Clinical/Scientific Notes

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COPPER DEFICIENCY MYELONEUROPATHY IN A PATIENT WITH WILSON DISEASE

Cases of copper deficiency myeloneuropathy (CDM) have been increasingly reported but hypocupremia remains to be an underrecognized cause of myelopathy.[1] As zinc reduces copper gastrointestinal absorption, excess zinc ingestion is an important cause of hypocupremia.[2]

Wilson disease (WD) is a disorder of copper metabolism characterized by impaired excretion of this metal, resulting in its accumulation in many organs, such as liver, brain, and cornea. Treatment options include penicillamine, trientine, and zinc.

We report the case of a patient with WD treated with zinc who developed a myeloneuropathy in the setting of copper deficiency.

Case report. A previously healthy woman developed depression, postural tremor, and dysarthria at the age of 29 years. Based on the presence of Kayser-Fleischer rings and a low ceruloplasmin level (4 mg/dL, normal range 20–60), a diagnosis of WD was made. She received penicillamine for 1 year with resolution of symptoms and signs. Due to adverse event, this medication was switched to zinc acetate at a dose of 150 mg three times daily.

At the age of 44 years, she began to complain of ascending numbness of the feet. Neurologic examination revealed decreased perception of touch and pinprick in the lower limbs to the knees. Joint position sense was absent at the toes and vibration perception was decreased in the toes and knees. Clinical findings suggested a peripheral neuropathy.

Laboratory evaluation showed normal hemoglobin level, macrocytosis (MCV 103 fL), leukopenia (2,700/mm^3), and thrombocytopenia (134,000/mm^3). Electrolytes, fasting glucose, folate, aspartate transaminase, alanine transaminase, alkaline phosphatase, bilirubin, erythrocyte sedimentation rate, renal function, thyroid function, antinuclear antibodies, serum, and urinary immunoelectrophoresis were normal. Thoracic, abdominal, and pelvic CT were unremarkable. Vitamin B_{12} level was >2,000 pg/mL (the patient had been using oral vitamin B_{12} before our first evaluation) and methylmalonic acid and homocysteine levels were within the normal limits. EMG showed a mild sensory axonal polyneuropathy.

Her neurologic condition deteriorated and numbness progressed over 2 months to include the hips and the fingers. Neurologic examination disclosed spreading of sensory loss to the iliac crests and the tip of the fingers, no vibration perception in the toes, and brisk reflexes in the lower limbs, with flexor plantar responses. A hypothesis of CDM was made. Serum copper was markedly low at 3.0 μg/dL (80–155) as was the serum ceruloplasmin, at 8.0 mg/dL. Free copper concentration could not be estimated. Serum zinc level was raised at 311 μg/dL (70–114). Urinary copper excretion was 7.4 μg/24 hours (3–18.8) at baseline and 170 μg after 1 g oral dose of penicillamine. MRI scan showed a longitudinal increased T2 signal in the posterior aspect of the spinal cord from C1 to C6, without gadolinium enhancement. Brain and thoracic MRI were normal. CSF analysis was unremarkable.

Once the diagnosis of CDM was made, treatment with zinc was stopped. The patient's neurologic deficit stabilized. Results for copper and zinc levels 4 months after zinc discontinuation were 37 μg/dL and 123 μg/dL, respectively.

Discussion. Our patient presented a myeloneuropathy with clinical and imaging characteristics of subacute combined degeneration, without vitamin B_{12} deficiency. Urinary copper excretion after 1 g of penicillamine was way below values commonly found in healthy volunteers.[3] These characteristics are indicative of CDM.

Zinc overload secondary to overuse of denture cream and over-the-counter cold remedies is the second most common cause of CDM.[4] Zinc induces intestinal expression of metallothionein, which has greater affinity for copper. Metallothionein-bound copper is not absorbed and is lost as the enterocytes are sloughed off into the intestinal tract.[5]

Previously, 2 cases of neurologic complications attributed to hypocupremia in patients with WD were reported: a case of axonal sensory neuropathy in a man treated with trientine and zinc[6] and CNS demyelination in a boy treated with penicillamine and zinc.[7]

Our report has important implications for the management of patients with WD. First, considering that myeloneuropathy is secondary to decoppering properties of zinc, any drug used for treating WD has the potential to induce CDM. Second, as sensory symptoms are not a feature of WD, patients on treatment who develop this kind of complaint should be evaluated for the presence of neuropathy or myelopathy. Finally, the treatment of CDM in patients with WD is limited to stopping the decoppering drug, since it seems unreasonable to give copper for these patients.

Patients with WD are also vulnerable to CDM. Physicians must be vigilant in recognizing the signs of myeloneuropathy when treating patients with WD, aiming at early diagnosis and prevention of neurologic deterioration.

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Disclosure: Dr. da Silva-Júnior, Dr. Machado, and Dr. Lucato report no disclosures. Dr. Cançado receives research support from Federico Foundation. Dr. Barbosa reports no disclosures.

Received August 18, 2010. Accepted in final form December 3, 2010.

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LAFORA BODIES IN SKELETAL MUSCLE ARE FIBER TYPE SPECIFIC

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Glycogen is the largest soluble cytosolic macromolecule, containing up to 55,000 glucoses per molecule. It is formed by glycogen synthase (GS) and branching enzyme (BE), which acting coordinately lead to branching after every sixth glucose and ultimately to a spherical shape that allows solubility. Polyglucosans are malformed glycogen molecules containing much less branching. They precipitate and accumulate into polyglucosan bodies (PB). PB characterize adult polyglucosan body disease (APBD) and Lafora disease (LD). In APBD, PB form in and often obstruct axons. APBD is an axonopathy with upper and lower motor neuron signs and no epilepsy. In LD, PB, called Lafora bodies (LB), occupy neuronal perikarya and dendrites. LD is a progressive myoclonus epilepsy, with no long tract or peripheral nerve deficits. APBD is caused by BE deficiency. LD is caused by mutations in the *EPM2A* and *EPM2B* genes encoding respectively the laforin phosphatase and the malin ubiquitin E3 ligase, which regulates laforin. In LD, glycogen becomes progressively phosphorylated, a pathologic process normally prevented by laforin. The charged phosphates unfold glycogen, expose its hydrophobic regions, and lead it to precipitate. GS precipitates with glycogen, but BE does not. Subsequent extension by GS unchecked by branching would convert the glycogen to polyglucosan.[1,2]

Supplemental data at www.neurology.org

The next step in LD research is to understand the basis of the progressive phosphorylation. What is known is that the phosphates accumulate not on but within glycogen,[1] indicating that they are added during cycles of glycogen breakdown and resynthesis, i.e., during glycogen metabolism, as it would be impossible to incorporate phosphate within the formed extremely dense glycogen sphere. While glycogen is ubiquitous, its conversion to polyglucosan in LD is not, occurring in only some cell types. Understanding particularities of glycogen metabolism in these cell types could provide valuable clues into the origin of the phosphorylation. In brain, LB form in neurons and not glia, even though astrocytes possess far more glycogen than neurons. In liver, LB form in periportal and not perivenous hepatocytes.[3] Skeletal muscle is composed of slow-twitch type I and fast-twitch type II fibers, the latter divided into IIA, IID, and IIB, where IIA are the slowest fast-twitch fibers, IIB the fastest, and IID intermediate. It is not known whether LB form in all myofiber types. We address this question in the present work.

Each myofiber type has a unique myosin ATPase. We fiber-typed quadriceps muscle from 12 month-old *Epm2a*$^{-/-}$ and *Epm2b*$^{-/-}$ mice (6 animals per genotype) using histochemical and immunohistochemical staining of mATPase isoforms. Results were similar in all animals: 97% of LB were in type IIB fibers (37.7% of type IIB fibers contained LB). A total of 2% of LB were in type IID fibers (<2% of IID fibers contained LB). A total of 1% in of LB