Case report

Copper deficiency myelopathy: A report of two cases

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Context: Copper deficiency myelopathy represents an often underdiagnosed, acquired neurological syndrome, clinically characterized by posterior column dysfunction. The main causes of copper deficiency are bariatric surgery, increased consumption of zinc, and malabsorption. However, even after a careful history taking and extensive laboratory researches, the etiology of copper deficiency remains undetermined in a significant percentage of cases. Patients affected by copper deficiency myelopathy usually present with sensory ataxia due to dorsal column dysfunction and sometimes with mild leg spasticity. In such patients, spinal cord magnetic resonance imaging (MRI) may show hyperintense lesions in T2-weighted sequences involving the posterior columns of cervical and thoracic cord. These MRI findings are not distinguishable from those of subacute combined degeneration associated with vitamin B12 deficiency.

Findings: Here, we describe two patients with gait ataxia and sensory symptoms in which a diagnosis of copper deficiency myelopathy was made. Both patients showed a significant clinical, neuroradiological, and neurophysiological improvement after proper supplementation therapy.

Conclusion: The patients herein described underline the importance to include serum copper and ceruloplasmin levels as part of the myelopathy diagnostic workup, especially in the cases of otherwise unexplained subacute myelopathy involving the posterior columns. Since copper deficiency myelopathy is a progressive syndrome, early diagnosis is mandatory in order to promptly provide a proper supplementation therapy and, thus, prevent an irreversible neurological damage.

Keywords: Ataxia, Copper, Evoked potentials, MRI, Spinal cord

Introduction

Copper deficiency myelopathy (CDM) represents an often underdiagnosed, acquired neurological syndrome clinically characterized by symptoms and signs related to posterior column dysfunction. The main causes of copper deficiency are gastrointestinal surgery, malabsorption, and excessive zinc ingestion; however, the etiology remains undetermined in a significant percentage of patients. CDM should be suspected in patients presenting with otherwise unexplained subacute ataxic myelopathy and, in such cases, prompt supplementation therapy is strongly recommended. Here, we describe two patients presenting with otherwise unexplained subacute myelopathy involving the posterior columns in which extensive investigations revealed copper deficiency. Both patients showed a significant clinical, neuroradiological, and neurophysiological improvement after oral copper supplementation.

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Case report

Case 1

In January 2012, a 50-year-old Caucasian woman presented to our neurological department complaining of subacute-onset numbness and tingling in the lateral region of the right thigh. A mild ataxic gait was evident at neurological examination. Her past medical and surgical history was unremarkable. She did not refer any infectious disease in the period before the onset of the symptoms, she did not smoke and consumed alcohol sparingly. She denied any recreational drug use and any denture cream use. Brain and spinal

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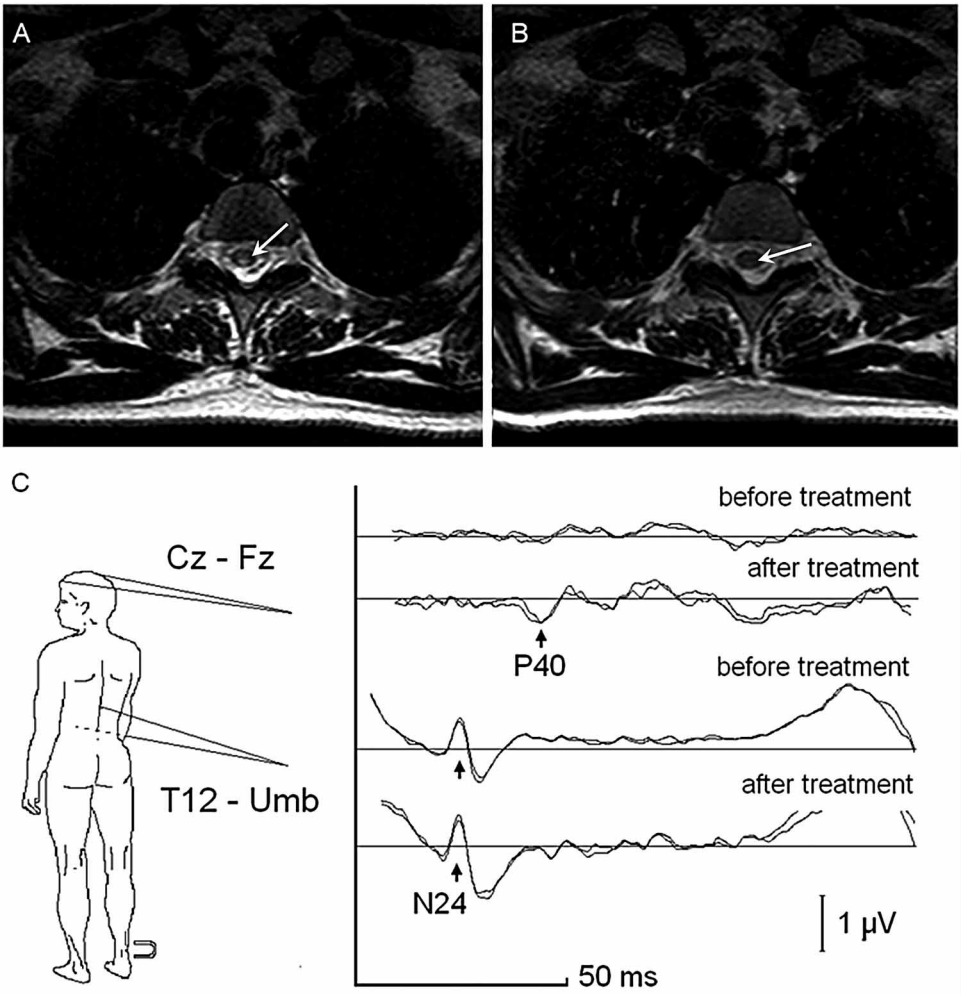

Figure 1 (A) Axial T2-weighted turbo spin-echo (T2-TSE) spinal cord MRI showing a hyperintense lesion (arrow) involving the dorsal midline of the thoracic spinal cord between D2 and D4. (B) Axial T2-TSE spinal cord MRI showing improvement of the spinal cord lesion (arrow) after prolonged oral copper supplementation. (C) Right tibial nerve SEPs evoked by tibial nerve. Tibial nerve SEPs recorded through surface electrodes show activation of dorsal horn interneurons of lumbar enlargement (N24 response), and of somatosensory cortex (P40 response). The figure shows the traces recorded before and after supplementation therapy.

cord magnetic resonance imaging (MRI) showed a lesion involving the dorsal columns of the thoracic spinal cord between D2 and D4 (Fig. 1A). Cobalamin, folate, and methylmalonate levels were all within the normal range. Inflammatory markers were negative. Cerebrospinal fluid (CSF) analysis revealed normal protein (27 mg/dl; normal values: 20–40 mg/dl) and glucose (53 mg/dl; normal values: 45–80 mg/dl) and no cells. Oligoclonal bands were absent and CSF Gram staining was negative. Molecular and serological tests for herpes simplex virus, varicella zoster virus, Epstein–Barr virus, enterovirus, and cytomegalovirus were all negative. Both serum and CSF resulted negative for onconeural (anti-Yo, anti-Hu, anti-Ri, anti-Cv2, anti-NMDAr, anti-GABAB, anti-GAD65, anti-amphiphysin, anti-LGI1, and anti-CASPR2) and aquaporin-4 antibodies. Electroneurography did not show any signs of polyneuropathy. Somatosensory pathways in the legs were investigated by recording somatosensory evoked potentials (SEPs), after tibial nerve stimulation. The patient presented normal lumbar enlargement responses, but cortical responses were absent, suggesting dysfunction of somatosensory conduction along the spinal dorsal columns. Visual evoked potentials were normal. Patient's symptoms did not improve after high-dose intravenous steroid therapy (methylprednisolone, 1000 mg/day for 5 days). Serum copper and ceruloplasmin concentrations were determined and resulted low (0.52 ng/ml (normal values: 0.75–1.45 ng/ml) and 22.0 g/ml (normal values: 22.9–43.1 g/ml), respectively), while 24-hour urinary copper levels were undetectable. Serum zinc concentration was normal. Full blood count did not reveal anemia or cytopenias. Oral copper supplementation of 8 mg/day was started

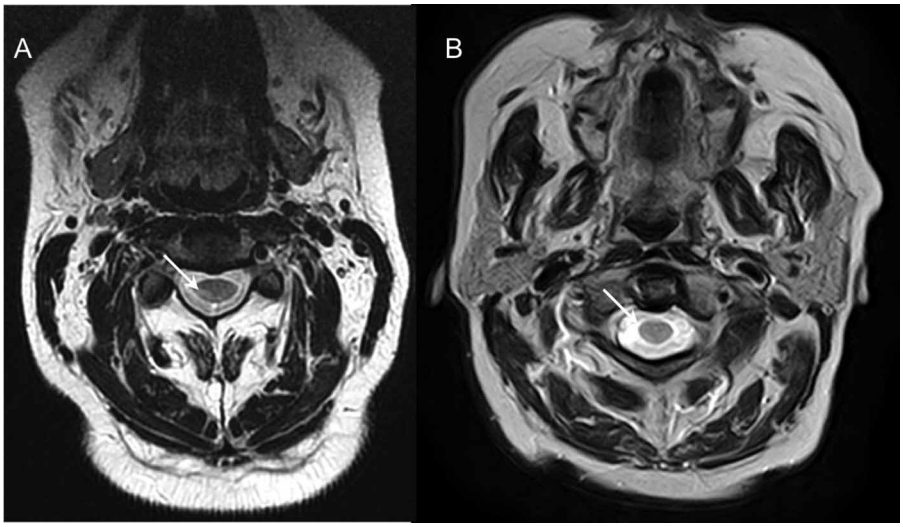

Figure 2 (A) Axial T2-weighted fast spin-echo (T2-FSE) spinal cord MRI showing the lesion involving the posterior columns (arrow) of the cervical spinal cord between C2 and C3. (B) Axial T2-weighted spinal cord MRI after 6 months of copper supplementation.

and resulted in progressive clinical improvement and normalization of serum copper levels after 8 months. Brain and spinal cord MRI performed after 8 months of therapy, in August 2012, showed a significant reduction of the hyperintensity involving the dorsal columns of the thoracic spinal cord (Fig. 1B), while SEP findings normalized (Fig. 1C). At the last visit in February 2014, the patient was completely asymptomatic.

Case 2

In June 2012, a 53-year-old Caucasian woman presented to our hospital with paresthesias at lower limbs and walking difficulties. Her previous clinical history was unremarkable. In particular, there was no history of spinal trauma, infection, or tumor. At neurological examination, she presented moderate gait ataxia, hypoesthesia with a C2 upper level, and a mild leg spasticity. Brain and spinal cord MRI showed a hyperintense lesion on T2-weighted images involving the dorsal columns of the cervical spinal cord between C2 and C3 (Fig. 2A). CSF analysis was unremarkable and oligoclonal bands were absent. Molecular and serological tests for common neurotropic viruses were negative. CSF and serum tested negative for onconeural and aquaporin-4 antibodies. Cobalamin, folate, and methylmalonate levels were normal. Serum copper concentration was 0.60 ng/ml, whereas ceruloplasmin concentration was near the lower reference limits (28.0 g/ml). Serum zinc was within the normal range. Also in this patient, 24-hour urinary copper levels were not detectable. Complete blood count revealed no abnormalities. Nerve conduction studies were completely normal, while SEPs recorded after tibial nerve stimulation showed normal spinal responses with absent cortical responses. Oral copper supplementation (8 mg/day) resulted in significant clinical and radiological (Fig. 2B) improvement after 6 months of therapy, in December 2012. At the last follow-up in December 2013, she had no residual ataxia and reported only occasional mild lower limb paresthesias.

Discussion

Copper is an essential trace element and represents a cofactor for many key enzymes such as cytochrome C oxidase, Cu/Zn superoxide dismutase, and dopamine β-hydroxylase. The absorption of copper in humans takes place in the stomach and proximal duodenum.[1] Copper deficiency is a well-recognized cause of several hematological manifestations, such as normocytic, macrocytic, and rarely microcytic anemia as well as leukopenia, which may have been attributed to myelodysplasia before the copper deficiency state is detected.[2] Given its ubiquitous distribution, dietary deficiency of copper is rare and is commonly secondary to bariatric surgery, malabsorption, and nephrotic syndromes. Moreover, copper deficiency may represent a complication of zinc, penicillamine, alkali therapy, and parenteral nutrition without copper supplementation.[1] However, in a significant percentage of patients the etiology of copper deficiency remains undetermined even after a careful history taking and extensive laboratory researches. Neurological manifestations of copper deficiency have been described only in the last years and can occur even in the absence of blood count abnormalities.[3] The incidence of CDM is higher in

women and during the fifth and sixth decades of life. Patients affected by CDM generally present with walking difficulties due to sensory ataxia and sometimes to mild leg spasticity. Bladder dysfunction is not common.[4] Sensory ataxia, due to dorsal column dysfunction, may be associated with paresthesias in upper and lower limbs. Unlike in our patients, copper deficiency may also associate with a sensory-motor polyneuropathy.[4] Spinal cord MRI may show hyperintense lesions in T2-weighted sequences involving the dorsal midline of cervical and thoracic cord.[5] MRI findings of CDM are not distinguishable from those of subacute combined degeneration associated with vitamin B12 deficiency and the reason for the preferential involvement of cervical and thoracic spinal dorsal columns is still unclear. As in our patients, T2 signal-intensity changes in the dorsal columns may reverse with time due to copper replacement therapy.[5]

Conclusion

The patients herein described underline the importance to include serum copper and ceruloplasmin levels as part of the myelopathy diagnostic workup, especially in the cases of otherwise unexplained subacute myelopathy involving the posterior columns. Since the CDM is a progressive syndrome, early diagnosis is mandatory because prompt supplementation therapy can prevent irreversible neurological damage.

Disclaimer statements

Contributors DP, GP, RR, DR and SS collected the data, analyzed the data, interpreted the data, wrote the article, and revised the article. RI, KAP and MNF interpreted the data, wrote the article, and revised the article.

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Conflicts of interest None.

Ethics approval Not applicable.

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