Clinical Review

Copper Deficiency

R. Hossain,[1] D.D. Grier[2]

Introduction

Unlike certain heavy metals such as iron or lead, which receive a great deal of attention during formal medical education, copper's role in the human body often goes neglected except during brief discussions of Wilson's disease or Menkes syndrome. This is not necessarily an educational oversight; manifestations of deficiency or excess are thought to be uncommon.[1,2] Still, knowledge of copper metabolism and deficiency has clinical utility. For example, patients with microcytic hypochromic anemia refractory to iron replacement therapy may actually have hypocupremia.[3] Deficiency of this trace element can also cause myelopathy that presents as subacute combined degeneration of the spinal cord, which is usually attributed to inadequate vitamin B_{12}.[4] These neurologic manifestations of copper deficiency are less likely to improve with increased duration of symptom.[5,6] Thus, the longer the clinician overlooks copper deficiency, the worse her patient's prognosis becomes. Copper deficiency, a recognized cause of anemia, neutropenia, myelopathy, and peripheral neuropathy, undoubtedly deserves physician attention.[4,7-11] In this review, we discuss copper's role in the human body, the pathogenesis of hematologic and neurologic manifestations of copper deficiency, and the clinical concepts that can aid in diagnosis and management.

Biochemistry and Physiology

Copper, a transition metal, can physiologically exist in either a reduced (Cu1+) or oxidized (Cu^{2+}) state. This ability to freely ferry electrons allows copper to participate in redox reactions. Approximately one dozen enzymes, mostly oxidoreductases and monooxygenases, exist that require copper for catalytic activity (Table 1).[12] These cupro-enzymes have reduced activity in a copper-deficient state. Numerous other copper-binding proteins exist in the body (Table 2).[13] Impaired function of these copper-utilizing enzymes and proteins can produce several features of copper deficiency, such as hypopigmentation, coagulopathy, and weakness.

Table 1: Abbreviated List of Copper-dependent Enzymes

Enzyme	Function
Ceruloplasmin	Iron oxidation and copper transport
Cyctochrome c oxidase	Electron transport
Dopamine β-monooxygenase	Norepinephrine synthesis
Copper-zinc superoxide dismutase	Superoxide removal
Hephaestin	Iron oxidation
Lysyl oxidase	Collagen cross-linking
Tyrosinase	Melanin synthesis

Table 2: Abbreviated List of Copper-binding Proteins

Protein	Function
Albumin	Plasma transport
Amyloid precursor protein	Cellular transport
ATP7A	Efflux, protein metallation
ATP7B	Efflux, ceruloplasmin metallation
Clotting factors V, VIII	Thrombosis
Ctr1, Ctr2	Influx transport
Metallothionein	Storage
Prion protein	Unknown
Transcuprein (α2-macroglobulin)	Plasma transport

After iron and zinc, copper is the third most prolific trace element in the human body.[14] It is an essential dietary micronutrient; the Recommended Dietary Allowance for adult men and women is 0.9 mg/day, although an argument has been made for higher intake (i.e., 2.3 mg/day).[15,16] In a typical Western diet, copper is usually found in vegetables, legumes, grains, and animal products (e.g., beef, fish, poultry).[17,18] Attaining adequate levels of copper through a regular diet is thought to be feasible; the median intake of copper from food is approximately 1.0 to 1.6 mg/day for adult men and women.[15] Thus, in healthy people in most parts of the world, acquired hypocupremia due to malnutrition is relatively infrequent.[19]

Dietary copper absorption occurs in the stomach and proximal duodenum.[15,20,21] The stomach promotes uptake via enhanced copper solubility; by creating an acidic environment, copper readily dissociates from copper-containing dietary macromolecules. Mechanisms underlying intestinal absorption include saturable-mediated transport at lower levels of dietary copper and nonsaturable-nonmediated (i.e., paracellular) transport at high levels. At the intestinal apical surface, membrane-bound copper transport protein (Ctr1) actively transports copper into the enterocytes.[22] (Figure 2) At the basolateral surface, Menkes protein (ATP7A) shuttles copper into the hepatic portal circulation; mutation in this protein underlies Menkes syndrome, leading to impaired copper absorption and symptoms of severe deficiency.[23] Albumin and transcuprein in the portal blood bind copper and deliver it to the liver parenchymal cells for uptake.[9,15]

Hepatocytes incorporate copper into superoxide dismutase, cytochrome c oxidase, and the carrier protein ceruloplasmin, while excess copper binds to metallothionein to form a nontoxic complex. Ceruloplasmin transports copper from the liver to systemic tissues. It then binds to peripheral cell surface receptors and releases copper into the cell, which integrates into the numerous proteins listed above.[24] Beyond copper transport, ceruloplasmin also facilitates iron metabolism

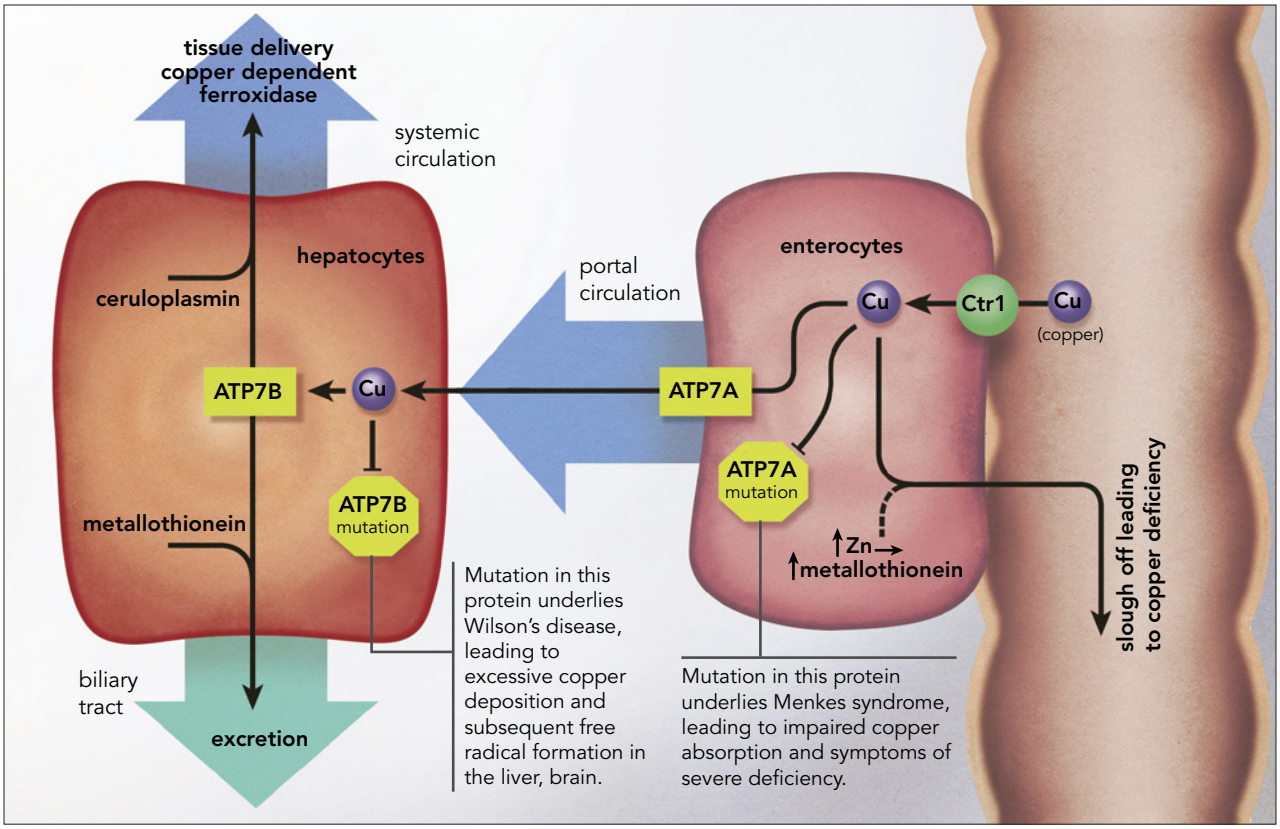

Figure 1. Summary of Copper physiology

Graphic by Wake Forest Baptist Medical Center, Creative Communications

via copper-dependent ferroxidase activity.[14] Ferric iron then can bind to transferrin for systemic transport. Hephaestin, another copper-dependent ferroxidase, is expressed in the duodenal mucosa and facilitates ferric iron transport across the basolateral surface for transferrin loading.[10]

Copper homeostasis is maintained and copper toxicity is avoided via biliary excretion.[9,15] Wilson P-type ATPase (ATP7B) mediates copper efflux from the hepatocyte into the biliary tract; mutation in this protein underlies Wilson's disease, leading to excessive copper deposition and subsequent free radical formation in the liver, brain, and other tissues.[25]

Pathogenesis

Copper deficiency limits copper-dependent enzymatic activity and leads to clinical features such as hair and skin hypopigmentation, osteoporosis, anemia, neutropenia, sensory ataxia, myelopathy, and peripheral neuropathy.[4,13,26,27] The manifestations of copper-deficient state in the blood (i.e., anemia, neutropenia) and nervous system (i.e., myelopathy) arise not due to impairment of singular enzymatic processes but rather multifactorial interplay.

Copper deficiency anemia (often microcytic, but normocytic and macrocytic varieties exist) results from the aforementioned interaction between copper-dependent ferroxidases and iron.[3,6,28,29] Decreased activity of ceruloplasmin and hephaestin leads to impaired iron absorption from the small bowel and diminished conversion of ferrous to ferric iron. These changes cause disruption of systemic transport by transferrin and inadequate incorporation of iron into protoporphyrin.[3,6,30,31] Poor heme synthesis, in conjunction with erythrocyte membrane fragility due to decreased copper-zinc superoxide dismutase activity, leads to mitochondrial iron accumulation and ringed sideroblast formation (Figure 2).[19]

Clear mechanisms underlying copper deficiency neutropenia have been elusive, although numerous plausible explanations have been put forward. These include loss of myeloid progenitor cells in the bone marrow, destruction of mature neutrophils due to increased clearance from the circulation, impaired egress of neutrophils from the marrow,

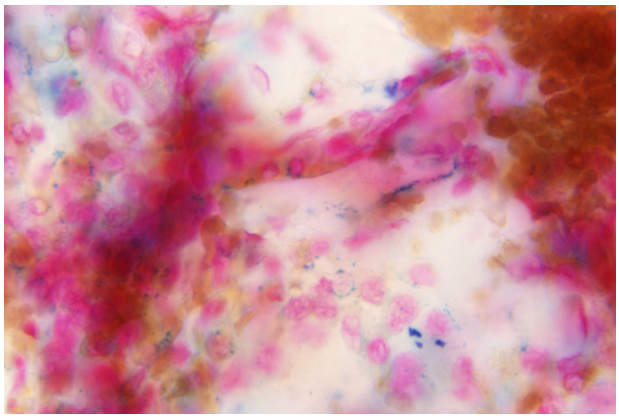

Figure 2. Prussian blue (iron) stain revealing ringed sideroblasts

and dysfunctional granulocytic maturation within the marrow.[3,9,30,32] CD34-positive progenitor cell maturation has been demonstrated to become arrested in a copper-deficient in vitro environment, lending credence to this premise.[33]

Hypocupremia-induced myelopathy produces a clinical and radiologic picture identical to subacute combined degeneration, leading to speculation that both disease processes may share a final common pathway.[9,34] It is currently unknown whether methionine synthase, an enzyme whose dysfunction causes subacute combined degeneration of the spinal cord, depends on copper for its catalytic activity. Thus, its involvement in copper deficiency myelopathy remains unclear.[59] An alternative proposed mechanism for the neurological features of copper deficiency involves cytochrome c oxidase dysfunction.[35] Copper deficiency in humans and ruminants produces a cytochrome enzyme with aberrant structure and kinetics. Impaired activity of any number of copper-dependent enzymes with critical roles in the nervous system (e.g., dopamine β-monooxygenase) can contribute to this disease process.

Risk Factors

Inadequate dietary copper intake infrequently leads to copper deficiency; however, numerous risk factors can impede adequate copper uptake. These include gastrointestinal tract surgery, zinc excess, prolonged total parenteral nutrition, and malabsorption enteropathies.[26,36]

Upper gastrointestinal tract surgery, gastrectomy, bariatric surgery, and small bowel resection or bypass all increase risk

of hypocupremia.[10,22,29,37,38] As mentioned above, gastric acidity facilitates copper dissociation from dietary macromolecules, promoting absorption further down the alimentary canal. Thus, procedures that produce a hypoacidemic environment compromise copper bioavailability.[37,39] Surgeries that bypass the duodenum, the primary site of copper absorption, provoke copper malabsorption. Nonetheless, copper deficiency after gastrointestinal tract surgery still remains uncommon, with one study demonstrating a 9.6% prevalence rate 0-60 months following Roux-en-Y gastric bypass.[39-41] Decades can pass following surgery before clinical manifestations arise.[3]

Zinc excess increases risk of hypocupremia by promoting intestinal sequestration of copper.[3,42,43] Hyperzincemia induces the upregulation of metallothionein within enterocytes, which has strong affinity for zinc but stronger affinity for copper.[23] The copper-metallothionein complex remains trapped within the intestinal cells. Eventually, the enterocytes slough off the mucosa, leading to copper depletion. Hyperzincemia most often results from excess oral zinc intake. While metal pica (i.e., penny ingestion) can cause zinc overload, especially in psychiatric patients, excess zinc more often results from inadvertent ingestion of denture adhesive (which is rich in zinc) or use of zinc lozenges for the common cold.[42,44-47]

Other risk factors for copper deficiency are based in principle on malnutrition. Prolonged total parenteral nutrition without copper supplementation is known to produce anemia and leukopenia, but manifests only after continued dependence (usually > 1 month).[14,48-50] Similarly, malabsorptive enteropathies (e.g. celiac disease) can create deficits of iron, vitamin B_{12}, folate, zinc, and copper.[51-53]

Clinical Features

The primary challenge in identifying copper deficiency is the nonspecific set of signs and symptoms that characterize it. Copper deficiency anemia can easily be attributed to iron deficiency, and copper deficiency myelopathy is often mistaken for vitamin B_{12} deficiency.[9,11,30] Furthermore, hematologic and neurologic abnormalities frequently occur together. Thus, awareness of the constellation of risk factors and features of copper deficiency is required.

Hematologically, copper deficiency most often produces anemia, ranging from microcytic to macrocytic, and neutropenia.[31] Cases of thrombocytopenia and pancytopenia, although rare, have also been documented.[6,14,19,49] Because copper deficiency mimics iron deficiency or megaloblastic anemia but remains refractory to replacement of those nutrients, bone marrow surveys are frequently conducted.[54] The bone marrow of copper-deficient patients demonstrate ringed sideroblasts, vacuolated myeloid and erythroid precursors (Figure 3), hemosiderin deposition in plasma cells, and overall left-shifted granulopoiesis and erythropoiesis.[11,19] These findings, in conjunction with hallmark erythroid hyperplasia and decreased myeloid to erythroid ratio, can be confused for a myelodysplastic syndrome.[3,6,29,30,55]

Neurologically, copper deficiency most often produces myelopathy or myeloneuropathy.[4,6,9,35] This presents as sensory ataxia with lower extremity spasticity, impaired proprioception, and loss of vibratory sensation.[56] Much like vitamin B_{12} deficiency, these features result from abnormalities in the posterior column of the spinal cord. Postmortem analyses reveal degeneration in the spinal cord pyramidal tract and posterior columns.[57] Sensory ataxic myelopathy can be exacerbated by cerebellar neuronal loss, leading to atrophy.[58] Peripheral neuropathy is another complication of copper deficiency, leading to paresthesias, impaired thermoception, and loss of nociception in the lower extremities.[4,56] Predictably, MRI T2 weighted imaging demonstrates increased signals in the dorsal column white matter identical to subacute combined degeneration.[6,57]

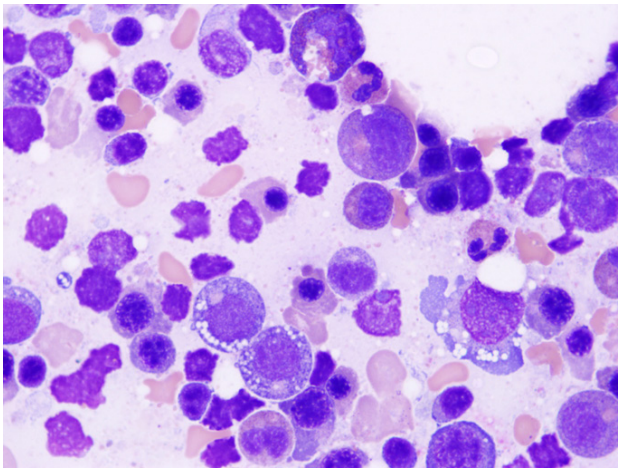

Figure 3. Bone marrow aspirate smear with vacuolated myeloid and erythroid precursors and mild erythroid atypia.

Diagnosis

Considering the low prevalence of copper deficiency and its nonspecific features, clinicians must rule out other disease entities while maintaining a high index of suspicion. Thus, complete blood count and vitamin B_{12} levels need to be assessed.[26] The normal range of serum copper levels is 0.75 – 1.45 µg/mL.[36] Measuring serum copper alone is generally sufficient to make a diagnosis of hypocupremia, but marginal copper deficiency may not be detected.[30] If serum copper levels remain normal despite symptoms that suggest copper deficiency, measurement of ceruloplasmin levels (normal range 22.9-40.1 mg/dL) can prove useful.[60] If tests confirm copper deficiency, subsequent evaluation of serum zinc levels (normal range 0.66-1.10 µg/mL) to assess zinc-induced hypocupremia is warranted; however, clinicians may find elevated serum zinc without any clear sources of exogenous zinc consumption.[3]

Treatment

Dosage, frequency, and formulation of copper replacement remain inexact due to lack of trials. Oral replacement is preferred, with routine administration of 2 mg/day until symptoms and serum copper levels normalize.61 For intravenous replacement, 2 – 4 mg/day for 6 days is recommended for severe deficiency, and 3 – 8 mg/day is recommended for mild to moderate deficiency until symptoms improve. After copper replacement therapy, neurologic deficits often do not improve, but hematologic derangements promptly normalize within 1 – 3 months.[5]

Authors

Author Affiliations: [1]Wake Forest School of Medicine, [2]Department of Pathology, Wake Forest School of Medicine, Dean of Admissions, Winston-Salem, NC 27157

Sources of Funding: There was no funding for this project.

Conflicts of Interest: The authors have no conflicts of interest to report.

Address correspondence to:
David D. Grier, M.D.
Associate Dean and Professor of Pathology
Wake Forest School of Medicine
Winston-Salem, NC, 27157
Phone: 336-716-4264
dgrier@wakehealth.edu

References

1. Williams DM. Copper deficiency in humans. Semin Hematol. 1983. 20:118-28.
2. Gaetke LM, Chow CK. Copper toxicity, oxidative stress, and antioxidant nutrients. Toxicology. 2003.189:147-63.
3. 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.
4. Kumar N, Gross JB Jr, Ahlskog JE. Copper deficiency myelopathy produces a clinical picture like subacute combined degeneration. Neurology. 2004. 63: 33-9.
5. Prodan CI, Rabadi M, Vincent AS, Cowan LD. Copper supplementation improves functional activities of daily living in adults with copper deficiency. J Clin Neuromuscul Dis. 2011. 12: 122-8.
6. Gabreyes AA, Abbasi HN, Forbes KP, McQuaker G, Duncan A, Morrison I. Hypocupremia associated cytopenia and myelopathy: a national retrospective review. Eur J Haematol. 2013. 90: 1-9.
7. Bottomley SS. Sideroblastic anemias. In: Greer JP, Foerster J, Lukens JN, Rodgers GM, Paraskevas F, Glader B, editors. Wintrobe's Clinical Hematology, 11th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004. 1011–1033.
8. Beutler E. Anemia resulting from other nutritional deficiencies. In: Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT, editors. Williams Hematology, 7th ed. New York: McGraw-Hill; 2006. 555–559.
9. Jaiser SR, Winston GP. Copper deficiency myelopathy. J Neurol. 2010. 257: 869-81.
10. Bertfield DL, Jumma O, Pitceathly RD, Sussman JD. Copper deficiency: an unusual case of myelopathy with neuropathy. Ann Clin Biochem. 2008. 45: 434-5.
11. Kumar N, Elliott MA, Hoyer JD, Harper CM Jr, Ahlskog JE, Phyliky RL. "Myelodysplasia," myeloneuropathy, and copper deficiency. Mayo Clin Proc. 2005. 80: 943-6.
12. Prohaska, J.R.Copper. In: J. Erdman, I. Macdonald&S. Zeisel, editors. Present Knowledge in Nutrition. Oxford, UK: Wiley-Blackwell; 2012. 873–896.
13. Prohaska JR. Impact of copper deficiency in humans. Ann N Y Acad Sci. 2014. 1314: 1-5.
14. Angotti LB, Post GR, Robinson NS, Lewis JA, Hudspeth MP, Lazarchick J. Pancytopenia with myelodysplasia due to copper deficiency. Pediatr Blood Cancer. 2008. 51:693-5.
15. Institute of Medicine (US) Panel on Micronutrients. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington (DC): National Academies Press (US); 2001.
16. Chambers A, Krewski D, Birkett N, Plunkett L, Hertzberg R, Danzeisen R, Aggett PJ, Starr TB, Baker S, Dourson M, Jones P, Keen CL, Meek B, Schoeny R, Slob W. An exposure-response curve for copper excess and deficiency. J Toxicol Environ Health B Crit Rev. 2010. 13:546-78.
17. Subar AF, Krebs-Smith SM, Cook A, Kahle LL. Dietary sources of nutrients among US adults, 1989 to 1991. J Am Diet Assoc. 1998. 98: 537-47.
18. Cotton PA, Subar AF, Friday JE, Cook A. Dietary sources of nutrients among US adults, 1994 to 1996. J Am Diet Assoc. 2004. 104:921-30.
19. Koca E, Buyukasik Y, Cetiner D, Yilmaz R, Sayinalp N, Yasavul U, Uner A. Copper deficiency with increased hematogones mimicking refractory anemia with excess blasts. Leuk Res. 2008. 32: 495-9.
20. Williams DM, Loukopoulos D, Lee GR, Cartwright GE. Role of copper in mitochondrial iron metabolism. Blood. 1976. 48: 77-85.
21. Mason KE. A conspectus of research on copper metabolism and requirements of man. J Nutr. 1979. 109: 1979-2066.
22. Shahidzadeh R, Sridhar S. Profound copper deficiency in a patient with gastric bypass. Am J Gastroenterol. 2008. 103:2660-2.

23. Willis MS, Monaghan SA, Miller ML, McKenna RW, Perkins WD, Levinson BS,Bhushan V, Kroft SH. Zinc-induced copper deficiency: a report of three casesinitially recognized on bone marrow examination. Am J Clin Pathol. 2005. 123:125-31.
24. Camakaris J, Voskoboinik I, Mercer JF. Molecular mechanisms of copper homeostasis. Biochem Biophys Res Commun. 1999. 261: 225-32. Bowcock AM, Farrer LA, Hebert JM, Agger M, Sternlieb I, Scheinberg IH, Buys CH, Scheffer H, Frydman M, Chajek-Saul T, et al. Eight closely linked loci place the Wilson disease locus within 13q14-q21. Am J Hum Genet. 1988. 43: 664-74.
25. Chhetri SK, Mills RJ, Shaunak S, Emsley HC. Copper deficiency. BMJ. 2014. 348: 3691.
26. Dembinski K, Gargasz AE, Dabrow S, Rodriguez L. Three distinct cases of copper deficiency in hospitalized pediatric patients. Clin Pediatr (Phila). 2012. 51: 759-62.
27. Haddad AS, Subbiah V, Lichtin AE, Theil KS, Maciejewski JP. Hypocupremia and bone marrow failure. Haematologica. 2008. 93: e1-5.
28. Gregg XT, Reddy V, Prchal JT. Copper deficiency masquerading as myelodysplastic syndrome. Blood. 2002. 100: 1493-5.
29. Huff JD, Keung YK, Thakuri M, Beaty MW, Hurd DD, Owen J, Molnár I. Copper deficiency causes reversible myelodysplasia. Am J Hematol. 2007. 82: 625-30.
30. Lazarchick J. Update on anemia and neutropenia in copper deficiency. Curr Opin Hematol. 2012. 19: 58-60.
31. Sochet AA, Jones A, Riggs CD Jr, Weibley RE. A 3-year-old boy with severe anemia and neutropenia. Pediatr Ann. 2013. 42: 15-7.
32. Peled T, Glukhman E, Hasson N, et al. Chelatable cellular copper modulates differentiation and self-renewal of cord blood-derived hematopoietic progenitor cells. Exp Hematol. 2005. 33: 1092–1100.
33. Verma R, Praharaj HN, Khanna VK, Garg RK, Singh MK, Malhotra HS. Study of micronutrients (copper, zinc and vitamin B12) in posterolateral myelopathies. J Neurol Sci. 2013. 329: 11-6.
34. Kumar N. Copper deficiency myelopathy (human swayback). Mayo Clin Proc. 2006. 81: 1371-84.
35. Kumar N, Butz JA, Burritt MF. Clinical significance of the laboratory determination of low serum copper in adults. Clin Chem Lab Med. 2007. 45: 1402-10.
36. Wu J, Ricker M, Muench J. Copper deficiency as cause of unexplained hematologic and neurologic deficits in patient with prior gastrointestinal surgery. J Am Board Fam Med. 2006. 19: 191-4.
37. Nakagawa M, Nagai K, Minami I, Wakabayashi M, Torigoe J, Kawano T. Copper-deficiency anemia after esophagectomy: A pitfall of postoperative enteral nutrition through jejunostomy. Int J Surg Case Rep. 2014. 5: 311-4.
38. Papamargaritis D, Aasheim ET, Sampson B, le Roux CW. Copper, selenium and zinc levels after bariatric surgery in patients recommended to take multivitamin-mineral supplementation. J Trace Elem Med Biol. 2014. pii: S0946-672X(14)00174-6.
39. Gletsu-Miller N, Broderius M, Frediani JK, Zhao VM, Griffith DP, Davis SS Jr, Sweeney JF, Lin E, Prohaska JR, Ziegler TR. Incidence and prevalence of copper deficiency following roux-en-y gastric bypass surgery. Int J Obes (Lond). 2012. 36: 328-35.
40. Gletsu-Miller N, Wright BN. Mineral malnutrition following bariatric surgery. Adv Nutr. 2013. 4: 506-17.
41. Sommerville RB, Baloh RH. Anemia, paresthesias, and gait ataxia in a 57-year-old denture wearer. Clin Chem. 2011. 57: 1103-6.
42. Dzieżyc K, Litwin T, Sobańska A, Członkowska A. Symptomatic copper deficiency in three Wilson's disease patients treated with zinc sulphate. Neurol Neurochir Pol. 2014. 48: 214-8.
43. Hassan HA, Netchvolodoff C, Raufman JP. Zinc-induced copper deficiency in a coin swallower. Am J Gastroenterol. 2000. 95: 2975-7.
44. Dhawan SS, Ryder KM, Pritchard E. Massive penny ingestion: the loot with local and systemic effects. J Emerg Med. 2008. 35: 33-7.
45. Doherty K, Connor M, Cruickshank R. Zinc-containing denture adhesive: a potential source of excess zinc resulting in copper deficiency myelopathy. Br Dent J. 2011. 210: 523-5.
46. Nations SP, Boyer PJ, Love LA, Burritt MF, Butz JA, Wolfe GI, Hynan LS, Reisch J, Trivedi JR. Denture cream: an unusual source of excess zinc, leading to hypocupremia and neurologic disease. Neurology. 2008. 71: 639-43.
47. Shike M. Copper in parenteral nutrition. Gastroenterology. 2009. 137: S13-7.
48. Fuhrman MP, Herrmann V, Masidonski P, Eby C. Pancytopenia after removal of copper from total parenteral nutrition. JPEN J Parenter Enteral Nutr. 2000. 24: 361-6.
49. Bozzetti F, Inglese MG, Terno G, Pupa A, Sequeira C, Migliavacca S. Hypocupremia in patients receiving total parenteral nutrition. JPEN J Parenter Enteral Nutr. 1983. 7: 563-6.
50. Goodman BP, Mistry DH, Pasha SF, Bosch PE. Copper deficiency myeloneuropathy due to occult celiac disease. Neurologist. 2009. 15: 355-6.
51. Halfdanarson TR, Kumar N, Hogan WJ, Murray JA. Copper deficiency in celiac disease. J Clin Gastroenterol. 2009. 43: 162-4.
52. Oxentenko AS, Murray JA. Celiac Disease: Ten Things That Every Gastroenterologist Should Know. Clin Gastroenterol Hepatol. 2014. pii: S1542-3565(14)01053-2.
53. Green R. Anemias beyond B12 and iron deficiency: the buzz about other B's, elementary, and nonelementary problems. Hematology Am Soc Hematol Educ Program. 2012. 2012: 492-8.
54. Robinson SD, Cooper B, Leday TV. Copper deficiency (hypocupremia) and pancytopenia late after gastric bypass surgery. Proc (Bayl Univ Med Cent). 2013. 26: 382-6.
55. Hammond N, Wang Y, Dimachkie MM, Barohn RJ. Nutritional neuropathies. Neurol Clin. 2013. 31: 477-89.
56. Gürsoy AE, Kolukısa M, Babacan-Yıldız G, Celebi A. Subacute Combined Degeneration of the Spinal Cord due to Different Etiologies and Improvement of MRI Findings. Case Rep Neurol Med. 2013. 2013: 159649.
57. Mittal SO, Machado DG. Hypocupremia: a possible association with late cortical cerebellar atrophy. Tremor Other Hyperkinet Mov (N Y). 2014. 4: 202.
58. Winston GP, Jaiser SR. Copper deficiency myelopathy and subacute combined degeneration of the cord - why is the phenotype so similar? Med Hypotheses. 2008. 71: 229-36.
59. Brewer GJ. Causes and diagnosis of copper deficiency. Am J Hematol. 2008. 83: 87-8.
60. Mechanick JI, Youdim A, Jones DB, Timothy Garvey W, Hurley DL, Molly McMahon M, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic and Bariatric Surgery. Surg Obes Relat Dis. 2013. 9: 159-91.