POINTS TO REMEMBER

- Copper deficiency can be a treatable cause of neurologic syndromes, including ataxia, neuropathy, spasticity, optic neuropathy, and motor neuron degeneration resembling amyotrophic lateral sclerosis.
- Copper deficiency is caused by copper malabsorption secondary to altered gastrointestinal tract anatomy (e.g., after bariatric surgery) or upregulation of copper-chelating proteins by excess zinc (e.g., from denture adhesive), although a significant percentage of cases remain idiopathic.
- A history of gastrointestinal surgery, as well as of denture adhesive use or zinc supplementation, should be routinely obtained in evaluating patients with sensorimotor neurologic disorders.
- Serum copper should also be measured in patients with unexplained cytopenia or a suspected myelodysplastic syndrome.
- Zinc and ceruloplasmin concentrations should also be checked when copper deficiency is suspected.
- When copper deficiency is identified in a patient with a history of gastrointestinal resection, other concomitant nutritional deficiencies should also be investigated.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures or Potential Conflicts of Interest: *No authors declared any potential conflicts of interest.*

References

1. Kumar N, Gross JB, Ahlskog JE. Copper deficiency myelopathy produces a clinical picture like subacute combined degeneration. Neurology 2004;63:33–9.
2. Kumar N, Ahlskog JE, Klein CJ, Port JD. Imaging features of copper deficiency myelopathy: a study of 25 cases. Neuroradiology 2006;48:78–83.
3. Schleper B, Stuerenberg HJ. Copper deficiency–associated myelopathy in a 46-year-old woman. J Neurol 2001;248:705–6.
4. Prodan CI, Holland NR, Wisdom PJ, Burstein SA, Bottomley SS. CNS demyelination associated with copper deficiency and hyperzincemia. Neurology 2002;59:1453–6.
5. Weihl CC, Lopate G. Motor neuron disease associated with copper deficiency. Muscle Nerve 2006;34:789–93.
6. Nations SP, Boyer PJ, Love LA, Burritt MF, Butz JA, Wolfe GI, et al. Denture cream: an unusual source of excess zinc, leading to hypocupremia and neurologic disease. Neurology 2008;71:639–43.
7. Naismith RT, Shepherd JB, Weihl CC, Tutlam NT, Cross AH. Acute and bilateral blindness due to optic neuropathy associated with copper deficiency. Arch Neurol 2009;66:1025–7.
8. Halfdanarson TR, Kumar N, Li CY, Phyliky RL, Hogan WJ. Hematological manifestations of copper deficiency: a retrospective review. Eur J Haematol 2008;80:523–31.
9. Van den Berghe PVE, Klomp LWJ. New developments in the regulation of intestinal copper absorption. Nutr Rev 2009;67:658–72.
10. Goodman BP, Mistry DH, Pasha SF, Bosch PE. Copper deficiency myeloneuropathy due to occult celiac disease. Neurologist 2009;15:355–6.

Commentary

Jonathan D. Gitlin*

Copper is an essential nutrient, readily available in the diet and rapidly absorbed through the gastrointestinal tract. Copper is abundant in dietary foods and water sources, and copper deficiency in humans is therefore uncommon. Nevertheless, acquired copper deficiency may occur when gastrointestinal uptake is impaired. The most common manifestations of copper deficiency are a decreased serum ceruloplasmin and anemia, neutropenia, or thrombocytopenia. If prolonged, copper deficiency will produce neurologic signs and symptoms that include sensory ataxia, hyperreflexia, and a spastic gait. If the deficiency is detected early, copper supplementation always resolves the serum and hematologic manifestations and prevents further neurologic deterioration. Neurologic recovery may be slow, however, and preferentially involves the sensory symptoms. Thus, copper deficiency is an important clinical problem that must be recognized early by the physician.

This case report raises several fascinating clinical issues. The reported findings are similar to those observed in patients with megaloblastic anemia and subacute combined degeneration due to vitamin B_{12} deficiency. The mechanisms of bone marrow dysplasia and neurologic degeneration in copper deficiency are unknown, and these findings remind us of the unexplored relationship between cobalamin and copper metabolism. This patient was also reported to have increased serum zinc, presumably from chronic ingestion of dental adhesive. Zinc ingestion

Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN.
* Address correspondence to the author at: Department of Pediatrics, Vanderbilt University School of Medicine, 2200 Children's Way, Nashville, TN 37232. E-mail jonathan.d.gitlin@vanderbilt.edu.
Received March 11, 2011; accepted March 21, 2011.
DOI: 10.1373/clinchem.2011.163485

is associated with copper deficiency, and patients have been identified with acquired copper deficiency of unknown etiology and increased serum zinc in the absence of exogenous zinc ingestion. These findings remind us that we have much to learn about the interplay of copper and zinc homeostasis and suggest that the resulting copper deficiency is likely more complex than the proposed interference with gastrointestinal tract absorption.

In the final analysis, case reports of rare diseases sharpen our diagnostic skills and reveal the hidden mysteries that remain to be explored in much of human physiology and disease.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures or Potential Conflicts of Interest: *No authors declared any potential conflicts of interest.*

Commentary

William L. Roberts*

This clinical case study is timely and interesting. A recent TV advertisement from a law firm aired in Utah and targeted victims who might have been harmed by zinc-containing denture adhesives. An Internet search on zinc toxicity identified 2 law firms that handle these cases and an advertisement for a zinc-free denture adhesive. Zinc toxicity may have causes other than excessive use of zinc-containing denture adhesives. Pennies minted in the US since 1983 contain 97.5% zinc. Zinc is highly reactive with gastric acid. Ingestion can cause local corrosion and systemic toxicity. Massive ingestion can be fatal *(1)*. Acute toxicity has resulted from storage of food or drink in galvanized containers. Toxicity due to ingestion of very large doses of zinc remains quite uncommon *(2)*. Pharmacologic intake of zinc (100–300 mg Zn/day) over a long period can lead to severe copper deficiency, like that described in this clinical case study. Ingestion of between the Recommended Daily Allowance of 15 mg/day and pharmacologic doses of 100 mg/day has been associated with adverse consequences *(2)*. Excessive absorption of zinc can also suppress iron absorption *(2)*.

Zinc is an essential cofactor in a number of cellular processes. A review of the literature on zinc and human health demonstrates that dietary zinc deficiency is a major health problem worldwide, with nearly 2×10^9 people affected *(3)*. Zinc deficiency is particularly problematic in infancy, with nearly 1×10^6 excess deaths due to pneumonia, diarrhea, and malaria occurring worldwide annually in children under 5 years. Adequate intake from foods can be difficult without fortification. Fortification programs are difficult to implement for the rural poor of less-developed countries. Obtaining an adequate intake of zinc in children is a major challenge worldwide, in contrast with the excessive intake from supplements and zinc-containing products in developed countries.

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Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:*

Employment or Leadership: W.L. Roberts, Academy of Clinical Laboratory Physicians and Scientists, and College of American Pathologists.
Consultant or Advisory Role: W.L. Roberts, ARUP Laboratories.
Stock Ownership: None declared.
Honoraria: None declared.
Research Funding: None declared.
Expert Testimony: None declared.

References

1. Bennett DR, Baird CJ, Chan KM, Crookes PF, Bremner CG, Gottlieb MM, Naritoku WY. Zinc toxicity following massive coin ingestion. Am J Forensic Med Pathol 1997;18:148–53.
2. Fosmire GJ. Zinc toxicity. Am J Clin Nutr 1990;51:225–7.
3. Prasad AS. Zinc deficiency. BMJ 2003;326:409–10.

ARUP Laboratories, Salt Lake City, UT.
* Address correspondence to the author at: ARUP Laboratories, 500 Chipeta Way, Salt Lake City, UT 84108. Fax 801-584-5207; e-mail william.roberts@aruplab.com.
Received March 15, 2011; accepted March 21, 2011.
DOI: 10.1373/clinchem.2011.163493