Copper Deficiency as Cause of Unexplained Hematologic and Neurologic Deficits in Patient with Prior Gastrointestinal Surgery

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Copper is a trace mineral essential to hematopoiesis and to the structure and function of the nervous system. Copper deficiency is a rare cause of anemia, leukopenia, and myeloneuropathy, but should be considered in the differential diagnosis in a patient with prior gastrointestinal surgery. We report the case of a 51-year-old woman admitted for nonspecific neurologic symptoms ultimately found to be due to copper malabsorption. (J Am Board Fam Med 2006;19:191–4.)

Case Reports

A 51-year-old female presented to the emergency department complaining of numbness and tingling in her distal lower extremities that had progressively worsened over the previous 4 weeks and had begun to affect her fingers 2 days before presentation. In addition, the patient stated that over the past 2 weeks she had experienced a progressively worsening shortness of breath, generalized weakness, fast heartbeat, and light-headedness.

She had undergone a gastrectomy 16 years ago with Roux-en-Y and partial small bowel resection for treatment of Zollinger-Ellison syndrome as well as a Whipple procedure for chronic pancreatitis. Since her surgeries, she received vitamin B12 supplementation intramuscularly and was converted to oral supplementation several months before her presentation in the emergency department.

On presentation, the patient’s vital signs included a temperature of 36.7°C, blood pressure of 121/84, pulse of 80, respiratory rate of 18, oxygen saturation of 100% on room air, and weight of 43.2 kg. Initial neurological evaluation revealed diminished sensitivity to light touch and vibration and decreased proprioception in her toes and ankles. Her Babinski’s reflex was positive bilaterally, and her Romberg was strongly positive. Her patellar and brachioradialis deep tendon reflexes were hyperreflexic bilaterally, but Achilles tendon reflexes were normal. Her cranial nerves were intact, and her sensation of pain and temperature were normal. Her motor strength was normal, but she had significant difficulty walking because of her sensory deficits. The physical examination was otherwise unremarkable.

Laboratory tests in the emergency department included a hematocrit of 17% (normal range, 33% to 44.6%) with a mean corpuscular volume (MCV) of 105.9 fl (normal range, 80 to 96 fl). At this point, the patient was admitted for management of anemia and further evaluation of neurologic symptoms. She received a transfusion of 2 units of packed red blood cells, which brought her hematocrit up to 27%. She was also started on 100 mcg of vitamin B12 intramuscularly daily and 1 mg of folate orally daily.

The patient’s neurological and laboratory findings were initially attributed to vitamin B12 or folate deficiency, given her history of gastrointestinal surgery and recent conversion to oral vitamin B12 supplementation. However, her vitamin B12 and folate levels were available by the third day of hospitalization, with a vitamin B12 level of 738 pg/mL (normal range, 200 to 950 pg/mL) and folate level greater than 24 ng/mL (normal level, >0.9 ng/mL). Methylmalonic acid was 0.77 μmol/L (normal level, <0.4 μmol/L) and homocysteine was 4.7 μmol/L (normal range, 4 to 12...
levels were normal, at 122,900/mm³. Serum iron, ferritin, and transferrin/ceruloplasmin level was found to be

dorsiflexion and plantar flexion of both ankles. strength in her iliopsoas and hamstrings and 3/5

ter the third day of hospitalization, she developed

did not show any significant lymphadenopathy. Af-

icademia, and pelvic computed tomography scan

angiography of the brain was then done with an

elopathy, which was normal. Magnetic resonance

with a high-resolution 3-Tesla MRI study for my-

columns of the cervical spine. This was followed up

showed a possible abnormal signal in the posterior

antibody test was negative.

Further laboratory studies were done, and her

ceruloplasmin level was found to be <10 mg/dL
(normal range, 20 to 60 mg/dL), suggesting copper
deficiency. The patient was started on 5.35 mg of
copper chloride intravenous supplementation daily
(equivalent to 2 mg of elemental copper). Her se-

serum copper level was not checked until the third
day of supplementation and was found to be low at

38 µg/dL (normal range, 80 to 155 µg/dL). Her copper level increased to 53 µg/dL by the sixth day
and to 72 µg/dL by the fourteenth day of treat-
ment. Because high serum zinc levels have been
associated with copper deficiency, the patient’s se-

The patient felt subjectively stronger by the
fourteenth day after initiation of treatment, en-

ing her to ambulate more stably with a walker or
cane, although her neurologic examination was ob-
jectively unchanged. She was then discharged from
the hospital on continued daily intravenous infu-
sions of copper chloride. Four months after dis-
charge (at the time of this writing), she was still
being treated with parenteral copper. Her copper
level had normalized to 97 µg/dL. Although her
symptoms had not improved since going home,
neither had they worsened.

Discussion

Copper deficiency is quite rare in humans because
it is a nutrient that is readily consumed and has a
very low daily requirement.1,2 It is present in le-
gumes, meats, and nuts, and is absorbed through
the mucosa of the stomach and proximal duode-
um. With the plentiful supply of dietary copper,
aquired copper deficiency is relatively uncommon
compared with other causes of neurologic and he-
matologic deficits, so it can be easily missed when
formulating differential diagnoses.

Copper is an essential trace metal that plays an
integral role in many of our physiologic processes,
including acting as a ligand to many proteins and
enzymes. It is crucial in the structure of dopamine
β-hydroxylase, the enzyme responsible for conver-
sion of dopamine to norepinephrine, which medi-
ates many neurologic functions. In addition, copper
helps form cytochrome oxidase, a component in
oxidative phosphorylation, and superoxide dis-
mutase, an antioxidant. Copper also acts as a ligand
to ferroxidase II, which oxidizes iron, allowing it to
be mobilized and transported from hepatic stores
to the bone marrow for use in erythropoiesis.2
Thus, copper deficiency results in excessive iron in
the liver but insufficient iron in the marrow for
effective erythropoiesis.3

Although rare, there are several potential causes
of copper deficiency. In previous reports, copper
deficiency has developed after gastric and bariatric
surgery, probably due to malabsorption.4–6 Copper
deficiency can also develop in patients receiving
intravenous hyperalimentation without copper sup-
plementation.7 It has also been found to be associ-
ated with hyperzincemia,8–10 although the causal
relationship is still unclear.11 In addition, Menkes
disease is a heritable disorder in which there is a

µmol/L). Her reticulocyte count was elevated to
3.1% (normal range, 0.5% to 1.5%), with an abso-

neutrophils. However, she had normal plate-
let counts and prothrombin times. Peripheral blood
smears showed nucleated red blood cells but no
polymorphic nucleated neutrophils. A bone mar-
row biopsy was considered but refused by the pa-
tient. Serum lead level was normal. Serum and
urine protein electrophoreses were normal. Cere-
brospinal fluid studies showed no evidence of in-
fecion and no oligoclonal bands. An antinuclear

Imaging included magnetic resonance imaging
(MRI) of the brain and cervical spine, which
showed a possible abnormal signal in the posterior
columns of the cervical spine. This was followed up
with a high-resolution 3-Tesla MRI study for my-
elopathy, which was normal. Magnetic resonance
angiography of the brain was then done with an
 incidental finding of frontal lobe developmental
angiography. This was followed up

ings included a white blood cell count of 2,000/
mm³ (normal range, 4,400 to 11,000/mm³), with
40% neutrophils. However, she had normal plate-
let counts and prothrombin times. Peripheral blood
smears showed nucleated red blood cells but no
polymorphic nucleated neutrophils. A bone mar-
row biopsy was considered but refused by the pa-
tient. Serum lead level was normal. Serum and
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at 96 µg/dL (normal range, 65 to 256 µg/dL).
failure to transport absorbed copper to the rest of the body from mucosal cells, which results in copper deficiency and its sequelae.\textsuperscript{12}

Deficiency in the enzymes that copper normally supports can lead to striking neurologic deficits, including myelopathy, polyneuropathy, ataxia, optic neuritis, and demyelination. The first documented case of copper deficiency-associated myelopathy was of a 46-year-old woman who developed tetraparesis and painful paresthesias almost 20 years after gastrectomy.\textsuperscript{13} In another study of 13 patients with acquired copper deficiency, all had gait difficulty and lower limb paresthesias, with impaired proprioception and vibration sense in the distal lower limbs.\textsuperscript{5} Nine of those patients also had reduced perceptions of pinprick and touch in a stocking distribution, and 10 had positive Babinski’s sign. Three of the 13 had increased T2 signal in the paramedian dorsal cervical cord.

Patients with copper deficiency can also develop profound hematopoietic deficits resulting in anemia and leukopenia, although not all patients with copper deficiency develop these manifestations. Sideroblastic changes and nuclear maturation defects causing anemia and neutropenia have been observed in erythroid precursors of patients with copper deficiency.\textsuperscript{1,14} A peripheral smear often reveals sideroblastic anemia with hypochromic microcytic red cells. Granulocyte levels can become very low, whereas platelet counts remain normal. In the study mentioned above in which 13 patients with copper deficiency were followed, 10 of the 13 had anemia or leukopenia.\textsuperscript{5} The MCV in anemia of copper deficiency is usually normal or increased, which can complicate the diagnosis, since megaloblastic anemia is also characteristic of vitamin B12 or folate deficiency.

Thus, the myelopathy, polyneuropathy, and anemia produced by copper deficiency can mimic the deficits seen with vitamin B12 or folate deficiency. Subacute combined degeneration from vitamin B12 deficiency involves the posterior and lateral columns of the spinal cord and sometimes the peripheral nerves. In previous reports of patients with B12 deficiency, symptoms at presentation included progressive sensory deficits, postural instability, paresthesias, and megaloblastic anemia.\textsuperscript{15,16} Likewise, a case report of a 38-year-old woman with folate deficiency describes a presentation with characteristics similar to ours, with peripheral neuropathy, macrocytosis, and gait ataxia.\textsuperscript{17}

The differential diagnosis of patients with presentations such as ours should include not only B12 and folate deficiency, but also problems such as central nervous system infection, multiple sclerosis, lupus, multiple myeloma, leukemia, or other malignancies. To diagnose copper deficiency, serum copper level should be measured; ceruloplasmin level is nonspecific and can be an acute phase reactant. Serum copper levels can be followed for adequacy of copper replacement therapy. Patients with copper deficiency have been successfully treated with oral copper in the past\textsuperscript{5} but not in the form of copper gluconate because of its poor bioavailability.\textsuperscript{18} Given that the cause of our patient’s deficiency was her abnormal gastrointestinal anatomy, we opted to treat her with parenteral copper chloride.

In prior case studies, neurologic improvement has been quite variable, although most patients seem to retain some deficit even with treatment, and relapses can occur.\textsuperscript{5,7,9,10,19,20} The hematologic deficits, however, generally correct within 2 months of beginning treatment.\textsuperscript{10,21}

**Conclusion**

Our patient had a history of extensive gastrointestinal surgeries and recent development of waxing and waning hematologic and neurologic deficits. Her symptoms were ultimately attributed to copper deficiency. Prompt diagnosis and treatment of copper deficiency may help prevent the development of further neurologic deficits. Physicians should be aware that copper deficiency is part of the differential diagnosis in patients with unexplained neurologic symptoms, anemia, and leukopenia, especially those who have had prior gastrointestinal surgery.

**References**

4. Kumar N, Ahlskog JE, Gross JB, Jr. Acquired hypo-


