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Case report

Symptomatic copper deficiency in three Wilson's disease patients treated with zinc sulphate

Karolina Dzieżyc [a], Tomasz Litwin [a], Anna Sobańska [b], Anna Członkowska [a,c,*]

[a] Second Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland
[b] Department of Clinical Neurophysiology, Institute of Psychiatry and Neurology, Warsaw, Poland
[c] Department of Clinical and Experimental Pharmacology, Medical University of Warsaw, Warsaw, Poland

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ABSTRACT

Wilson's disease (WD) is caused by excess of copper that leads to accumulation of copper mainly in the liver, brain and needs life-long decoppering therapy. However, overtreatment with anti-copper agents may lead to copper deficiency which may cause neurological and hematological symptoms. Copper is an important cofactor for many enzymes. This report describes three WD patients with diagnosed copper deficiency during zinc sulphate (ZS) treatment. After 5–16 years of therapy all patients developed leucopenia. Spinal cord injury was manifested in two of the patients. One of them also presented myopathy. In conclusion, copper deficiency may occur in different time after treatment onset, therefore regular copper metabolism and hematological monitoring is necessary.

1. Introduction

Wilson's disease (WD) is an inherited copper metabolism disease that leads to accumulation of copper in the liver, brain, cornea, and other organs. The clinical course of WD may be highly variable and includes hepatic, neurological, and psychiatric symptoms [1,2]. WD is an autosomal recessive disorder caused by mutation of the *ATP7B* gene on chromosome 13 [3], which encodes a copper-transporting P-type ATPase [4]. The aim of WD treatment is to remove excess of copper and prevent its re-accumulation [5,6]. There are two different therapeutic approaches in WD. The first group of drugs (d-penicillamine, trientine) are chelating agents which act by promoting the urinary excretion of copper. The second group (zinc salts) interfere with intestinal uptake of copper [7,8].

Clinical symptoms of WD are caused by excess of copper. However, copper is needed because it acts as important cofactor for many important enzymes that have a role in functioning of the nervous system including cytochrome-c oxidase, copper-zinc superoxide dismutase, and dopamine β-hydroxylase [9].

Possible causes of copper deficiency include hereditary conditions such as Menkes Disease and acquired causes: malnutrition, parenteral or enteral feeding without copper supplementation, gastrectomy, proximal bowel resection, over-treatment by zinc salts or copper chelating agent [10].

* *Corresponding author at*: Institute of Psychiatry and Neurology, Second Department of Neurology, Sobieskiego 9, 02-957 Warsaw, Poland. Tel.: +48 22 4582537; fax: +48 22 8424023.
E-mail address: czlonkow@ipin.edu.pl (A. Członkowska).

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Copper deficiency may present both hematological (anemia, neutropenia, thrombocytopenia) and neurological (axonal neuropathy, myelopathy, posterior spinal column dysfunction, central nervous system demyelination, myopathy) signs. MRI findings include changes in dorsal columns of spinal cord radiologically similar to those caused by vitamin B12 deficiency and demyelination lesions in brain [10–17]. Electrophysiological studies may indicate axonal neuropathy, central conduction delay in somatosensory pathways, prolonged visual evoked potentials, myopathic changes [17,18].

Copper deficiency in WD may be caused by too excessive treatment with anti-copper agents. We report three patients with WD who were diagnosed with copper deficiency during zinc sulphate (ZS) treatment.

2. Case reports

2.1. *Patient 1*

A 37-year-old woman with WD diagnosed 16 years ago and since then treated with anti-copper agent. She complained of paraesthesias in the fingers and toes for 3 months and she felt weakness of the lower limbs during fast walking over the past 1 month. She was diagnosed in presymtomatic phase of the disease (without hepatic, neurologic signs, no Kayser–Fleischer rings). Diagnosis was confirmed by genetic studies. Her brother was a proband. Since diagnosis she was taking ZS in daily dose 180 mg of elementary zinc. She regularly visited our clinic and earlier she had never had neurological symptoms. Hematological tests were always normal. Copper metabolism did not indicate overtreatment. Additionally, laboratory test results had revealed leucopenia 1 month before symptoms started (Table 1).

On admission to our clinic her neurological examination was normal. Copper metabolism test results showed very low concentration of serum ceruloplasmin and serum copper. Copper urinary excretion was also low. Zinc serum concentration was very high (Table 1). Somatosensory evoked potentials (SEPs) showed impaired conduction in the dorsal column, especially in thoracic spine. Nerve conduction studies were within normal limits. Electromyography (EMG) was suggestive of myopathy. A few low-amplitude, short duration motor units were noted. There was no denervation and recruitment was normal. MRI of cervical spine, showed linear increased T2 signal lesion in the posterior column of the cervical cord from C2 to C7-Th1 (Fig. 1A and C). Brain MRI was normal.

Vitamin B12 level was in normal range. We recognized copper deficiency. Liver tests results were normal, so we decided to withdraw ZS to increase serum copper concentration. After one month white cell blood count was normal. Follow-up copper metabolism test results showed increase serum ceruloplasmin concentration (5 mg/dl) and serum copper concentration (20 μg/dl). She did not report lower limbs weakness and paraesthesias in the fingers and toes were less pronounced. MRI of cervical spine showed marked diminished dorsal columns compared to previous examination (Fig. 1B and D). On the second examination myopathic

Table 1 – Copper metabolism parameters and hematological parameters in three WD patients with copper deficiency.

Patient no	Serum ceruloplasmin (mg/dl) normal range 25–45	Total serum copper (μg/dl) normal range 70–140	Urinary copper excretion (μg/24 h) normal range 0–50	Serum zinc (μg/dl) normal range 50–120	WBC (K/μl) normal range 4.5–10.5	Neutrophils ($\times 10^9$/L), normal range 2.0–7.5	RBC (M/μl) normal range 4.10–5.10	HGB (g/dl) normal range 12–15.5	PLT (K/μl) normal range 140–440
Patient 1									
WD diagnosis (1996)	9.25	35	135	–	5.9	3.8	4.5	13.7	189
Overtreatment (2012)	**0.92**	**<5**	**11**	474	2.9	2.1	4.7	13.5	186
Follow-up after 6 months (2013)	5	20	12.5	–	6.0	4.1	4.5	12.9	197
Patient 2									
WD diagnosis (2008)	7.7	105	394	–	5.2	3.5	4.1	12.2	155
Overtreatment (2012)	**0.5**	**<5**	**6**	192	1.86	0.89	4.0	12.0	256
Follow-up after 12 months (2013)	1.18	5	10.5	–	3.3	2.0	4.2	12.5	274
Patient 3									
WD diagnosis (2007)	14	44	15	–	4.7	3.0	4.9	14.5	244
Overtreatment (2012)	**0.9**	**7**	**12**	247	2.3	0.17	3.2	10.0	190
Follow-up after 12 months (2013)	17	44	10	–	7.3	5.1	5.0	14.7	285

Values marked in bold indicate copper metabolism parameters at the time of overtreatment.