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Acquired Copper Deficiency: A Potentially Serious and Preventable Complication Following Gastric Bypass Surgery

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Abstract

Copper is an essential cofactor in many enzymatic reactions vital to the normal function of the hematologic, vascular, skeletal, antioxidant, and neurologic systems. Copper deficiency in the United States is believed to be relatively rare but has been described in the setting of zinc supplementation, myelodysplastic syndrome, use of parenteral nutrition and chronic tube feeding, and in various malabsorptive syndromes, including following gastrectomy and gastric bypass surgery. Features of copper deficiency include hematologic abnormalities (anemia, neutropenia, and leukopenia) and myeloneuropathy; the latter is a rarer and often unrecognized complication of copper deficiency. We here describe two patients who presented with severe gait abnormalities and anemia combined with neutropenia several years after roux-en-Y gastric bypass (RYGB) surgery for obesity who were found to be severely copper deficient. Intravenous copper repletion resulted in the rapid correction of hematologic indices; combined intravenous and oral copper supplementation and eventual oral copper supplements alone normalized serum copper levels in each patient but resulted in only partial resolution of the neurologic deficits. This report serves to alert physicians of the association between RYGB procedures and subsequent copper deficiency in order to avoid diagnostic delays and to improve treatment outcomes.

Keywords

Copper deficiency; gastric bypass surgery; neutropenia; myelopathy; anemia

Copper deficiency is a well-documented cause of neurologic disease and hematologic abnormalities, including anemia with neutropenia, in adults [1–5]. The neurologic manifestations may be similar to the myeloneuropathy observed with vitamin B12 deficiency [2,5]. Though copper deficiency is thought to be rare in developed countries, the neurologic symptoms can be profound and are frequently irreversible, making awareness and early diagnosis essential [1]. Copper deficiency in the United States is believed to be rare but has been described in the

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setting of gastrectomy and gastric bypass surgery [6–10], zinc supplementation [1], myelodysplastic syndrome [2–5], use of chronic tube feedings, especially via jejunostomy [11–13], and use of parenteral nutrition[11, 14–15].

Roux-en-Y gastric bypass (RYGB) surgery for morbid obesity is becoming increasingly common in the United States; most procedures bypass the duodenum and between 100–200 cm of proximal jejunum – the sites of most copper absorption in humans [7, 16–17]. RYGB patients are routinely prescribed multivitamin-mineral preparations, iron, calcium and vitamin B12, but copper is not routinely supplemented as a specific nutrient and little information on copper depletion after RYGB is available [6–7]. We here report two patients followed prospectively by all of the authors in both the inpatient and outpatient setting at Emory University Hospital and The Emory Clinic. The patients each presented more than ten years after RYGB with severe gait abnormalities, anemia and severe neutropenia in association with severe copper depletion. The hematologic indices rapidly normalized with copper intravenous and oral repletion, but the neurologic deficits and symptoms showed only modest improvement over a several month period of observation.

Case 1

A 53 year-old Caucasian woman was referred to the Neurology Service of Emory University School of Medicine for evaluation of abnormal gait and anemia. The patient initially noted a sensation of painful paresthesias in her feet bilaterally that worsened in severity over time and progressed to the level of her thigh. Over an eight-month period, her ability to ambulate gradually deteriorated such that that on presentation, the patient required a wheelchair. Her past medical history included RYGB surgery for morbid obesity approximately 21 years prior to presentation but no other significant past medical history. She received 1000 μg vitamin B12 subcutaneously monthly for many years, but otherwise received no vitamin or mineral supplementation. Physical exam revealed absent positional and vibratory sensation in the lower extremities to the knee. Fine touch sensation was decreased in a stocking distribution to the level of her thighs, and she had 3+ knee and ankle reflexes bilaterally with an absent Babinski sign. Her gait was broad-based and unsteady. She displayed an intact mental status and cranial nerve examination was unremarkable. She had normal strength, bulk, and tone throughout. Her physical examination was otherwise normal.

Initial laboratory examination revealed hyopochromic anemia [hemoglobin= 9.6 gm/dL (normal=11.4–24.4 gm/dL), MCV= 95.7 fL (normal= 79.3–94.8 fL), MCHC= 32.1 gm/dL, (normal=33.5–35.5 gm/dL), white blood cell (WBC) count 4.7 10^3/mcL (normal 3.6–11.1 10^3/mcL)] and severe neutropenia (absolute neutrophil count = 403 cells/uL). Blood platelet count, iron studies, folate, vitamin B12, homocysteine and thiamine levels and syphilis serologies were normal. The patient's serum vitamin B6 level was low at 2.8 ng/mL (normal= 5–30 ng/mL). The serum 25-hydroxy vitamin D concentration was below normal at 11 ng/mL (normal = 20–57 ng/mL). The serum zinc level was elevated at 228 μg/dL (normal = 60–120 μg/dL). A bone marrow biopsy performed to rule out myelodysplastic syndrome revealed sideroblasts but was otherwise unremarkable. An MRI of the brain showed T2-hyperintensity in the white matter but was otherwise normal and a subsequent lumbar fluid examination was normal. After the initial evaluation failed to identify an etiology, the patient was referred to the Winship Cancer Institute of Emory University, where an extremely low serum copper concentration of 4 ug/dL (normal = 80–155 ug/dL), and ceruloplasmin concentration of 3 mg/dL (normal = 21–53 mg/dL) were identified.

The patient was admitted to Emory University Hospital (EUH) and received intravenous copper at 2.4 mg/day over a six-day period and intravenous vitamin B6 (50 mg/day) over 3 days. She was then discharged home and weekly intravenous copper infusions (copper 2.4 mg over 2–3

hours) were arranged based on serial blood copper levels. In addition, the patient was prescribed a complete high-potency oral multivitamin-mineral preparation twice daily (Women's Ultra Mega®, General Nutrition Centers, Inc., Pittsburgh, PA), oral vitamin B6 (50 mg/day) and oral copper gluconate (two 2 mg tablets taken twice daily for a total of 8 mg oral copper per day). One month after intravenous copper replacement was initiated, both her plasma hematologic indices and serum copper levels had returned to normal. The patient's paresthesias improved; however, vibratory sensation and proprioception remained absent in the lower extremities. Four months after discharge from the hospital, the patient was able to ambulate with a cane, intravenous copper was discontinued and blood copper levels were maintained within the normal range on oral copper supplementation of 8 mg/day. During the period of observation and copper repletion, the patient reported chronic sharp pain in her legs bilaterally, which worsened over time and then gradually improved.

Case 2

A 58 year-old Caucasian woman presented with unsteady gait, numbness and paresthesias involving the lower extremities and hands in a stocking-glove distribution. She had initially noted numbness in her feet that progressed over an approximately twelve-month period, coincident with increasing difficulty walking. On presentation, she was confined to a wheelchair. Her past medical history was significant for an unspecified gastric bypass surgery approximately ten years prior to presentation for severe recurrent peptic ulcer disease. She received 400 μg vitamin B12 subcutaneously monthly for many years, but otherwise received no vitamin or mineral supplementation. Physical examination revealed markedly decreased vibratory sensation and proprioception in the lower extremities bilaterally. Both pin-prick and light touch sensations were moderately reduced below the knees. Her gait was ataxic and she was unable to perform a heal-to-shin test. Strength, bulk, tone, and reflexes were normal throughout. Her physical examination was otherwise normal.

Initial laboratory examination demonstrated anemia (hemoglobin = 8.5 g/dL, MCV= 98.4 fL, MCHC = 33.6gm/dl, leukopenia (WBC =1.9 10^3/mcL) and severe neutropenia (absolute neutrophil count = 475 cells/μL), Blood platelet count, iron studies, folate, vitamin B12, homocysteine and thiamine concentrations, and syphilis serologies were within normal limits. A bone marrow biopsy showed a hypocellular but otherwise normal marrow. An MRI showed T2-hyperintensity in the dorsal columns of the cervical spine and the results of a lumbar puncture examination were unremarkable. Electrophysiology studies revealed a predominately sensory generalized neuropathy. Further laboratory examination demonstrated that the patient was markedly copper deficient, with a serum copper concentration of 2 ug/dL and a serum ceruloplasmin concentration of 2mg/dL, respectively.

Upon replacement with intravenous copper as an inpatient at EUH (2.4 mg daily for 6 days), followed by weekly intravenous copper (2.4 mg) combined with oral supplementation of 8 mg copper/daily, the patient's hematologic indices normalized after week and her sensation to light touch slowly improved over a several week period. Four months following diagnosis of severe copper deficiency, she remained ataxic due to a residual deficit in proprioception and vibratory sensation in her lower extremities and required a cane for ambulation. However, 7 months following copper repletion (21 weeks of combined intravenous and oral copper therapy followed by 7 weeks of oral copper therapy alone) the patient did not need any assistance in walking and her lower extremity neuropathy continued to improve.

Discussion

Copper is a trace element essential to all species [16–17]. It is a cofactor in several oxidative enzymes vital to the function of hematopoietic, vascular and skeletal tissues, as well as the

structure and function of the nervous system, including superoxide dismutase (oxygen radical scavenger), cytochrome-c oxidase (mitochondrial respiration), lysyl oxidase (collagen and elastin synthesis) and ceruloplasmin ferroxidase/haephestin (iron metabolism) [16–17]. Animal studies suggest that the duodenum is the major site of copper absorption, but some absorption also occurs in the stomach and ileum [18–19]. Gastric pH has an important role in freeing copper bound to foodstuffs, which frees copper from natural organic complexes and ligands [19]. In humans the major site of absorption of dietary copper remains unclear [16].

Gastric surgery (gastrectomy, gastric-bypass) and zinc supplementation have previously been identified as causes of copper deficiency [6–10]. The intended gastric restrictive-small bowel malabsorptive effects of RYGB contribute to weight loss, but may also profoundly affect patient's nutritional status, depending on the level of nutrient intake and supplementation [8–10]. It is reported that between 12 to 33%% of patients following RYGB develop vitamin B12 deficiency and up to 52% of patients may be iron deficient [8–9]. Low blood levels of fat-soluble vitamins, zinc, and folate are also commonly noted unless specifically supplemented [9–10]. While copper deficiency may be a relatively rare occurrence, albeit one which is likely under reported in RYGB, the number of individuals undergoing this surgical procedures annually is increasing dramatically, creating a large population at risk for copper deficiency.

The clinical scenarios of the two patients we report is consistent with previous reports of copper deficiency in adults [2,6–7]. Patients characteristically present with gait abnormalities and peripheral neuropathies remotely following gastric bypass procedures. Deficits localize to the lower extremities and include paresthesias, impaired vibratory sensation and proprioception, and frequently a Babinski or Chaddock's sign [2,6]. Strength and touch perception are not prominently affected in most cases. MRI changes are not always noted but the most consistent finding on spine MRI in patients with copper deficiency myelopathy is increased T2 signal in the dorsal columns, as seen in our patients reported here [4, 20]. Electrophysiology studies indicate a primary dysfunction in the posterior column of the spinal cord [2,4]. The precise pathophysiology underlying the symptoms is unclear, but it has been hypothesized that oxidative damage as a result of diminished superoxide activity leads to demyelination and axonal degeneration in the central nervous system [3].

On laboratory examination, patients with copper deficiency classically exhibit hypochromic anemia and neutropenia [17,21]. Iron studies show normal or elevated ferritin levels, suggesting adequate iron stores, while the mean corpuscular volume is variable. Bone marrow examination typically shows ringed sideroblasts (as in our case 1), indicating abnormal accumulation of mitochondrial iron [22]. This observation is attributed to the diminished activity of the cupric enzyme mitochondrial cytochrome-c oxidase, which plays a key role in the transfer of iron to the cytosol for incorporation into heme [23]. Ceruloplasmin ferroxidase is also thought to contribute to anemia, as it is essential in the loading of transferrin with iron in the liver and is markedly diminished in parallel with copper [24]. Additional laboratory abnormalities in bariatric patients are common, including B12 and folate deficiency, however, in all previously reported cases, the neurologic symptoms progressed and the hematologic derangements persisted following B12 and folate supplementation.

Of interest, a variety of neurologic complications have been reported after weight loss surgery. Chang et al described cases of postoperative polyneuropathy - acute post-gastric reduction surgery (APGARS) neuropathy, as a polynutritional, multisystem disorder characterized by protracted postoperative vomiting, hyporeflexia, and muscular weakness [25]. These authors recently reported the results of a questionnaire survey of bariatric surgeons on features of APGARS. A total of 109 cases of neuropathy were described by 257 respondents. Vitamin B 12 and/or thiamine deficiency were present in 40 (40%); common diagnoses reported were Wernicke's encephalopathy, thiamine deficiency, and Guillain-Barré Syndrome [25]. In light of

our findings and other reports [2–7, 26], it is likely that at least some cases of APGARS are secondary to copper depletion or overt deficiency.

Treatment of copper deficiency consists of parenteral and oral copper replacement until normal copper levels in blood are achieved. Our two patients each received intermittent IV copper in combination with daily oral therapy until copper levels in blood were consistently within the normal range. Within weeks of therapy, serum copper and ceruloplasmin levels returned to normal and have remained so with daily oral therapy following several weeks of IV repletion (Table 1 and Table 2). Despite malabsorption being the likely mechanism underlying copper deficiency after RYGB, oral supplementation has been found to correct copper deficiency, suggesting that super-saturation of intestinal copper transport systems is a reliable way to maintain adequate serum levels [16].

The response to copper replacement in is variable and likely depends on the degree and duration of depletion. The hematologic abnormalities have been reported to correct within four to six weeks (as in our subjects); however, improvements in neurologic symptoms are modest and often difficult to demonstrate objectively. As described in the current report, paresthesias may resolve, but significant gait abnormalities may remain, consistent with clinical observations in reported cases [1,2,4 6–7].

Based on our clinical observations, we advocate that greater awareness of the potential for copper depletion and hematologic and neurologic abnormalities must occur in physicians caring for patients after RYGB surgery. In our cases presented here, copper deficiency was a remote surgical complication, and thus the subjects presented to non-surgical practitioners. The growing number of patients undergoing malabsorptive surgical procedures for obesity strongly suggests that the incidence of copper depletion and hematologic and neurologic sequelae will increase in the future. Most importantly, the neurologic sequelae of copper deficiency may be irreversible, making early diagnosis and prompt treatment essential to successful outcomes. In our case histories, biochemical evidence for copper deficiency was associated with severe neurologic abnormalities that were not completely reversed after ostensibly adequate copper repletion. Therefore, baseline and serial copper status monitoring should be considered in patients after RYGB. For now, specific at-risk subpopulations have not been identified and the optimal time course and cost-effectiveness for such screening is unknown. Thus, we feel that rigorous, prospective trials on the incidence and prevalence of copper deficiency and associated morbidity in RYGB patients, as well as studies on the optimal therapeutic approach to reverse copper depletion, are needed in this growing patient population. We have examined the composition of several commonly prescribed multivitamin-mineral preparations for bariatric patients. The zinc to copper ratio in these is typically 15 mg zinc to 1–2 mg copper, which may be an inappropriately high Zn/Cu ratio for RYGB patients.

In conclusion, we describe two patients who presented with severe copper deficiency more than ten years after RYGB surgery. Following intravenous and subsequent oral copper supplementation, hematologic abnormalities rapidly resolved, but only mild improvement was noted in the neurologic findings and symptoms. An increasing number of patients elect to have bariatric procedures each year, placing a large population at risk for complex nutrient deficiencies, including copper deficiency [9]. However, the symptoms associated with copper deficiency may become profound and then irreversible. Thus, greater awareness of copper deficiency and its association with malabsorptive bariatric surgical procedures such as RYGB is needed to ensure early diagnosis and appropriate therapy.

References

1. Prodan CI, Holland NR, Wisdom PJ, Burstein SA, et al. CNS demyelination associated with copper deficiency and hyperzincemia. Neurology 2002;59:1453–1456. [PubMed: 12427906]
2. Kumar N, Gross JB, Ahlskog JE. Copper deficiency myelopathy produces a clinical picture like subacute combined degeneration. Neurology 2004;63:33–39. [PubMed: 15249607]
3. Dunlap WM, James W, Hume D. Anemia and neutropenia caused by copper deficiency. Ann Intern Med 1974;80:470–476. [PubMed: 4220265]
4. Schleper B, Stuerenburg HJ. Copper deficiency-associated myelopathy in a 46-year-old woman. J Neurol 2001;248:705–706. [PubMed: 11569901]
5. Angotti LB, Post GR, Robinson NS, Lewis JA, Hudspeth MP, Lazarchick J. Pancytopenia with myelodysplasia due to copper deficiency. Pediatr Blood Cancer. 2008 Jul 11;[Epub ahead of print]
6. Tan JC, Burns DL, Royden Jones H. Severe ataxia, myelopathy, and peripheral neuropathy due to aquired copper deficiency in a patient with history of gastrectomy. JPEN J Parenteral Enteral Nutr 2006;30:446–450.
7. Kumar N, Ahlskog JE, Gross JB Jr. Acquired hypocupremia after gastric surgery. Clin Gastroenterol Hepatol 2004;2:1074–1079. [PubMed: 15625652]
8. Fujioka K. Follow-up of nutritional and metabolic problems after bariatric surgery. Diab Care 2005;28:481–484.
9. Alverez-Leite J. Nutrient deficiency secondary to bariatric surgery. Curr Opin Clin Nutr Metab Care 2004;7:569–575. [PubMed: 15295278]
10. Steinbrook R. Surgery for severe obesity. N Eng J Med 2004;350:1075–1079.
11. Jayakumar S, Micallef-Eynaud PD, Lyon TBD, Cramb R, Jilaihawi AN, Prakash D. Acquired copper deficiency following prolonged jejunostomy feeds. Ann. Clin. Biochem 2005;42:227–231. [PubMed: 15949160]
12. Camblor M, De la Cuerda C, Bretón I, Pérez-Rus G, Alvarez S, García P. Copper deficiency with pancytopenia due to enteral nutrition through jejunostomy. Clin Nutr 1997;16:129–133. [PubMed: 16844585]
13. Chen CC, Takeshima F, Miyazaki T, Murase K, Ohtani H, Isomoto H, Shikuwa S, Omagari K, Mizuta Y, Ozono Y, Kohno S. Clinicopathological analysis of hematological disorders in tube-fed patients with copper deficiency. Intern Med 2007;46:839–844. [PubMed: 17575375]
14. Forbes GM, Forbes A. Micronutrient status in patients receiving home parenteral nutrition. Nutrition 1997;13:941–944. [PubMed: 9433708]
15. Sriram K, O'Gara JA, Strunk JR, Peterson JK. Neutropenia due to copper deficiency in total parenteral nutrition. JPEN J Parenter Enteral Nutr 1986;10:530–532. [PubMed: 3093712]
16. Bertinato J, Abbe MRL. Maintaining copper homeostasis: regulation of copper-traficking proteins in response to copper deficiency or overload. J Nutri Biochem 2004;15:316–322.
17. Turnlund, JR.; Copper. Modern Nutrition in Health and Disease. Vol. 10th ed. Shils, ME.; Shike, M.; Ross, AC., editors. Lippincott: Williams and Wilkins; 2006. p. 286-299.
18. Van Campen DR, Mitchell EA. Absorption of Cu^{64}, Zn^{65}, Mo^{99}, and Fe^{59} from ligated segments of the rat gastrointestinal tract. J Nutr 1965;86:120–124. [PubMed: 14302118]
19. Gollan JL. Studies on the nature of complexes formed by copper with human alimentary secretions and their influences on copper absorption. Clin Sci Mol Med 1975;49:237–245. [PubMed: 240530]
20. Kumar N, Ahlskog JE, Klein CJ, Port JD. Imaging features of copper deficiency mylelopathy: a study of 25 cases. Neuroradiology 2006;48:78–83. [PubMed: 16261334]
21. Linder MC, Hazegh-Azam M. Copper biochemistry and molecular biology. Am J Clin Nutr 1996;63:797S–811S. [PubMed: 8615367]
22. Nagano T, Toyoda T, Tanabe H, Nagoto T, Tsuchida T, et al. Clinical features of hematological disorders caused by copper deficiency during long-term enteral nutrition. Intern Med 2005;44:554–559. [PubMed: 16020879]
23. Williams DM, Loukopoulos D, Lee GR, Cartwright GE. Role of copper in mitochondrial iron metabolism. Blood 1976;48:77–85. [PubMed: 947406]

24. Sharp P. The molecular basis of copper and iron interactions. Proc Nutr Soc 2004;63:563–569. [PubMed: 15831128]

25. Chang CG, Adams-Huet B, Provost DA. Acute post-gastric reduction surgery (APGARS) neuropathy. Obes Surg 2004;14:182–189. [PubMed: 15018746]

26. Goldberg ME, Laczek J, Napierkowski JJ. Copper deficiency: a rare cause of ataxia following gastric bypass surgery. Am J Gastroenterol 2008;103:1318–1319. [PubMed: 18477365]

Table 1

Case 1

Day following diagnosis	1	5	14	35	110	125	175
Serum Cu (80–100 mcg/dL)	4	43	105	101	101	116	127
Ceruloplasmin (21–53 mg/dl)	3	12	32	31	35	32	48
Reticulocyte count (0.020–0.076 10^6/mcL)	0.033	0.088	0.082	0.055	0.035		
Hemoglobin (11.4–14.7 gm/dL)	9.5	9.4	13.2	12.5	10.1	11.1	11.1
Hematocrit (33.3–41.4 %)	28.7	28.6	41	38.7	31.3	34.3	33.7
WBC 10^3/mcL	1.3		12.6	6.0	6.1	5.9	8.7
Absolute neutrophil count (1500–8000 cells/uL)	592	490	10584	3420	3111	3481	6090
Form of copper administered	IV	IV	IV/PO	IV/PO	PO	PO	PO

Normal laboratory ranges in parenthesis.

IV = copper 2.4mg/day; IV/PO = copper 2.4mg IV/week and copper 8 mg po/day; PO = copper 8 mg po/day

Table 2

Case 2

Day following diagnosis	1	8	12	22	63	133	197
Serum Cu (80–100 mcg/dL)	2	46	64	86	93	107	103
Ceruloplasmin (21–53 mg/dl)	<2	N/A	N/A	31	25		34
Reticulocyte count (0.020–0.076 10^6/mcL)	0.070	0.155	0.111	0.090	0.031	0.045	
Hemoglobin (11.4–14.7 gm/dL)	7.7	9.7	10.9	11.1	11.5	12.6	12.9
Hematocrit (33.3–41.4 %)	21.9	29.8	32.8	33.5	34.4	36.8	37.4
WBC 10^3/mcL	1.5	4.3	4.3	11.2	9.5	10.0	9.2
Absolute neutrophil count (1500–8000 cells/uL)	456	2193	4602	8848	7030	7500	6440
Form of copper administered	IV	IV/PO	IV/PO	IV/PO	IV/PO	IV/PO	PO

Normal laboratory ranges in parenthesis.

IV = copper 2.4mg/day; IV/PO = copper 2.4mg IV/week and copper 8 mg po/day; PO = copper 8 mg po/day