ABSTRACT
Copper deficiency has been associated with a clinical syndrome, myeloneuropathy. and radiographic changes resembling B12 deficiency in the cervical spinal cord. We report two cases of copper deficiency myeloneuropathy, with cervical MR imaging findings resembling B12 deficiency, which showed partial clinical improvement with treatment.

Key words: Copper, myeloneuropathy, vitamin B12, zinc

INTRODUCTION
Copper deficiency is an increasingly reported but under recognized cause of neurologic dysfunction. This potentially treatable disorder manifests clinically as a profound sensory ataxia and can be associated with spastic gait and upper motor sign in the limb, mimicking vitamin B12 deficiency myeloneuropathy. Potential causes of Copper deficiency are, nephrotic syndrome, parenteral nutrition, excessive zinc intake especially after prolonged intake of zinc containing vitamin, use of denture adhesives contain mixed zinc salt. The well recognized disorders of hereditary copper deficiency are “Menkes disease” and “Occipital horn syndrome” where there is failure to mobilize copper absorbed into the mucosal cells due to mutations in the ATP7A gene, which encodes copper-transporting ATPase. Clioquinol, a copper zinc chelating antibiotic, caused subacute myelo-optico-neuropathy in nearly 10000 patients in Japan before the banning of its use in 1970. Other cause of copper deficiency is malabsorption after gastric surgery. Causes of myeloneuropathy resembling subacute combined degeneration of cord due to vitamin B12 deficiency are nitrous oxide toxicity, vacuolar myelopathy in HIV, Podophyllin toxicity. Other causes of myeloneuropathy are Tropical spatic paraparesis, Hereditary Spastic Paraparesis, adult onset Tay ach’s disease and Adrenoleukodystrophy.

CASE REPORT
Case-1 – 1
A 23-year-old male, not a known diabetic or hypertensive presented with insidious onset and gradually progressive stiffness, imbalance while walking, numbness in both lower extremities and diminished hearing since 15 months. There was no preceding history of fever, skin rashes, chronic diarrhea, pulmonary tuberculosis, spinal trauma or bladder and bowel dysfunction. General physical and systemic examinations were normal. Neurological examination revealed normal higher cortical functions and did not reveal any cranial nerve abnormality except bilateral sensori neural hearing loss. Hypertonia and extensor plantar response were detected without any muscle atrophy in both lower limbs. Deep tendon reflexes were brisk in both upper and lower limb but ankle jerk was absent in both side. Slight weakness (MRC 4/5) was also detected in both lower and upper limb. Romberg test was also positive. Routine hematological was suggestive of microcytic anemia but biochemical investigations were within normal limits. Rheumatoid factor and C- reactive protein were negative. An antibody for HIV 1 & 2 by rapid HIV tri dot was non-reactive. Antinuclear antibody index was 0.79 (< 1.0 ANA negative). Serum vitamin B12 -527 pg/ml (211-911), serum homocysteine 8.42 umol/l (5.46-16.20) and serum methyl malonic acid, zinc, ceruloplasmin were normal. Thyroid function test was normal. Serum copper was 58 ug/dl (70-140). Magnetic resonance imaging (MRI) of brain was normal. MRI of cervical spine showed long segment intramedullary T2 hyperintensity involving posterior columns extending from C2 to C7 level. Motor and sensory median and ulnar nerves conduction were normal. In lower limbs peroneal CMAP were not recordable with absent F waves bilaterally. Tibial motor conductions and sural SNAPs were normal.

Case- 2
A 55-year-old married female, not a known diabetic or hypertensive presented with insidious onset and gradually progressive stiffness and pain in both limbs below knees with minimal difficulty in arising from squatting position of four months duration. There was no prior history of fever, skin rashes, chronic diarrhea, pulmonary tuberculosis, spinal trauma or
bladder and bowel dysfunction. General physical and systemic examinations were normal. Neurological examination revealed normal higher cortical functions and cranial nerves. Motor system examination of both upper limbs was normal. In lower extremities, there was motor weakness 4+/5 (MRC grade) with spasticity and brisk deep tendon reflexes in both lower limbs. Planter responses were extensor bilaterally. Both spinthalamic and proprioceptive sensations were normal. Gait was spastic. Routine hematological and biochemical investigations were normal except microcytic anemia. Rheumatoid factor and Anti nuclear antibody was negative. Serum vitamin B12 -673 pg/ml (211-911) was also normal. ELISA for HIV 1 & 2 was non-reactive. serum homocysteine 8.9 umol/l (5.46-16.20) and serum methyl malonic acid were normal. Thyroid profile was normal. MRI of brain showed age related cerebral atrophy with mild subcortical and periventricular white matter ischemic changes. MRI of cervical and dorsal spine showed intramedullary T2 hyperintensity extending from C3 to C7 level. Motor and sensory nerve conduction in all limbs were normal. Both cases were treated with copper gluconate 6 mg per day for 1 week, followed by 4 mg per day for 1 week, followed by long-term supplementation with 2 mg per day oral copper thereafter to maintain normal serum levels. Patients were also advised to increase their dietary intake of foods that are high in copper, such as legumes, shellfish, chocolate, mushrooms, liver, and nuts. Neurological signs like spasticity did not improve but sensory symptoms of paresthesia and sensory ataxia were improving on follow up visits.

DISCUSSION

Copper deficiency is an increasingly recognized cause of neurologic degeneration and is also an established cause of anemia and the myelodysplastic syndrome. Copper is an important cofactor in several enzymatic processes important in the function of the central nervous system, including cytochrome-c oxidase, copper-zinc superoxide dismutase, and dopamine hydroxylase. The hematological effects of copper deficiency include sideroblastic anemia, leukopenia and neutropenia. Acquired copper deficiency is also thought to affect cardiovascular and bone health. Effects on the nervous system have been characterized in the past so many years; they include myeloneuropathy with spastic gait, distal parasthesias and sensory ataxia, which closely mimic the symptoms and radiographic findings in patients with subacute combined degeneration associated with vitamin B12 deficiency. Rarely, copper deficiency is associated with isolated demyelination of the optic nerve and in the CNS, peripheral neuropathies, or myopathy. High concentrations of zinc have long been known to lead to copper deficiency. Zinc interferes with the absorption of copper from food. High intakes of zinc can result in increased expression of endogenous chelating proteins such as metallothioneins that have a greater affinity for copper than for zinc. Another effect is the sequestration of copper in enterocytes of the stomach and proximal duodenum, which are sloughed off and eventually excreted in the feces. Abnormalities on T2-weighted MRI include areas of increased signal in the dorsolateral cervical and thoracic spinal cord, with or without swelling. Our patient had a slight signal increase in the dorsolateral cervical cord and no swelling. Nonspecific white-matter changes can sometimes be seen on brain MRI; copper deficiency can also cause microcytic or normocytic anemia. Leucopenia, neutropenia or myelodysplastic syndrome has also been reported. Our patients had microcytic anemia only. Proposed treatment protocol of copper deficiency is short period of replacement with high oral doses of copper, in the form of copper gluconate or copper chloride, (e.g. 6 mg per day for 1 week, followed by 4 mg per day for 1 week) followed by long-term supplementation with 2 mg per day oral copper thereafter to maintain normal serum levels. Some patients with a long or recurrent history of copper deficiency have been reported who require increased doses of copper replacement in order to maintain normal serum copper levels. Hematological abnormalities related to copper deficiency myeloneuropathy always resolve with copper supplementation. Neurological signs generally stabilize but do not improve, although some symptoms might show subjective sensory improvement. In our case, hematological abnormality improved completely with improvement of sensory features but the motor features like spasticity did not improve.

CONCLUSION

Copper deficiency is an uncommon cause of myeloneuropathy. Populations at the highest risk are elderly people, patients who have undergone gastric-bypass surgery, those with renal disease or malabsorption states, and individuals who use supplemental zinc and/or over-the-counter medications or preparations that are high in zinc. Thought of another diagnosis is essential because a broad range of conditions have symptoms that overlap with those of copper deficiency. Investigation and treatment of copper deficiencies should not be delayed because, once present, the neurological symptoms of copper deficiency can be stabilized but are generally permanent.

REFERENCES


8. Tarnlund JR Copper. In Modern nutrition in health and disease, 2000; 241 (Eds Shils ME et al.) Philadelphia: Lippincott


