Myelopolyneuropathy and Pancytopenia Due to Copper Deficiency and High Zinc Levels of Unknown Origin

Further Support for Existence of a New Zinc Overload Syndrome

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Objective: To describe a patient with idiopathic zinc overload without an identifiable source and secondary copper deficiency causing myelopolyneuropathy and pancytopenia.

Design: Case report.

Patient and Results: A 46-year-old man presented with severe bone marrow suppression and subsequently developed progressive myelopathy with sensory ataxia. No identifiable cause of myelopathy was detected, and his neuroimaging findings were unremarkable. Plasma analysis demonstrated a low copper level and an increased zinc level (10 µg/dL [12.6-18.9 µmol/L] and 184 µg/dL [28.2 µmol/L], respectively; normal range for both, 80-120 µg/dL [12.6-18.9 µmol/L and 12.3-18.4 µmol/L, respectively) and a low level of ceruloplasmin. There was no evidence for an external source of zinc. Daily oral supplementation with 2 mg resulted in the prompt reversal of hematologic abnormalities, improved but still subnormal plasma copper levels, and normalization of ceruloplasmin values. The patient’s neurologic condition deteriorated further, with worsening of myelopathy and development of polyneuropathy. Analyses of plasma copper and zinc levels demonstrated persisting hyperzincemia and subnormal copper levels during 4 years of follow-up. Increased copper supplementation to 8 mg/d partially reversed his neurologic signs. A clinical investigation of 6 siblings and 1 surviving parent did not identify family members with similar abnormalities.

Conclusions: Persistent hyperzincemia without an identifiable external source appears to be a primary metabolic defect, while copper deficiency is a secondary phenomenon, causing hematologic and neurologic abnormalities. Two unrelated patients with similar idiopathic hyperzincemia and hypocupremia have been recently described. This suggests the existence of a new metabolic disorder with idiopathic zinc overload.

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Several patients with documented excessive zinc intake and bone marrow suppression have been described. Hematologic abnormalities are due to zinc-induced copper deficiency, and copper supplementation with removal of the external zinc source promptly reverses pancytopenia. Although copper deficiency has been associated with neurodegeneration in humans and animals, to our knowledge no neurologic abnormalities have been described in patients with excessive zinc ingestion, presumably because of the short duration of the copper deficiency.

In 2000, Prodan and Holland described a 45-year-old man who had marked hyperzincemia and reduced copper levels; there was no evidence for an external source of zinc. The patient presented with severe anemia and brain demyelination. Originally, an elevated zinc level was suggested as a cause of the demyelination. However, recent follow-up clinical data by Prodan et al on the first patient and data on a female patient with similar laboratory and neurologic abnormalities have been reported. It is now suggested that zinc-induced hypocupremia was responsible for the demyelination.

Herein, we report an additional case of severe copper deficiency and hyperzincemia without an identifiable external source. The patient developed progressive myelopathy and polyneuropathy together with severe anemia. Copper supplementation completely reversed his hematologic abnormalities, but he had only partial improvement of his neurologic symptoms during 4 years of follow-up. We also propose possible pathophysiologic features and suggest that the primary abnormality is zinc overload causing secondary copper deficiency.
A previously healthy individual began to complain of chest pain and shortness of breath at age 46 years. Severe normocytic anemia with a hemoglobin level of 7.9 g/dL and a hematocrit of 24% was found. A few weeks later, he noticed progressive numbness, weakness of both lower extremities, and poor balance. An examination in November 1997, approximately 5 months after the onset of neurologic symptoms, revealed an intact mental status, normal cranial nerve evaluation findings, and full strength. Deep tendon reflexes were grade 2+ on the Medical Research Council scale in the upper extremities and abnormally brisk in the lower extremities, with bilateral plantar flexor response. A sensory examination demonstrated markedly reduced position sensation in the lower extremities, and it was completely absent in the toes and ankles; vibration sensation was absent in the toes, reduced in the ankles, but normal in other segments. The patient had signs of sensory ataxia without any cerebellar signs; his gait was wide based. Results of magnetic resonance imaging of the whole spine were unremarkable. Repeat testing of urinary copper demonstrated a level of 3.97 mg/d. Repeat testing of the 24-hour levels of urinary copper demonstrated a value of 0.03 mg/d, and the ceruloplasmin level was 22 mg/dL. His hematologic values normalized after approximately 3 months of copper therapy. However, the patient experienced a gradual worsening of his neurologic symptoms and started to use a walker because of poor balance. He reported numbness and pain affecting his legs and hands. Neurologic examination findings were remarkable for mild spasticity affecting his lower extremities, brisk deep tendon reflexes in the upper extremities and knees, absent ankle deep tendon reflexes, and a bilateral extensor plantar response. He also developed distal weakness of the dorsiflexors of his feet corresponding to grade 3/5 on the Medical Research Council scale. Sensory examination findings demonstrated an absence of vibratory sensation up to the pelvis and markedly diminished vibratory sensation in both hands; positional sensation at the toes and ankles was absent and markedly reduced at the fingers. The patient continued to have marked sensory ataxia and a positive Romberg sign. Magnetic resonance imaging of the brain was performed and demonstrated one 3-mm area of increased signal on T2-weighted images in the left centrum semiovale. Findings from repeat cerebral and thoracic magnetic resonance imaging were unchanged. The patient continued to deny any zinc intake, which was confirmed by his family members. The copper and zinc content in the drinking water in the patient’s house was within normal limits. The patient underwent liver biopsy 4 months after the initiation of copper replacement therapy. Histologic examination findings revealed only mild steatosis; the copper content of the liver was 6 µg/g (normal range, 20-50 µg/g) of dry weight, and the zinc content was 363 µg/g (normal range, 250-450 µg/g) of dry weight. Repeat electromyographic examination findings remained normal without any signs of denervation. However, the results from nerve conduction studies revealed a slowing of conduction velocities in the lower extremities, ranging from 32 to 33 m/sec, that could not be attributed to any technical factors, with normal conduction velocities in the upper extremities. The sensory and motor response amplitudes were reduced by approximately 30%. Somatosensory evoked potentials obtained after stimulation of the tibial nerve showed a poor signal-to-noise ratio, suggestive of a peripheral conductive block; somatosensory evoked potentials following median nerve stimulation demonstrated prolonged N13 to N20 interpeak latency, indicative of a conduction delay within the cervical cord.

The patient’s copper dosage was increased to 4 mg/d and ultimately to 8 mg/d orally, but compliance re-
mained poor. In June 2000, he began to use a wheelchair because of poor balance and weakness. His neurologic examination findings demonstrated a more profound loss of proprioception in the upper extremities and a worsening of spasticity in the lower extremities. There was no change in his distal foot weakness. His hematologic values remained normal.

The patient was reexamined 1 year later, 2 1/2 years after initiation of copper therapy. He reported better compliance with copper supplementation and, again, denied any exposure to zinc. By that time, he had been disabled for more than 3 years and was not able to work. His neurologic examination findings showed improvement of distal strength in both feet, corresponding to grade 4/5 on the Medical Research Council scale. Moreover, he had marked improvement in the positional and vibratory sensation in both upper extremities. Proprioception also had improved in the lower extremities, and he was able to identify passive movements in his ankles but not in his toes. Deep tendon reflexes in the upper extremities and knees remained brisk and were absent in both ankles; plantar response was extensor bilaterally. He was able to walk without an assistive device. His examination findings 1 year later had not significantly changed.

There was no family history of similar abnormalities. His father died at age 64 years from a cardiac cause and had no history of neurologic problems. There was no history of consanguinity between his parents. He had 5 brothers and 1 sister. His mother and all siblings underwent complete neurologic examinations; all findings were within normal limits. Serum copper and zinc levels were also measured; the levels for serum copper varied from 87 to 99 µg/dL (13.7-15.6 µmol/L) and for zinc from 73 to 82 µg/dL (11.2-12.5 µmol/L) (both within normal limits).

**COMMENT**

Herein, we describe a patient with elevated zinc and reduced copper plasma levels who developed pancytopenia, progressive myelopathy, and subsequent polyneuropathy. The hematologic abnormalities responded to copper supplementation, but there has been only a partial improvement in the central and peripheral nervous system involvement. The main laboratory abnormality present in our patient appears to be hyperzincemia, which has persisted during a 4-year follow-up. Plasma zinc levels obtained during this time have remained significantly elevated. Moreover, measurements of the levels of 24-hour zinc excretion demonstrated an approximately 10-fold increase above the normal values. This suggests a significant zinc overload; however, zinc storage in the liver was not excessive, as documented by normal values for hepatic zinc content on liver biopsy. The cause of the high plasma and urine zinc levels remains unknown in this patient. A high intake of zinc must be considered in this situation, but we did not identify any intentional or inadvertent ingestion of zinc. One possibility was a questionable occupational exposure (welding), but the persistence of hyperzincemia for more than 3 years after the patient was disabled and unable to work argues against this explanation. The remaining theories include a high intestinal absorption of zinc or a diminished intestinal excretion of zinc, both factors believed to be involved in maintaining a normal zinc balance. Neither has been studied in this patient to date.

Copper deficiency is a secondary phenomenon, similar to that seen in patients with documented excessive zinc ingestion or in patients with Wilson disease who are deliberately treated with zinc to induce a negative copper balance. This happens because of intestinal metallothionein induction by zinc, which blocks copper absorption. Furthermore, a depleted copper content in the liver tissue suggests a prolonged state of copper deficiency. Oral copper supplementation resulted in normalization of ceruloplasmin values and a significant rise in the plasma copper level, suggesting that the blockage of intestinal absorption of copper could be overcome with sufficient copper intake. However, the highest documented plasma copper level was below normal at 67 µg/dL (10.5 µmol/L) (normal range, 80–120 µg/dL [12.6-18.9 µmol/L]), and it is unclear whether this was due to an insufficient copper dosage, patient noncompliance, or other factors.

The clinical presentation of our patient was consistent with myelopathy with predominant involvement of the dorsal columns. Later in the course of the disease, we detected electrophysiologic changes suggestive of polyneuropathy. Myelopathy associated with chronic copper deficiency has been described in a 46-year-old woman with a history of gastrointestinal resection. The pathophysiology of copper deficiency syndrome in that patient was different from what we found in our patient because her zinc levels were normal and impaired copper absorption due to a short-bowel syndrome explained the reduced copper levels. However, this supports the concept that copper deficiency alone, and not hyperzincemia, is the cause of neurodegeneration. Elevated plasma zinc levels caused by the increased binding of zinc to albumin can be benign and without any clinical abnormalities. Hyperzincemia associated with autoimmune disorders has been described in a few patients. They had normal plasma copper levels, and their clinical symptoms were due to functional hypozincemia. Abnormalities in calprotectin metabolism causing zinc sequestration have been suggested as a cause of the disorder.

Idiopathic hyperzincemia associated with copper deficiency has been described in 2 unrelated patients who developed signs of widespread brain demyelination. Our patient had almost identical biochemical abnormalities, suggesting that this may be the same metabolic syndrome. He did not have any signs of brain demyelination. It is unclear whether his myelopathy was due to an axonal degeneration or demyelination of the spinal cord, or both, that was not detected by magnetic resonance imaging. Electrophysiologic study results (nerve conduction studies and somatosensory evoked potentials) suggested the presence of demyelinating polyneuropathy, but a detailed histologic characterization was not possible as the patient refused sural nerve biopsy. Axonal degeneration and demyelination have been observed in experimentally induced copper deficiency and in swayback, a naturally occurring enzootic ataxia. Menkes (kinky hair) disease is another example of a copper
deficiency affecting the central nervous system. It is caused by a defective copper transport across the blood-brain barrier. The pathologic features of Menkes disease are complex and present at birth. Widespread neuronal loss is the most conspicuous neuropathologic feature, but abnormal myelination is also prominent; however, myelopathy and polyneuropathy are not features of Menkes disease. The cause of the difference in clinical presentations between our patient and those of the 2 individuals described by Prodan et al. remains unclear; the initial copper and zinc levels, and presumed duration of untreated copper deficiency, do not appear to be sufficiently different to account for this variability.

We evaluated the patient's 6 siblings, and all had normal zinc and copper levels and normal neurologic examination findings. The 2 individuals described by Prodan et al. with idiopathic hyperzincemia and secondary copper deficiency also had normal family histories although measurement of copper and zinc levels in first-degree relatives was not reported. However, no identifiable factors suggesting an acquired process have been identified in any of these 3 individuals. The presence of the same biochemical abnormality in a female argues against an X-linked inheritance, but we cannot exclude a possibility of autosomal recessive or autosomal dominant inheritance, with reduced penetrance or new mutations. The pathophysiologic characteristics of this proposed new metabolic syndrome remain unknown, but a tendency to an increased absorption of zinc, similar to iron overload in hematochromatosis, or a decreased excretion of zinc, similar to copper overload in Wilson disease, is possible. Both of these scenarios would result in an increased expression of intestinal metallothionein, causing the blockage of copper absorption and subsequent secondary copper deficiency.

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