper deficiency–associated myelopathy had a history of gastrectomy.2 Patient 1 in the present study and the 2 other patients recently described5 also had histories of gastrointestinal surgical procedures. Decreased absorption of copper following gastrectomy is a likely cause for the copper deficiency noted in patient 1.

Copper deficiency–induced ataxic myelopathy in animals1 is associated with a similar distribution of spinal lesions.10 Pathologic studies11 in animals with swain disease have shown wallerian degeneration characterized by demyelination and microcavitation of the neuropil in the white matter of the spinal cord.

The elevated serum and urinary zinc levels seen in patient 2 deserve further comment. Zinc interferes with intestinal copper absorption by inducing intestinal synthesis of metallothionein, which has a greater affinity for copper.12 The bound copper is lost as the enterocytes slough off into the intestinal lumen. Conversely, increased copper absorption has been noted in zinc-deficient animals, and a high dietary copper level can depress zinc absorption.13 Two patients with idiopathic hypocupremia, hyperzincemia, and extensive central nervous system demyelination have been described.1 One of these patients had been described earlier as having deficits secondary to zinc toxicity.14 This patient showed gradual improvement while taking oral copper, despite a persistent elevation in zinc levels. Perhaps the elevated zinc level in patient 2 was secondary to the copper-deficient state rather than causing copper deficiency. A recent report4 of copper deficiency myeloneuropathy suggests that a zinc overload syndrome may be the reason for copper deficiency. A relationship between the high dose of iron and the development of copper deficiency in patient 3 is open to speculation. Iron excess in guinea pigs has been associated with a reduced hepatic copper level.15 A metal-ion transporter in rats, DCT1, that has a broad substrate range, including iron, zinc, and copper, has been identified.16 The anemia noted in our 3 patients may have been induced by the copper deficiency state. The recognized hematologic manifestations of acquired copper deficiency in humans include anemia, neutropenia, sideroblastosis, and megaloblastic changes.7

Experimental evidence17 suggests that the copper transporter CTR1 is the primary avenue for copper uptake in mammalian cells. Studies18 in Saccharomyces cerevisiae have identified a family of cytoplasmic proteins termed metallochaperones that have a role in intracellular copper trafficking. The mammalian metallochaperone ATOX1 (or HAH1) interacts with Menkes and Wilson disease, causing copper-transporting adenosine triphosphatases located in the trans-Golgi network of cells.19,20 The gene responsible for Menkes disease (ATP7A) encodes a P-type adenosine triphosphatase that has multiple copper-binding motifs near its amino terminus.21 Wilson disease is a disorder of copper excess and results from mutations in a gene (ATP7B) that encodes a P-type aden-
osine triphosphatase and it is closely homologous to the gene mutated in Menkes disease. Defects in copper transport underlie the copper deficiency of Menkes disease and the copper toxicity of Wilson disease. Unidentified defects at the level of the copper transporter, metallochaperones, or the Menkes protein could be responsible for the hypocupremia in some patients. Copper accumulation in the lower bowel, presumably due to a defect in mucosal transport, has been described in a patient with a progressive neurological disease and hypocupremia. Failure to increase the reduced serum copper level with oral copper administration in patient 2 suggests the possibility of an absorptive defect.

The 3 patients described herein suggest that copper deficiency myeloneuropathy is a distinct clinical entity that has been rarely recognized previously. The clinical presentation is that of a progressive syndrome with clinical, electrophysiological, and radiographic evidence of a myelopathy with predilection for the posterior columns and corticospinal tracts. The clues are a low serum copper or ceruloplasmin level; however, these analytes have typically not been included as part of the usual myelopathy workup. Recognition of this entity is important because prompt recognition can prevent irreversible neurological damage. Recent knowledge regarding copper transport is likely to provide information on the cause of the hypocupremic state and subsequent insights into therapeutic options.

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