CLINICAL VIGNETTE

Cervical Myelopathy Related to Copper Deficiency

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Case Presentation

A 73-year-old female presented to the primary care office with tingling of bilateral hands and feet, sensation of cold in the legs and gait imbalance. Physical examination was significant for mildly decreased sensation in bilateral feet, with normal gait although she subjectively complained of instability. Her medical history significant for essential hypertension, hyperlipidemia, and hypothyroidism, alcohol use disorder. Initial labs were normal including negative HIV, TSH, CK, non-reactive RPR and unremarkable comprehensive metabolic panel. Hemoglobin A1c was 5.2, folic acid and vitamin B12 were high. CBC was significant for leukopenia with WBC count of 3.17, hemoglobin 11.6, MCV 107.4, absolute neutrophil count decreased at 0.94. No monoclonal proteins were identified in serum and urine protein electrophoresis and immunofixation. The patient was taking numerous dietary supplements, all of which were discontinued. She had previously been consuming 3-4 hard liquor drinks daily, which she had decreased to 2 drinks per day.

Patient was started on gabapentin and was referred to Neurology for urgent evaluation. She was seen by the neurologist, and MRI of the cervical spine revealed edema within the cervical spine from C3-C5 prompting hospitalization for expedited evaluation. Her gait imbalance worsened and she required a cane for ambulation. Lower extremity numbness had ascended to her knees. Repeat physical examination, revealed diminished vibration sensation to the mid-thigh and mid elbow bilaterally. Reflexes were +2 in the upper extremities except for absent bilateral brachioradialis reflexes and absent bilateral ankle jerk and knee reflexes.

Testing during her hospitalization revealed an extremely low Copper level. She had persistent leukopenia, macrocytosis, positive anti-nuclear antibody test, and normal TSH. Zinc level was normal at 124 mcg/dL (upper limit of normal 130 mcg/dL). Imaging was repeated and MRI of the brain-revealed few nonspecific frontal and parietal FLAIR hyperintensities not in the typical location for demyelination which may be normal for age, but did not exclude subtle demyelination. Cervical spine MRI and Thoracic Spine MRI showed no cord signal abnormality or abnormal enhancement and multilevel degenerative changes of cervical spine without significant canal or foraminal stenosis. She also had a lumbar puncture and cerebrospinal fluid (CSF) studies were unremarkable. The patient was started on copper replacement and discharged home with stable neurological symptoms.

Discussion

Copper deficiency myelopathy has been recognized as an often underdiagnosed, acquired neurological syndrome, clinically characterized by posterior column dysfunction.[1,2] Copper deficiency myeloneuropathy is reported more in women with reported cases ranging from 30 to 82 years.[3] Copper is a component of enzymes that have a critical role in the structure and function of the nervous system including electron transfer in key enzymatic pathways including cytochrome-c-oxidase for electron transport and oxidative phosphorylation, monoamine oxidase for serotonin synthesis, and ceruloplasmin for brain iron homeostasis. The main causes of copper deficiency are conditions causing impaired copper absorption in the upper GI tract, including bariatric surgery, increased consumption of zinc, and malabsorption. The neurologic manifestations may be delayed by years following gastric surgery. Copper and zinc are competitively absorbed from the gastrointestinal tract and overuse of zinc supplements and parenteral zinc overloading during chronic hemodialysis have also been linked to copper deficiency myelopathy.[4]

Patients affected by copper deficiency myelopathy usually present with a subacute gait disorder with sensory ataxia due to dorsal column dysfunction and sometimes with mild leg spasticity. Physical examination reveals long tract signs with spasticity in the legs and Babinski response, along with impaired vibration and position sense and a positive Romberg sign. Hematologic abnormalities include anemia and leukopenia. In one study of 55 case reports, cytopenias were found in 78% of the patients, particularly anemia.

Diagnosis is based on clinical findings and laboratory indicators of copper deficiency. Vitamin B 12 levels should also be checked as copper and vitamin B12 deficiency can co-exist, particularly in patients with a history of gastric surgery. Patients who present with a myelopathy should also have imaging of the spinal cord to exclude other conditions. Such patients' spinal MRI may show hyperintense lesions in T2-weighted sequences involving the posterior columns of cervical and thoracic cord. These MRI findings are similar to those of subacute combined degeneration associated with vitamin B12 deficiency.[3] Low serum copper and ceruloplasmin levels confirm the diagnosis and, in contrast to Wilson's disease, urinary copper levels are typically low.[5] When excessive zinc ingestion is suspected or when the cause of copper deficiency is unknown, serum zinc and 24-hour urinary zinc excretion levels should be obtained. A significant elevation in these should prompt an investigation for

an exogenous source of zinc. Although lumbar puncture and CSF studies are not routinely indicated, a slight non- specific elevation in the CSF protein can be seen.

Treatment includes copper supplementation, however, no studies have addressed the optimal dose, duration or form of copper supplementation. Elemental copper is typically used for oral replacement at a standard dose of 2 mg of elemental copper per day. This may be administered intravenously over two hours daily for five days, and periodically thereafter. Some patients require higher doses and replacement doses are empiric based on periodic monitoring of serum copper levels. In those suspected of excess Zinc ingestion, discontinuing zinc supplementation may suffice without the need for additional copper supplementation. It is also important to treat other deficiencies such as vitamin B12, vitamin D, Vitamin E and iron if indicated. The duration and severity of symptoms prior to supplementation may influence prognosis. Copper supplementation usually prevents further neurologic deterioration, but improvement of neurologic signs and symptoms is often subjective and variable with most patients ending up with residual deficits.[3] The hematologic abnormalities usually show a prompt and complete response.

Our patient was diagnosed with copper deficiency myelopathy, thought to be related to excessive zinc ingestion based on history and zinc level close to upper limit of normal. She received oral copper supplementation with significant improvement in her lower extremity weakness, however she continues to have residual peripheral neuropathy. Although a rare cause of myeloneuropathy, copper deficiency should be considered in the right clinical setting as early diagnosis and treatment leads to better response.

REFERENCES

1. **Plantone D, Primiano G, Renna R, Restuccia D, Iorio R, Patanella KA, Ferilli MN, Servidei S**. Copper deficiency myelopathy: A report of two cases. *J Spinal Cord Med*. 2015 Jul;38(4):559-62. doi: 10.1179/2045772314Y.0000000268. Epub 2014 Oct 24. PMID: 25343982; PMCID: PMC4612215.
2. **Williams DM**. Copper deficiency in humans. *Semin Hematol*. 1983 Apr;20(2):118-28. PMID: 6410510.
3. **Kumar N, Ahlskog JE, Klein CJ, Port JD**. Imaging features of copper deficiency myelopathy: a study of 25 cases. *Neuroradiology*. 2006 Feb;48(2):78-83. doi: 10.1007/s00234-005-0016-5. Epub 2005 Oct 28. PMID: 16261334.
4. **Yaldizli O, Johansson U, Gizewski ER, Maschke M**. Copper deficiency myelopathy induced by repetitive parenteral zinc supplementation during chronic hemodialysis. *J Neurol*. 2006 Nov;253(11):1507-9. doi: 10.1007/s00415-006-0259-z. Epub 2006 Sep 13. PMID: 16972121.
5. **Jaiser SR, Winston GP**. Copper deficiency myelopathy. *J Neurol*. 2010 Jun;257(6):869-81. doi: 10.1007/s00415-010-5511-x. Epub 2010 Mar 16. PMID: 20232210; PMCID: PMC3691478.