A RARE CASE OF POSTERIOR MYELOPATHY SECONDARY TO COPPER DEFICIENCY AND MILD HYPERZINCEMIA OF UNKNOWN ORIGIN

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We describe a case of a 41-year-old woman, without significant past medical history, who developed a subacute ataxic paraparesis associated with low back pain. At neurological examination she presented mild bilateral proximal lower limb hyposthenia, hyperreflexia and severe distal hypopallesthesia. Spinal cord 3.0 T-MRI showed a thin hyperintense FS-Echo T2 longitudinally extensive lesion involving the posterior columns of cervical cord (from C2 to C6), without contrast enhancement. Lower limb somatosensory evoked potential amplitude was reduced.

She underwent a complete diagnostic work-up comprehensive of:

- Routine laboratory evaluations, thyroid function tests, serum electrophoresis
- Serum cobalamin and folate and urinary metylmalonate levels
- CSF analysis (including cell counts, protein, glucose and oligoclonal bands)
- Serum antibodies against Aquaporin 4 and Myelin Oligodendrocyte Glycoprotein
- Rheumatological screening tests (including ANA reflex, c-ANCA, p-ANCA, cryoglobulin, Rheumatoid Factor, LAC test, anti beta2glycoprotein, anti cardiolipin, complementaemia, celiac antibodies, thyroid antibodies)
- Serology for neurotropic viruses (including HSV1-2, CMV, EBV, HBV, HCV, HIV, HTLV1-2)
- Serology for Borrelia Burgdorferi and Treponema Pallidum
- Brain MRI

All these examinations were normal. Serum copper level was under normal limits (26 ug/mL, nv 65-165), ceruloplasmin was normal and serum zinc concentration was upon normal value (1093 ug/L, nv 600-1080). Patient denied any history of zinc abuse and she didn't use dental adhesive. We treated her with oral copper supplementation with a mild clinical improvement.

RECOMMENDED COPPER INTAKE (mg/dL)

- Newborn: 0.2
- Children (1-10 years): 0.4-0.7
- Adolescents: 0.8 - 1
- Adults: 0.9
- Pregnancy: 1.2
- Breastfeeding: 1.6

RICHEST FOOD SOURCE
Nuts
Seeds
Chocolate
Shellfish

CAUSES OF HYPOCUPREMIA

Bariatric surgery (gastrectomy or gastric bypass surgery)
Hyperzincemia (zinc supplements , increased use of zinc containing denture cream)
Chelating agents such as Penicillamine (Wilson's disease therapy) and tetrathiomolybdate (anticancer and Wilson's disease therapy).
Prematurity
Malabsorption (including celiac disease)
Parenteral nutrition without copper supplementation
Menkes disease (mutation ATP7B)
MEDNIK Syndrome (mutation SLC33A1)
Proton pump inhibitors (PPIs) therapy

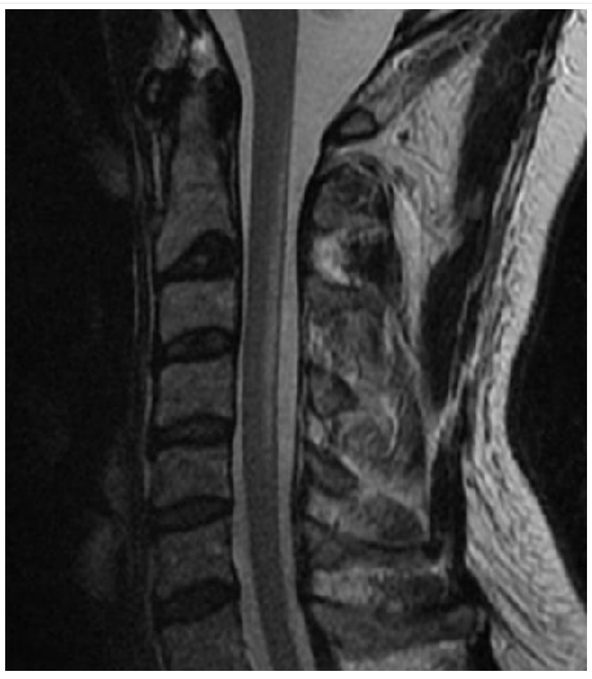
HYPOCUPREMIA CONSEQUENCES

- Anemia
- Pancytopenia (similar to myelodisplastic syndrome)
- Peripheral neuropathy
- Optic neuropathy
- Posterior myelopathy
- Cerebellar atrophy

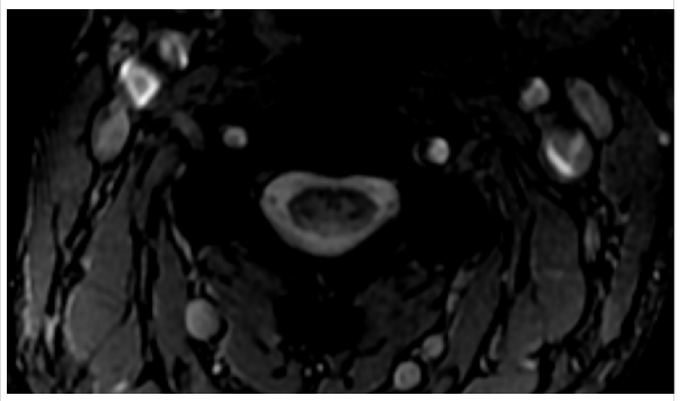
COPPER-DEPENDENT ENZYMES

- Cytochrome-*c* oxidase
- Cu/Zn-SOD
- Metallothionein
- Dopamine-b-monooxygenase
- (Tyrosinase (catechol oxidase)
- Ceruloplasmin (extracellular)
- *S*-Adenosylhomocysteine
- Protein-lysine-6-oxidase
- Hephaestin

HYPOCUPREMIA
↓
OXYDATIVE METABOLISM DEFICIENCY
↓
MYTOCONDRIAL DEFICIENCY



Sagittal T2 Cervical Spine 3T MRI: longitudinally extensive transverse myelitis involving the posterior columns of cervical cord (from C2 to C6), without contrast enhancement



Axial T2 Cervical Spine 3.0 T MRI: posterior columns hyperintensity

COPPER BYOLOGICAL ROLE

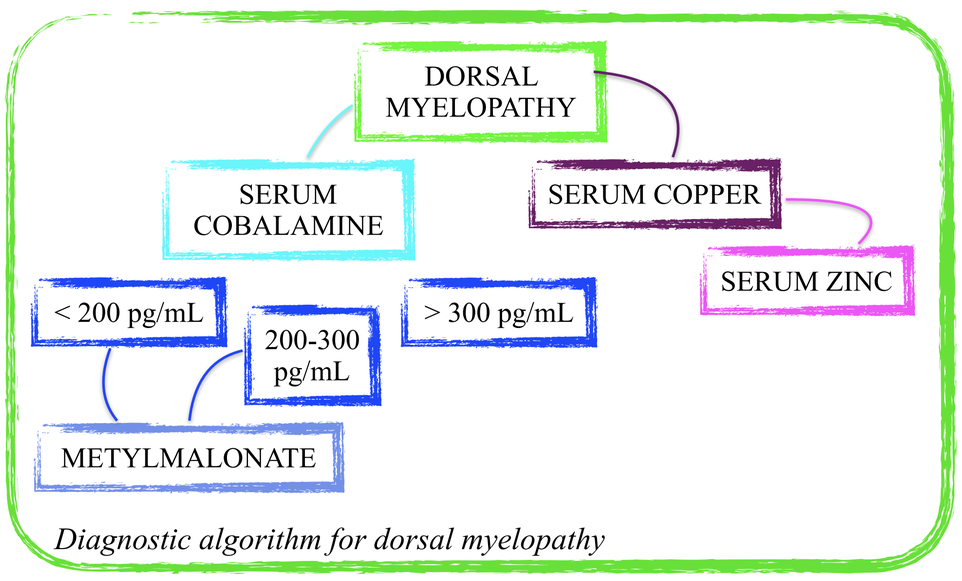
- **Methyonine synthase cofactor**
- **S-adenosylhomocysteine hydrolases (SAAH) modulator**

Human **methionine synthase** is cobalamin and copper dependent. This enzyme transfers the methyl group from methyltetrahydrofolate to homocysteine, thus generating tetrahydrofolate and methionine.

Other metabolic pathways to convert homocysteine to methionine include

- Betaine-homocysteine methyltransferase
- Trans-sulphuration pathway to glutathione (irreversible)

SAHH hydrolyses SAH, a strong inhibitor of methyltransferase. Low copper concentration leads to a reduction in enzyme levels. Alterate enzyme function can reduce methylation ratio and lead to failure of myelin maintenance.



Diagnostic algorithm for dorsal myelopathy

Methylation cycle impairment and subsequent reduction in methylation ratio and myelin damage

RADIOLOGICAL DIFFERENTIAL DIAGNOSIS:

- **Inflammatory disease** (Neuromyelitis Optica, Sjogren's syndrome, LES, Behcet's disease, Sarcoidosis, primary CNS angiitis/ vasculitis, Multiple Sclerosis)
- **Metabolic disease (**Vitamin B12 deficiency)
- **Infectious disease** (HIV, HTLV I-II, Neurosyphilis, CMV, HSV, VZV, Arboviral and Parasitic infections)
- **Vascular disease** (dural artero-venous fistula, spinal cord infarction)
- **Intramedullary spinal neoplasms**
- **Radiation myelopathy**

CONCLUSIONS

Copper is an ubiquitous essential trace metal that works as an enzymatic cofactor in several critical metabolic pathways. Potential causes of hypocupremia include: bariatric surgery, malabsorption, nephrotic syndrome, parenteral nutrition without copper supplementation, genetic syndromes (Menkes syndrome, MEDNIK syndrome), hyperzincemia. Hypocupremia is commonly associated with cyotopenias, peripheral neuropathy and posterior myelopathy. While hematological manifestations are promptly reversible with timely oral copper supplementation, neurological symptoms are generally irreversible. Hypocupremia is an underestimated mimic of subacute combined degeneration of the spinal cord due to cobalamin deficiency. Clinicians must be aware of this treatable disorder and we suggest that copper dosage must be included in the diagnostic work-up of a posterior myelopathy of unknown origin in order to start supplementation as soon as possible to avoid the progression of the disease.

BYBLIOGRAPHY

- G.P. Winston et S.R. Jaiser, *Copper deficiency myelopathy and subacute combined degeneration of the cord – Why is the phenotype so similar?* Medical Hypotheses (2008) 71, 229–236
- P. Zatta et A.Frank *Copper deficiency and neurological disorders in man and animals* Brain Research Reviews (2007) 54, 19–33