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Copper Deficiency: Like a Bad Penny

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Copper is an indispensable trace element. A deficiency of this element can creep up on the clinician like a bad penny if not equipped to recognize the clinical signs, symptoms, and an understanding of which patient populations are at risk. Copper is involved in the proper function of numerous organs and metabolic processes such as iron metabolism, neurotransmission, connective tissue formation, and others. Although a once rare deficiency state seen most often in parenteral nutrition deficient solutions, Roux-en-Y gastric bypass surgeries have brought this deficiency state into awareness. The purpose of this article is to identify patients at risk for copper deficiency, review the signs and symptoms, as well as provide recommendations for treatment and monitoring.

CASE

A long time nutritionally stable 33 year-old male with a history of short bowel syndrome due to necrotizing enterocolitis (NEC) as an infant presented for follow up in GI clinic with persistent leukopenia and neutropenia in the setting of recently increased stool output. The patient's anatomy included approximately 30cm of small bowel anastomosed directly to 50cm of colon. The nutrition and hydration regimen included: oral intake of a short bowel diet, nocturnal infusion of 6 cans of Peptamen 1.5 via PEG, and 3 liters IV fluid. Teduglutide had been used x 2 years.

The patient's baseline stool output markedly increased from 2.2 L to ~ 5 L per day, just before a hospital admission for this same problem 5 months prior, in the setting of a central line infection. His white blood count (WBC) and absolute neutrophil count (ANC) at that time were 1.81 k/uL and 960/mL. The cause of his increased stool output was unclear. CT enterography and stool studies for infection were unrevealing. Efforts to reduce the volume of stool output after discharge were moderately successful with a regimen of codeine 30 mg tid, Imodium 4mg qid, and gentle soluble fiber supplementation (Benefiber). On follow up in GI clinic, he was found to be persistently leukopenic, with WBC 1.89 k/uL and ANC 840/mL. A copper level was tested and found to be <0.10 mcg/mL (reference: 0.75 - 1.45 mcg/mL). Dietary copper intake had until then included 6mg/day from tube feedings and 2 mg/day from oral multivitamin, which is significantly greater than the typical daily intake of 1.2-1.6 mg/day. The patient was started on 2 mg/day of IV copper gluconate supplementation added to his IV fluids for 6 weeks. On subsequent recheck 3 weeks later after therapy, the patient's copper level had increased to 0.91 mcg/mL. At that same check, his WBC and ANC had both normalized to 6.09 k/uL and 4220/mL respectively (Table 1).

Significant clinical events, such as a change in approach to nutrition (e.g.: transition from parenteral to enteral nutrition), or significant change

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Table 1. Pre and Post Treatment of Copper Deficiency

Lab Parameter	Initial Clinic Visit Jan. 2018	3 Weeks Later Post Copper Repletion
White blood cells (k/uL) (reference: 4.00 – 11.00 k/uL)	1.89 (↓)	6.09
Hemoglobin (g/dL) (reference: 14.0 – 18.0 g/dL)	11.9 (↓)	12.2 (↓)
Platelets (k/uL) (reference: 150 – 450 k/uL)	95 (↓)	161
% neutrophils (Calc. %) (reference: 47 – 82%)	44.5% (↓)	69.3%
Abs. Neutrophil count (/uL) (reference: 1800 – 8000/uL)	890 (↓)	4220
Copper (mcg/mL) (reference: 0.75 – 1.45 mcg/mL)	<0.10 (↓)	0.91
Ceruloplasmin (mg/dL) (reference: 25.0 – 63.0 mg/dL)	<6.0 (↓)	23.7 (↓)

Table 2. Patients at Risk For Copper Deficiency[4,8-11]

- Gastrectomy/gastric surgery bypassing duodenum & between 100-200cm of jejunum (primary site for copper absorption)
  - Roux-en-y gastric bypass in particular with patients supplemented with zinc and no copper
  - Jejuno-ileal bypass
- Celiac disease
- Excess zinc ingestion
  - Ingestion of pennies secondary to Pica
  - Denture cream
  - Zinc supplements
  - Chronic use of zinc containing cold remedies (such as Cold-EEZE, Zicam, or other zinc lozenges)
- Parenteral nutrition without or insufficient copper added
- Enteral feeding
  - Inadequate copper content of formula, or volume provided does not contain enough copper for that individual
  - Jejunal access
- Prolonged continuous renal replacement therapy (CRRT) (> 2 weeks)
- Nephrotic syndrome – excess loss
  - Increased permeability of glomerulus to ceruloplasmin
- Penicillamine
  - Facilitates renal copper excretion through chelation
- Alkaline therapy for renal tubular acidosis
- Menke's kinky hair disease
  - X-linked recessive multisystemic lethal disorder of copper metabolism
- Occipital horn disease
  - Occipital horn syndrome, formerly considered a variant of Ehlers-Danlos syndrome, an X-linked recessive connective tissue disorder; considered a milder variant of Menkes disease
- Wilson's disease
  - Serum copper is low, which may seem paradoxical given that Wilson's disease is a disease of copper excess, however it is sequestered in the liver; 95% of plasma copper is carried by ceruloplasmin which is often low in Wilson's disease

in ostomy output can lead to either, subtle or overt, vitamin and trace element deficiencies. In this case, early recognition of copper deficiency helped to avoid potential downstream complications of more significant deficiency.

INTRODUCTION

When you think of copper, what comes to mind? Copper pipes, pennies, copper pots and pans? What about an essential trace element that when deficient may result in neurological deficits, anemia, and neutropenia?

Copper Absorption

Copper is primarily absorbed in the stomach and proximal duodenum. It is involved in hematopoiesis, hemoglobin synthesis, neurotransmission, superoxide synthesis, formation of connective tissue and plays a role in the structure and function of the nervous system.[1]

Patients at Risk for Copper Deficiency

Risk factors for deficiency include malabsorptive diseases such as celiac disease, Crohn's disease, gastrointestinal surgery, jejunal feedings, which

Table 3. Citations of Copper Deficiency in Enterally-Fed Patients

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occur distal to the primary sites of absorption, and prolonged parenteral nutrition without adequate supplementation (for complete list see Table 2).[2,3,4]

Bariatric Surgery

Bariatric surgeries in which a large portion of the stomach and duodenum are bypassed can lead to copper deficiency. Low serum copper levels have been reported in 10% of patients 2 years after Roux-en-Y bypass surgery.[5,6] Although a recent systematic review corroborated that 10% of RYGB patients develop asymptomatic copper deficiency, only a total of 34 cases of symptomatic copper deficiency have been reported in the literature, occurring on

Table 4. Copper Deficient Terminology, Definitions, Signs and Symptoms

Term	Definition	Signs and Symptoms
	Neurological	
Ataxia	Loss of muscle control or coordination of voluntary movements	• Poor coordination • Stumbling, falling • Slurred speech • Difficulty with fine motor tasks
Myelopathy	Nerve injury to spinal cord due to severe compression	• Neck/arm/leg/back pain • Numbness, tingling, weakness • Difficulty walking • Balance issues • Loss of bowel/bladder control
Myeloneuropathy	Simultaneous damage of the tracts of the spinal cord and peripheral nerves in lower limbs	• Difficulty walking • Weakness of lower limbs • Ataxic gait • Sensory manifestations in glove and stocking distribution
Optic Neuropathy	Damage to the optic nerve	• Eye pain • Loss of peripheral vision • Loss of sight • Double vision
Peripheral Neuropathy	Damage to the peripheral nervous system which interferes with signals between the CNS (brain and spinal cord) and the rest of the body	• Weakness, numbness, and pain • Usually occurs in hands and feet
	Hematological	
Pancytopenia	Low counts for all 3 types of blood cells: white blood cells, red blood cells and platelets	• Prone to infection • Fatigue • Easy bleeding/bruising • Unresponsive to iron supplementation
Leukopenia/ Neutropenia	**Leukopenia** is an umbrella referring to a reduction in any white blood cell type. **Neutropenia** is a type of **leukopenia** referring specifically to a decrease in neutrophils, the most common type of white blood cell.	• Signs of infection- fever, chills, sweating
Myelodysplastic Syndromes (MDS)	A group of diverse bone marrow disorders that may cause anemia, neutropenia and thrombocytopenia. Copper deficiency may mimic MDS	• Infection • Anemia • Spontaneous bleeding • Easy bruising

average 8.6 years after surgery with 97% being female.[6] Of the 34 cases with symptoms, only 1 patient consumed a multivitamin with minerals.

Excess Zinc

Excess oral zinc supplements, including zinc-containing denture creams, have also led to copper deficiency. Copper and zinc are competitively absorbed in the proximal small bowel, both of which become bound to metallothionein (MT) and are stored within enterocytes. MT has a higher binding affinity to copper than to zinc and the MT-copper (Cu) complex is preferentially retained in the intestinal cells. Synthesis of MT is regulated by the amount of zinc ingested and when excessive amounts are consumed, more MT proteins are produced, forming more MT-Cu complexes, which are then excreted. Massive zinc ingestion thereby decreases copper absorption, leading to an increase in copper excretion.[7]

Enteral Feeding and Copper Deficiency

Many cases of copper deficiency in enterally fed patients have been reported in the literature. The reasons for the copper deficiency were attributed to the following: inadequate copper in the commercial formula, fiber-containing formula, jejunal delivery of feeding (however one report included two patients with gastrostomy feeding that were found deficient) (Table 3). What is interesting is that in Japan, copper deficiency was treated in some with cocoa powder, a good source of copper.

Signs and Symptoms of Copper Deficiency

Symptoms of copper deficiency include anemia, neutropenia, and pancytopenia (Table 4). Anemia may be macrocytic, normocytic or microcytic. Patients may also present with neurologic deficits including peripheral neuropathy, ataxia and muscle weakness.[4] Copper deficiency has also been associated with myelopathy or myeloneuropathy

Table 5. Copper Replacement Options

General Suggestions

- RDA = adult men and women is 900µg/day
- ◆ Do not take with iron or zinc supplements – if patient needs both, take them at different times of the day
- Recheck serum copper in 4 weeks
- Do not check too soon after beginning supplementation.
- Net amount absorbed increases as the amount in diet increases, but absorption is more efficient when intake is low.

Route	Copper Supplement Dose	Comments
Oral / Enteral	Copper gluconate	◆ 2-8 mg daily or every other day
	Copper sulfate	◆ May not be well absorbed in alkaline medium
	Copper citrate	◆ Most common type of dietary copper on the market; concerns about bioavailability
	Chelated copper (glycinate or bisglycinate)	◆ A complex consisting of elemental copper and another molecule (typically an amino acid); claims to be more bioavailable, passing easily through intestinal tract and directly into bloodstream (no scientific proof available).
	Copper oxide	◆ Low bioavailability
	Cocoa powder	◆ 10 g pure cocoa powder (4 teaspoons) ◆ Some reports of tachycardia
IV	Copper gluconate	◆ 1.5-4 mg over 2 hours x 5-6 days ◆ In those refractory to IV repletion, consider retention of IV copper may improve if infused over a longer period of time (8-12 hours) like magnesium.
	Copper chloride	◆ Used as an additive to TPN

resembling B12 deficiency which includes a spastic ataxic gait and sensory ataxia caused by dorsal spinal column degeneration.[4,12] In addition, cases of optic neuropathy leading to blindness have been reported.[13,14]

In Kumar's review of 34 cases with copper deficiency, 56% had neurological deficits, four of whom also presented with optic neuropathy. Anemia occurred in 50% of the patients, 12% had pancytopenia and 23.5% leukopenia/neutropenia in addition to anemia.[6] Neurologic deficits may be present without hematologic manifestations.

Diagnosing a Copper Deficiency

Serum copper levels are used to diagnose a deficiency. It is important to remember that during the inflammatory response, ceruloplasmin, an acute-phase protein that increases during inflammation and transports 80-95% of copper, can lead to elevated blood copper levels.[4] Altarelli suggests

Table 6. Summary Considerations in the Copper Deficient Patient

Copper Pearls	◆ If it looks like, smells like, and acts like B12 deficiency, it might be copper ◆ Symptomatic copper deficiency is probably underreported especially if it was initially thought to be a B12 deficiency; so it probably does not take 8-10 years to develop after RYGB, but it seems to take that long to diagnose ◆ If the patient has progressed from cane—walker—wheelchair, think copper deficiency ◆ Best route of supplementation is unknown; if it is due to a malabsorptive condition, consider starting supplementation with IV route ◆ Serum copper levels may take days to weeks to normalize, anemia may take months and neurologic resolution may be incomplete ◆ Comb neurology journals and ophthalmology journals for case reports regarding copper deficiency
Labs	◆ CBC w/ differential ◆ Obtain baseline folate and B12 level ◆ Also consider B6, Vitamin E, thiamine if myeloneuropathy present ◆ Serum copper o Can be lowered by corticosteroids, corticotropin o A positive acute phase reactant, it can be increased under a number of conditions due to increased concentrations of ceruloplasmin such as: oral contraceptive use, pregnancy, infections, inflammation, myocardial infarction, rheumatoid arthritis, dilated cardiomyopathy, malignancy ◆ Ceruloplasmin o Acute phase protein--increases in acute or chronic infection, inflammatory states, malignancy, liver disease, myocardial infarction, oral contraceptive use o Lowered in: ▪ Nephrotic syndrome ▪ Menkes syndrome ▪ Wilson's disease ▪ Chronic hepatitis ◆ WBC w/ differential o Low neutrophil count ◆ Erythrocyte superoxide dismutase activity – not available at UVA o Not as specific as serum copper or ceruloplasmin concentration, although may be more sensitive o Increased activity in alcoholism and Down's syndrome ◆ Cytochrome C oxidase activity - not readily available everywhere

(Table 6. continued on page 30)

Table 6. Summary Considerations in the Copper Deficient Patient

(Table 6. Continued from page 29)

Considerations if deficient or refractory to repletion	◆ In patients with exclusive long-term jejunal feeding, consider checking CBC w/ differential, copper and ceruloplasmin at 3 months, 6 months, and 12 months; if stable check annually after that. ◆ Inorganic copper is absorbed in the stomach and proximal duodenum under acidic conditions, while cuproprotein copper is absorbed below the level of the pancreatic duct (i.e., alkaline conditions) ◆ If copper is orally supplemented: o May alter bioavailability (19,20): ▪ Phytates/fiber ▪ Antacids ▪ High dose vitamin C ▪ Iron ▪ Fructose ◆ Stop PPI/H2 blockers ▪ If PPI cannot be stopped: suggest taking copper an hour before the daily dose of PPI assuming that the gastric pH may be on its way down after 22-23 hours. ◆ Zinc o Zinc induces synthesis of metallothionein in the intestinal mucosa cells, but copper binds more avidly to metallothionein displacing zinc that will then be absorbed, while copper remains bound to metallothionein in the mucosa instead of entering the body. This copper is returned to the intestinal lumen with natural turnover of sloughed mucosal cells and excreted. o Stop denture cream with zinc o No zinc lozenges o Do not exceed zinc to copper ratio of 10:1 – 30:1 might precipitate copper deficiency (check vitamin/mineral supplement content it taking) ◆ Ensure denture cream does not contain zinc ◆ IV fluids o Urinary copper losses were double those of orally fed individuals. This probably reflects the fact that in oral feeding copper reaches the liver first, where it is incorporated into ceruloplasmin and only then arrives at the kidneys as a nonfilterable complex. In intravenous feeding, part of the infused copper reaches the kidneys in a filterable form, and this is liable to be lost in the urine.[21]

using low serum ceruloplasmin (<20 mg/dL) in addition to low serum copper levels with an elevated C-reactive protein to diagnose deficiency.[4] According to Rohm et al., serum ceruloplasmin level may be more reliable if the deficiency is mild. MRI of the spinal cord shows increased T2 signal in the posterior dorsal column of the spinal cord during deficiency.[1]

Copper Replacement

Little evidence other than case reports exists on the appropriate amount, route or duration of copper needed to correct a deficiency. Copper repletion may not completely resolve deficits, but it appears to halt further neurological deterioration.[1] Resolution of hematologic manifestations should return to normal within 4 to 12 weeks.[4,8]

The American Society for Metabolic and Bariatric Surgery (ASMBS) issued repletion recommendations for copper based on the severity of the deficiency.[15] For mild to moderate deficiency based on low hematologic indices, use 3–8 mg/d of oral copper sulfate or gluconate until levels normalize. In cases of severe deficiency, use 2–4 mg/d IV copper for 6 days or until levels normalize

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and neurologic symptoms resolve. Once serum copper levels are normal, they should be monitored every 3 months. Several authors recommend 2-4 mg per day of elemental oral copper or IV route for a brief period of 5 days.[4,16] According to Kumar's practice, the repletion regimen involves 8 mg oral elemental copper for 1 week, 6 mg for the second week, 4 mg for the third week and 2 mg thereafter.[17] If symptoms do not resolve or there is rapid deterioration, the author recommends 2 mg IV copper over 2 hours for 5 days. It has been recommended to continue to check copper levels periodically since cases of symptomatic and biochemical relapse have been reported. ASMBS recommends using supplemental copper when patients are consuming zinc supplements (1 mg copper for 8-15 mg zinc) although these specific amounts have not been studied.[18] See Table 5 for replacement options for copper.

CONCLUSION

Copper deficiency, while once rare, has received increased attention in recent years due to an increase in case reports, particularly in the bariatric literature. A trace element, copper is involved in many physiologic functions. Early recognition is imperative to prevent deficiency, but once deficient, to reverse the consequences of deficiency and prevent permanent damage from neurological complications. After reading this article, the clinician should be well equipped to not only identify copper deficiency, but to treat and monitor response to treatment. Table 6 includes final thoughts on treatment, monitoring, or considerations for patient's refractory to oral copper treatment. ■

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Answers to this month's crossword puzzle:

1 T	M	2 A	V	3 A		4 S	T	5 E	A	6 T	O	7 S	8 I	9 S
W		C		M		K		X		O		10 P	R	E
11 O	R	I	F	I	C	E		12 C	A	R	R	I	E	R
		D		N		W		E		P		R		A
13 P	E	R	I	O	14 D		15 I	R	R	I	T	A	N	T
O		E			I			P		D		L		O
16 U	N	F	O	L	D		17 S	T	A	I	N		18 S	N
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21 D	I	U	R	22 E	S	I	23 S		24 M	Y		25 O	W	N
		X		L		26 S	A	27 M	E			T		
28 E	R		29 N	A	S	O	G	A	S	30 T	R	I	C	
T		31 F		S				I		U		L		32 A
33 H	E	A	R	T	B	34 U	R	N		35 M	O	I	S	T
I		I		I		N		36 L	E	O		T		E
37 C	O	L	E	C	T	O	M	Y		38 R	A	Y	S	