Hypocupremia secondary to excessive zinc supplementation and gastric surgery

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Practical Implications

Consider investigating additional nutritional deficiencies and appropriate replacement when one deficiency is detected, keeping in mind that vitamin B₁₂ and copper deficiencies can be seen together.

In humans, copper deficiency is a rare cause of myeloneuropathy. The neurologic syndrome was first recognized in ruminants afflicted with an ataxic myelopathy colloquially referred to as “swayback disease,” which describes the characteristic swaying hindquarters in animals. The incidence and recognition of acquired copper deficiency in humans is increasing alongside the frequency of bariatric surgery and other gastrointestinal surgeries¹ and excessive zinc ingestion.² Copper is primarily absorbed through the stomach and duodenum and is important in the normal function of both the central and peripheral nervous systems.³ Excessive zinc consumption causes increased expression of metallothionein in enterocytes, which preferentially binds copper. As a result, most of the copper ingested is not absorbed but rather sloughed off with the enterocytes into the lumen.²

Copper deficiency causes a subacute progressive myeloneuropathy with gait instability secondary to sensory ataxia. This resembles the subacute combined degeneration seen in cobalamin deficiency. MRI occasionally demonstrates T2 hyperintensity in the dorsal columns, typically in the cervical spinal cord. In addition to myeloneuropathy, other abnormalities due to copper deficiency include leukopenia, sideroblastic anemia, and myelodysplastic syndrome.⁴

Case report

A 73-year-old man was admitted for 1 year of progressive peripheral neuropathy and gait instability. Past medical history was notable for esophageal carcinoma treated with esophagectomy/partial gastrectomy and macular degeneration. His symptoms began as paresthesia in the hands and feet 1 year prior to admission. Laboratory testing with his outpatient physician showed normocytic anemia, a low-normal level of vitamin B₁₂, low copper at 10 µg/dL (normal 72–166 µg/dL), and normal methylmalonic acid level, hemoglobin A1c, thyroid function, and serum immunoelectrophoresis. EMG demonstrated a length-dependent sensorimotor polyneuropathy with mixed features of axonal and myelin involvement. He was treated for cobalamin deficiency. Despite treatment, over the next several months his symptoms progressed to sensory loss extending proximally in both the upper and lower extremities with increasingly frequent falls.

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Figure T2 hyperintensity in the posterior columns on axial section

On admission to our service, the patient's neurologic examination was notable for loss of pinprick and temperature to the elbows and thighs and loss of vibration to the elbows and groin bilaterally. Strength was normal in all extremities. Deep tendon reflexes were normal throughout. Plantar responses were extensor bilaterally. He was unable to stand without assistance due to severe truncal ataxia, but there was no limb ataxia, dysdiadochokinesia, or dysmetria. Laboratory testing showed a normal leukocyte count and mild normocytic anemia. A repeat vitamin B₁₂ was normal. Rapid plasma reagin, HIV, anti-neutrophil cytoplasmic antibodies, and paraneoplastic panel were all negative. Fecal examination for intestinal parasites was negative. Copper and ceruloplasmin levels were reduced to 10 µg/dL (normal 72–166 µg/dL) and 12.9 mg/dL (normal 15–30 mg/dL), respectively. Serum zinc levels were 176 µg/dL (normal 56–134 µg/dL). An MRI of the cervical spine demonstrated T2 hyperintensity in the posterior columns from the C2–C3 level to the C5–C6 level (figure), and a diagnosis of copper deficiency myelopathy was made.

The patient was treated with 8 mg of IV copper daily for 1 week followed by oral supplementation of 2 mg daily. After 6 weeks, his copper level was 126 µg/dL. His paresthesias had resolved and he had mild improvement in sensation; however, he was still unable to walk unassisted and continued to have sensory deficits.

DISCUSSION

The patient's progressive neurologic deficits were best explained by hypocupremia secondary to malabsorption of copper from his esophagectomy and excessive zinc consumption in the form of an ocular multivitamin. The Age-Related Eye Disease Study 2 (AREDS2) ocular multivitamin capsule that patient took for his macular degeneration contained 40 mg of zinc, which he took twice daily. The recommended daily intake of zinc is 11 mg per day; our patient was taking more than 7 times the daily recommended amount.⁵

Copper deficiency is an underdiagnosed cause of neurologic dysfunction with increasing incidence and should be kept in the differential by clinicians, especially in the setting of gastric surgery and zinc supplementation. This case illustrates the importance of investigating additional nutritional deficiencies and appropriate replacement when one deficiency is detected, keeping in mind that vitamin B₁₂ and copper deficiencies can be seen together. Response to replacement is variable, with some improvement in neurologic function reported, although cessation of progression is the more common outcome. Other nutritional deficiencies that can lead to a myelopathy include vitamin B₁₂ and vitamin E (see reference 4 for a discussion of the differential diagnosis).

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