A 55-Year-Old Man with Neurologic, Hematologic Abnormalities

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What's the Take Home?

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Introduction. A 55-year-old man presents with a subacute history of an unsteady, stumbling gait resulting in several falls during the last 2 weeks.

Patient history. The patient states that he is not dizzy—no sensation of the room spinning or vertigo. He does note, however, tingling sensations in both hands and feet. He believes his strength remains normal.

He has a long and complicated medical and surgical history related to severe alcoholism when he was younger. In his 30s, he had several hospital admissions for a variety of complications, most frequently gastrointestinal (GI) bleeding and acute and chronic pancreatitis. He had some form of gastric resection during that time and has had trouble maintaining his weight since. He has learned to eat small frequent meals since consuming larger portions causes GI distress. He also developed diabetes mellitus and now requires small doses of insulin, to which he is quite sensitive.

Although the patient no longer smokes, he has a 20-pack-year history. He has not consumed alcohol for 15 years.

The patient's physical examination reveals a thin (128 pounds) man with normal vital signs. He has a broad-based, even staggering, gait. HEENT is negative for both jaundice and nystagmus. His chest is clear, and no issues with his heart. The patient's abdomen is soft and non-tender without organomegaly. There is a large 20-cm scar in the midline of his abdomen. There is no edema. He has a broad-based ataxic gait. There is no tremor or other cerebellar signs. He has significantly diminished proprioception in both feet and, to a lesser extent, both wrists and hands, which is bilateral and symmetrical. His strength seems normal, as are his deep tendon reflexes.

The patient's laboratory findings revealed anemia, and an examination of his blood smear confirmed severe neutropenia with hyperlobulated PMN forms present and RBC macrocytosis (Table 1).

Table 1. Laboratory findings

Test	Result	Notes
Hemoglobin	8.0 g/dL	Anemia
Mean corpuscular volume (MCV)	109 fL	Macrocytic
White blood cell count (WBC)	1.6 K/μL	Leukopenia

Absolute neutrophil count (ANC)	0.21 K/μL	Severe neutropenia
Platelets	151 K/μL	Normal range
Blood smear findings	–	Severe neutropenia; hyperlobulated PMNs; macrocytosis
Sodium	121 mmol/L	Hyponatremia
Blood urea nitrogen (BUN)	9 mg/dL	Normal range
Creatinine	0.8 mg/dL	Normal range
Lactate dehydrogenase (LDH)	Normal	–
Transaminases	Normal	–
Ferritin	584 μg/dL	Elevated
Albumin	2.9 g/dL	Low
Vitamin B12	399 pmol/L	Normal range
Methylmalonic acid	Pending	Ordered
Folate	8.6 ng/mL	Normal range

In response to the neurologic signs and symptoms, an MRI of the brain and spine was performed, which was negative for tumor or disc disease. However, hyperintense signals were present in the posterior and paramidline areas of the cervical cord.

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Tray "User-defined shortcuts" opened.

Correct answer. C. Obtain a serum copper level.

Discussion. When one encounters a case presentation that involves hematologic and neurologic tests, the general reflex is to diagnose vitamin B12 deficiency. But the world changes—as does the medicine and pathology practiced within it.

This case represents an unusual diagnosis that I believe is becoming ever more common due to advanced medical and surgical treatments, which cause secondary derangements in physiology, exposing patients to the formerly rare diagnosis of copper deficiency. In the last 6 months, for example, I have personally seen and diagnosed two patients with copper deficiency after treating only one or two in the previous decade.

There are similarities between copper absorption and iron absorption in the human GI tract. To briefly summarize, the site of most copper absorption is the stomach and proximal duodenum via a membrane transport channel protein located at the apical membrane of intestinal cells.[1] Copper is thus transferred into these enterocytes and then into the blood, eventually arriving at that omnipotent storage and regulation organ, the liver. There, protein metallochaperone molecules uptake, transfer, and assign copper to its various sites and functions in the body.[1]

As with so many metabolic syndromes, protein deficiencies and other genetic lesions with loss of function will result in ineffective copper absorption, transport, storage, and utilization.

The physiology discussed above generates a pathophysiologic differential that includes inadequate intake (e.g., malnutrition, parenteral alimentation, anorexia), increased copper losses, or depressed absorption (e.g., malabsorption syndromes of sprue, inflammatory bowel disease, post-gastrectomy, and bariatric surgeries) wherein the copper absorptive areas are diseased, removed, or bypassed.[1,2] Finally, there is the issue of excess zinc intake, which can be found in those who use cold remedies and dental pastes. Zinc uses a GI binding protein that also binds copper and thus interferes with its absorption.[1]

The above discussion opens the patient demographics to determine who is at risk for copper deficiency. A simple but effective listing includes:

- Gastric bypass surgeries (increasingly common)
- Enteral or parenteral nutrition with inadequate copper
- Zinc overuse (e.g., cold remedies)
- Chronic renal replacement therapy (CRRT)
- Coeliac sprue (the classic association)

When such patients present with hematologic and/or neurologic syndromes, copper deficiency should be a priority consideration. But what are the typical clinical presentations of significant copper deficiency?

The hematology manifestation will present as weakness and fatigue caused by severe anemia. Both macrocytic and microcytic forms are reported in the literature4, with macrocytosis as the most common. The other cell line most frequently involved is the WBC with neutropenia, often severe (less than 2.0 K) accompanying the macrocytic anemia in more than 50% of cases.[1] The platelets, again without explanation of mechanism, are frequently unaffected.[1] The blood picture mimics myelodysplasia and often results in a bone marrow biopsy with pathology findings consistent with that diagnosis. Clues that myelodysplasia is not the correct diagnosis will include the absence of any cytogenetic abnormalities and the somewhat unique presence of cytoplasmic vacuolization of bone marrow red blood cell (RBC) and WBC precursors.[3]

The neurological presentation is an ataxia syndrome resembling classic subacute combined degeneration of vitamin B12 deficiency. The ataxia manifests as an unsteady gait and an inability to stand, which can be severe and disabling. There is usually concomitant paresthesia of the hands and feet such that the ataxia is classified as a sensory form. If MRI is performed, the hyperintense signaling of subacute combined degeneration with involvement of lateral and posterior tracts essentially identical to B12 deficiency can be found.[4] The MRI of Parkinson disease or normal pressure hydrocephalus is different and those two syndromes are not associated with abnormal blood findings, making Answer D incorrect.

The above findings should prompt an urgent measurement of serum copper levels. Readers will recognize the similarities to B12 deficiency in both the blood and neurologic findings. Indeed, I suspect a vast majority of any such patients will have had measurements of B12 and methylmalonic acid well before this point in the workup and perhaps even had empirically initiated parenteral B12 to bypass any malabsorptive cause such as autoimmune pernicious anemia, which makes Answer A incorrect.

Regarding a diagnosis, when the patient seems to have B12 deficiency (either neurologically or hematologically) yet his or her B12 laboratory findings indicate no such deficit, proceed to evaluation for copper deficiency. If the patient has demographic risk comorbidities, such as gastric bypass, other gastric surgeries, or malabsorption issues, consider copper deficiency early.

A diagnosis is a simple measuring of serum copper. Clinicians should consider measuring zinc as well since excessive amounts of zinc are a cause for copper deficiency and over-the-counter medicine usage can be overlooked. Once the diagnosis is secured, further investigations as to causation will be guided by clinical findings.

Treatment and management. Since these patients are generally severely anemic with neurologic symptoms, parenteral (IV) copper is initially indicated for the first week or so. Copper gluconate 2-4 mg/day for a week is the usual dosage with oral copper gluconate 4-8 mg/d thereafter, while monitoring for normalization of serum copper levels in severe cases.

Lower dosage is often adequate for patients with a less severe diagnosis. Attention to restoration of normal copper levels is required because so many malabsorptive situations are in play with copper deficiency.[1-4]

One more comparison to B12 deficiency needs be mentioned. Like B12 deficiency, the hematology of copper deficiency is generally reversible with copper replenishment. We generally see prompt improvement in 4 weeks and normalization in 12 weeks. And like B12 deficiency, the neurology is less amenable to therapy. At least 50% and perhaps 75% of cases will show no or minimal resolution even after several years of copper normalization.[1,4]

Patient follow-up. The normal B12 levels were somewhat of a surprise considering the clinical presentation. In fact, parenteral B12 had been initiated once it was secure that specimens for B12 measurement were obtained. Thus, a second round of testing including serum copper and zinc were obtained the next day. Pending the results, clinicians performed a bone marrow biopsy to detect possible MDS syndromes. Megaloblastic change was seen with the additional finding of vacuolization in RBC and WBC precursors. Cytogenetics on the marrow specimen were completely negative for any abnormal MDS related abnormalities. Results for copper (normal: 75-145 ugm/dL) were less than 10 ugm/dL and for zinc 100 ugm/dL (normal 65-110 ugm/dL) consistent with severe copper deficiency not related to zinc intake excess. There was no such history on repeated inquiry.

Due to the quite severe hematologic and neurologic syndromes and the rather complex set of social and medical comorbidities, the patient stayed in the hospital for 7 days while receiving IV copper gluconate 2 mg/d. He was then discharged with oral copper gluconate in doses of 4 mg/d. At 4 weeks, his WBC had increased to 7.0 K and his hemoglobin level went up to13 gm/dL The MCV decreased to 95 u. Although he was still quite significantly ataxic, he was still able to ambulate to a degree with a walker. After 3 months, his CBC had normalized. His copper level was 106 ugm/dL. He was still ataxic but showed some improvement. Appropriate attention to copper supplementation in his diet and enteric regimens protocols, specifically oral copper gluconate 4 mg/d, will continue.

What's the Take Home? Although copper deficiency was once a true "medical zebra" diagnosis at the very end of any differential, it is now being seen and reported much more frequently. The demographics of who is at risk for clinically significant copper deficiency indicates a population becoming progressively larger—those undergoing gastrectomy/gastric bypass, chronic and ongoing enteral and parenteral nutrition cases, excess zinc ingestion as preventatives for colds come to mind. All are essentially iatrogenic situations, which tip copper balance negatively to the point of deficiency. Thus, there are situations where the diagnosis needs early consideration. Copper deficiency will present in hematologic and/or neurologic syndromes, most often both. The classic hematology presentation is anemia, often severe and macrocytic with severe neutropenia yet preserved platelet counts. The neurologic presentation is usually a gait disturbance—a sensory ataxia essentially a subacute combined degeneration syndrome. Common considerations in copper deficiency

cases are thus B12 deficiency and myelodysplasias. Serum copper should be checked in all such cases. Once confirmed copper supplementation is relatively straight forward and results in full hematologic recovery in 4-12 weeks. As with B12 deficiency, however, neurologic recovery is not guaranteed and roughly half the cases will be left with some degree of neurologic (e.g ataxia syndrome) deficit.

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