

Copper deficiency myelopathy secondary to parenteral zinc supplementation during chronic dialysis

Jamir Pitton Rissardo, Ana Letícia Fornari Caprara

Medicine department, Federal University of Santa Maria, Rio Grande do Sul, Brasil

Abstract

Copper deficiency myelopathy secondary to parenteral zinc supplementation during chronic hemodialysis has rarely reported in the literature. An elderly woman presenting with unsteady gait and paresthesia in lower limbs was admitted to our hospital. She has been having chronic renal insufficiency managed with hemodialysis and zinc-supplementation for the past ten years. The neurological examination showed that light touch, vibration, proprioception and the deep tendon reflexes were symmetrically reduced in both lower limbs. The spine-MRI revealed hyperintensity lesions on thoracic segments. The laboratory tests showed anemia, elevated zinc, and reduced copper and ceruloplasmin levels. Zinc-supplementation was discontinued and elemental copper was started. Two weeks later, the patient had a full recovery. In the follow-up six months later, all the laboratory tests were normal and investigations to search for immune suppression, vasculitis, and infection was negative.

Keywords: Copper, dialysis, myelopathy

INTRODUCTION

Acquired copper deficiency (ACD) has recently been recognized as an uncommon cause of myelopathy in humans.¹ In this context, one of the etiologies to the deficiency of this trace metal is zinc overload, which could occur due to excessive denture cream or supplement use.² To the authors' knowledge, there is only one case of copper deficiency myelopathy secondary to parenteral zinc supplementation during chronic hemodialysis reported in the literature.³ We report here an elderly woman on long term dialysis who developed gait disturbances probably due to copper deficiency from excessive zinc levels from zinc supplementation.

CASE REPORT

A 65-year-old female was admitted to our hospital due to progressive unsteady gait and paresthesia in lower limbs of three months onset. Her medical history included chronic renal insufficiency managed with hemodialysis three to five times per week for the past ten years. During each dialysis, 100-150mg of zinc was added to the hemodialysis solution for trace elements substitution. The neurological examination revealed the vibratory sensation, proprioception, and deep tendon reflexes were symmetrically reduced in both lower limbs with light touch decreased at below 6th-10th

thoracic level. The Romberg test was positive and the muscle strength scored 5 (Medical Research Council) in all muscle groups.

The cranial computed tomography scan and brain magnetic resonance imaging (MRI) were normal. The spine MRI showed hyperintensity lesions on 1st-2nd and 8th-9th thoracic segments. The laboratory tests were within normal limits, except for anemia, elevated zinc, and reduced copper and ceruloplasmin levels (Table 1). The cerebrospinal fluid examination was normal. The conduction study showed normal motor conduction at tibial nerve with 13.0mV of amplitude (normal >4.0mV) and 48.0m/s of conduction velocity (normal > 41m/s), but the sensory conduction at fibular nerve display 5mV of amplitude (normal >6.0mV) and 53.0m/s of conduction velocity (normal >40m/s).

Parenteral zinc supplementation during dialysis was discontinued and elemental copper was started at a dose of 2 mg/day intravenously for seven days followed by 8 mg/day per oral.

Two weeks later, the patient had a full recovery and the copper dose was progressively decreased every week until the 2 mg/day, which was maintained thereafter. In the follow-up six months later, all the laboratory tests were normal and an investigation to search for immune suppression, vasculitis, and infection was negative.

Address correspondence to: Mr. Jamir Pitton Rissardo, Medicine department, Federal University of Santa Maria, Rua Roraima, Santa Maria, Rio Grande do Sul, Brasil, Tel: +55 (55) 3220-8000, E-mail: jamirrissardo@gmail.com

Table 1: Laboratory analysis

Parameter (normal range)	Initial	2 weeks	6 months
Hemoglobin, blood (12-16 g/dL)	9	10.23	13.5
Erythrocyte count ($3.5-5.5 \times 10^{12}/L$)	2.7	3.0	4.0
Mean corpuscular hemoglobin (27-33 pg)	35	33	29
Mean corpuscular volume (78-98 fL)	111	98	90
Cobalamin (180-900 pg/mL)	970	1010	996
Methylmalonic acid (70-270 nm/L)	150	175	154
Homocysteine (4,44-13,56 umol/L)	7.67	8.32	6.8
Folate (3-17 ng/ml)	10	11.3	10.7
Zinc (70-120 ug/dL)	250	100	98
Copper (80-190 ug/dL)	35	78	140
Ceruloplasmin (21-53 mg/dL)	8	21	35
Erythrocyte sedimentation rate (0-20 mm/h)	1	6	4
C-reactive protein (<0.2 mg/L)	<0.2	<0.2	<0.2

DISCUSSION

The first report of association between ACD and myelopathy in humans was by Schleper & Stuerenburg in 2001.¹ They presented an adult woman who developed myelitis over more than one year in association with copper deficiency. Schleper & Stuerenburg mentioned that this association have already been well established in different animal species and was also known as swayback or enzootic ataxia. After this report, other cases were being published reaching more than one hundred in PubMed.

In the review by Jaiser and Winston, the most common cause of ACD was previous upper gastrointestinal surgery (47%) followed by idiopathic (20%), zinc overload (16%), malabsorption (15%), and iron supplements (2%).² Also, dietary copper deficiency has already been described in premature infants fed on milk formulas without copper and in prolonged total parenteral nutrition.⁴ However, the last two mentioned are rare causes because of the ubiquitous distribution in food and low daily requirement (approximately 1 mg/d) of copper. Thus, in a patient presenting with ACD, the surgical history should be looked for. If this is negative, a quantitative analysis of the zinc intake should be performed.²

The ACD causing myelopathy secondary to parenteral zinc supplementation during dialysis has rarely reported in the literature. We performed a literature search in English-language publication with Embase, Google Scholar, Lilacs, Medline, Scielo, and ScienceDirect, on a set of terms that

included copper, myelopathy, and dialysis. We identified one case and compared the reported case with our patient (Table 2).³

In both cases (Table 2), the subjects received zinc at the recommended dose to avoid hypozincemia. However, our patient recovered over a short time with few sequelae. One possible explanation could be that the amount of zinc administered in our patient was lower than that reported by Yaldizli *et al.*³

Barlow reported the histologic changes in the lesions of swayback during the first nine months of post-natal life in lambs. He showed that the deficiency of copper, either acquired or secondary, could lead to a Wallerian degeneration characterized by axonal swelling, demyelination, and microcavitation of the neuropil in the brainstem, cerebellar cortex, hippocampus, and mainly spinal cord.⁵ In this context, to date, the pathophysiology of copper's role in metabolic myelopathy have been based on veterinary reports. Little is known in humans.

The mechanism to explain the zinc supplementation leading to serum copper decrease is based on the upregulation of metallothionein (MTT). In a balanced copper and zinc intake, copper's entry to the enterocyte by two types of copper channels, the divalent metal transporter 1 and copper transport protein 1.² When inside the cell, copper could be bonded by MTT or be free. The copper-bonded remains in the enterocyte and is eventually lost in the feces with the epithelial desquamation. However, copper-free can be transported from the enterocyte to the circulation

Table 2: Case reports of patients with copper deficiency myelopathy secondary to zinc supplementation during dialysis

References	Yaldizli <i>et al.</i> ³	Present case
Age(y)/Sex	61/F	65/F
Presenting symptoms	Gait ataxia, lower limb weakness and numbness of her feet over 6m	Unsteady gait and paresthesia in lower limbs over 3m
Time of chronic renal insufficiency	6y	10y
Supplemental Zn on hemodialysis solution	140 mg	100-140 mg
Hematological disorder	Megaloblastic anemia	Megaloblastic anemia
Copper (NR)	50 (65–165 µg/dl)	35 (80-190 µg/dL)
Ceruloplasmin (NR)	0.13 (0.2–0.6 g/dl)	8 (21-53 mg/dL)
Zinc (NR)	35 (13–18 µmol/l)	250 (70-120 µg/dL)
Neuroimaging	Spinal lesions locations	3 rd – 6 th cervical, mainly dorsal column
	T2-W	Hyperintense
	Gadolinium-enhancement	No
Management	1) Zn discontinued 2) 600mg Cu gluconate PO	1) Zn discontinued 2) 2mg elemental Cu IV for 7d followed by 8mg for two weeks, and taper week dose until the 2mg/day, this dose was maintained thereafter
Follow-up	Clinical symptoms began to improve within 2wks. After 7m, able to walk a distance of 10 meters without help.	Full recovery within 2wks.

Cu, copper; F, female; IV, intravenously; m, month; mg, milligram; NR, normal range; PO, per oral; wks, weeks; y, year; Zn, zinc.

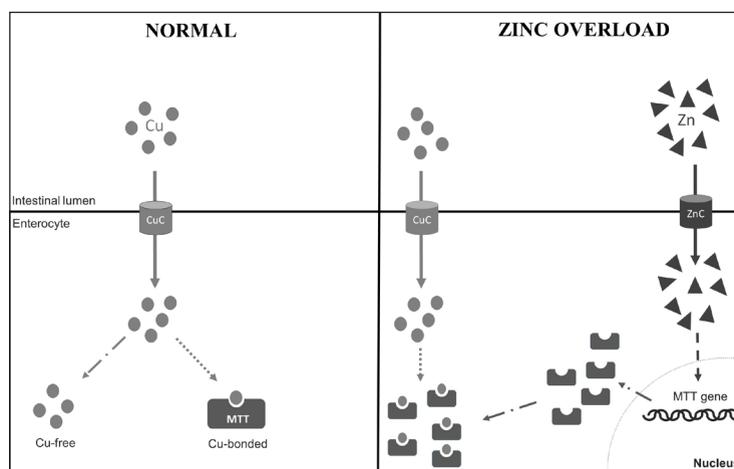


Figure 1. Relation between zinc and copper in the enterocyte. In copper-zinc normal intake and in zinc overload intake. Abbreviations: copper (Cu); copper channel (CuC); metallothionein (MTT); metallothionein gene (MTT gene); zinc (Zn); zinc channel (ZnC).

by ATPase 7A and consequently is not being lost.⁶ In the zinc overload state, the excessive zinc increase the synthesis of MTT as shown in rat models.⁷ The MTT binds with more affinity to copper than zinc. Therefore, a larger portion of copper is excreted, thus there is a decrease in blood levels of copper (Figure 1).^{2,8}

In the study by Bustamante *et al*, the serum copper and ceruloplasmin in sixty-eight patients with chronic renal insufficiency were investigated. It was found that uremic status did not increase the serum copper or serum ceruloplasmin. Nevertheless, in the hemodialysis group, there was a progressive increase in serum levels of copper and ceruloplasmin. It was assumed that these rise were due to a probable release of copper from the dialysis membrane content.⁹ Thus Bustamante *et al.*'s study may explain why there have been so few clinical cases of copper deficiency in chronic dialysis patients reported in the literature, even in those individuals who take zinc supplements.¹⁰

patients: A systematic review and meta-analysis of 15 randomized controlled trials. *BioMed Research International* 2017;2017.

DISCLOSURE

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