CASE REPORT

Development of liver failure after 20 years of zinc sulfate administration in a patient with neurological phenotype of Wilson's disease

Marek Hartleb[1], Sylwia Sikora-Gruca[1], Marek Stobiński[1], Katarzyna Roj[1], Jerzy Kwapuliński[2]

[1] Department of Gastroenterology, Silesian Medical School, Katowice, Poland

[2] Department of Toxicology, Silesian Medical School, Sosnowiec, Poland

Hartleb M, Sikora-Gruca S, Stobiński M, Roj K, Kwapuliński J. Development of liver failure after 20 years of zinc sulfate administration in a patient with neurological phenotype of Wilson's disease. Folia Gastroenterol Hepatol 2006; 4 (4): 168 – 170.

Abstract. *In Wilson's disease, zinc may be considered as initial therapy for asymptomatic patients or for those not tolerant to penicillamine or trientine. A major advantage of treatment with zinc salts is lack of serious side effects, however, the long-term efficacy of this therapy in relation to phenotype and stage of Wilson's disease is not well characterized. We present a patient with neurological phenotype of Wilson's disease who after 20 years of uninterrupted use of zinc sulfate, developed fatal hepatic failure.*

Key words: *Wilson's disease, liver failure, zinc salts*

The clinical image of Wilson's disease is variable and can generally be divided into neurological, hepatic and mixed phenotypes. Irrespective of the phenotype, the untreated disease always has a progressive course and most commonly ends in hepatic failure or neurological disaster. By contrast, well-monitored pharmacological treatment inhibits progression of this disease (2).

Wilson's disease requires lifelong treatment. In all therapies the goal is to remove accumulated copper and to prevent its reaccumulation. Several drugs may be implemented in patients with Wilson's disease. The most widely used drug is penicillamine (Cuprenil) that is a copper chelator with well-known efficacy and potential side effects. Trientine and tetrathiomolybdate, drugs still not accessible in our country, are other chelating drugs that are under investigation for initial treatment of Wilson's disease with hepatic and/or neurological manifestation. Zinc salts block the intestinal absorption of dietary copper by stimulating the synthesis of metallothioneins. Zinc may be considered as an initial treatment for asymptomatic patients or for those intolerant of penicillamine or trientine (1,6). In addition, due to low toxicity, therapy with this drug may be a beneficial option in pregnant women with Wilson's disease. Recent treatment guidelines, endorsed by neurological societies, advise against the use of chelating agents, because these drugs may aggravate copper intoxication and cause neurological deterioration in the initial stage of treatment (5).

A major advantage of zinc therapy is lack of serious side effects, however, the long-term efficacy of zinc salts in relation to phenotype and stage of Wilson's disease is not well characterized. The main concern is that zinc, being not able to clear away the accumulated copper, cannot also prevent an increase of free copper in the blood in the case of its accelerated release from tissue stores, which may occur at any

moment during a patient's life. We report on a patient with neurological phenotype of Wilson's disease who after 20 years of uninterrupted use of zinc sulfate developed hepatic failure.

Case report

A 37-year-old man was admitted to our department because of impending liver failure. At the age of 17 years he was consulted by his school psychologist for asocial behaviour and diminished ability to concentrate. As soon as neurological symptoms appeared such as dysarthria, salivation and intention tremor, the patient was screened for Wilson's disease. The ceruloplasmin serum level was 2.3 mg/dL (normal is 20-60 mg/dL) and the total copper serum level was 44.4 µg/dL (normal 80-130 µg/dL). Hepatic laboratory results and abdominal ultrasound were normal at that time. A standard dose of penicillamine was introduced, but it was quickly stopped because of development of extensive mucocutaneous exanthema, interpreted as an allergic reaction to the drug. The patient was switched to zinc sulfate (Zincteral®) 800 mg daily (180 mg of zinc), which was followed by gradual withdrawal of the neurological symptoms. The drug was well tolerated and the patient showed good adherence to therapy. He was told not to take the drug at the time of meals and to avoid foods rich in copper. Over the following 20 years he was regularly seen by neurologists who found his clinical neurological state to be satisfactory. The patient did not present clinical symptoms attributable to chronic liver disease such like fatigue or ascites. His routine hepatic tests were also within normal ranges. He was not consulted by a hepatologist and to our knowledge the effectiveness of therapy was not monitored by serum level of non-ceruloplasmin bound copper or urinary copper output.

In November 2005, i.e. 2 months prior to hospitalization the patient developed lower limb swelling, ascites and icterus. On admission the results of laboratory studies were as follows: total bilirubin 6.94 mg/dL (119 µmol/L), unbound bilirubin 3.2 mg/dL (55 µmol/L), ALT 107 U/L (1.78 µkat/L), AST 190 U/L (3.17 µkat/L), alkaline phosphatase 156 U/L (2.60 µkat/L), γ-glutamyltransferase 431 U/L (7.18 µkat/L), total protein 6.14 g/dL, albumin 2.2 g/dL, sodium 129 mmol/L, creatinine 1.25 mg/dL (110.5 µmol/L), INR 2.22 (prothrombin index 30%). The alpha-fetoprotein serum level was 15.5 ng/mL (normal <8 ng/mL). Ceruloplasmin and total copper serum levels were 13.5 mg/dL and 91 µg/dL, respectively. The urinary copper excretion was 2592 µg/day (normal is <80 µg) and calculated free copper level was 50.5 µg/dL. On ultrasound there was enlargement of both the liver and spleen with longitudinal spans of these organs 18 cm and 20 cm respectively. On slit lamp examination the Kayser-Fleischer ring was found. The patient was qualified for liver transplantation. Liver biopsy on the transjugular route was performed. Histopathology showed extensive fibrosis (stage IV) with foci of necrotic hepatocytes and moderate inflammatory infiltrate composed of lymphocytes and neutrophilic granulocytes. Staining for copper was positive. The hepatic concentration of copper measured by atomic absorption spectrometry was 360 µg/g of dry liver (normal < 50 µg/g). The symptoms of liver deficiency continuously deteriorated and after 15 days of hospitalization, while being prepared for liver transplantation, the patient developed hepatic encephalopathy associated with marked fibrinolysis, which caused the patient's death after a further 4 days of intensive symptomatic treatment.

Discussion

It is widely accepted that patients with symptomatic Wilson's disease should be offered chelation therapy with penicillamine or trientine, which remove copper from potentially toxic sites (3,4). Unfortunately, penicillamine has been incriminated in a variety of side effects that lead to discontinuation of the drug in 10 % to 15 % of patients. Zinc salts may be administered as a maintenance therapy after adequate decoppering has been achieved, however, in certain clinical circumstances early switching from chelating agents to zinc salts may be justified (1). Moreover, the interest in use of zinc salts has increased since it had been proposed that the therapeutic priority in Wilson's disease should be rather to normalize the free copper concentration in blood than mobilizing of accumulated copper from tissues, where it is bound to ceruloplasmin or metallothioneins.

In this report the patient was allergic to penicillamine and zinc preparation was used as a first-line treatment. Despite good adherence to this therapy and withdrawal of neurological symptoms the patient developed hepatic failure after 20 years of uneventful clinical course. There was strong evidence that copper homeostasis has not been obtained as both the free copper in serum and hepatic copper concentra-

tion were significantly elevated. Moreover, there was histopathological evidence of liver cirrhosis.

Clinical evaluation of response to treatment is based on withdrawal of hepatic or neurological clinical signs of disease and periodical monitoring for reduction of the level of non-ceruloplasmin-bound copper in the serum (free serum copper) and/or urinary copper output. The ultimate goal is to reduce serum free copper to less than 10 μg/dL, while levels above 25 μg/dL indicate inadequate treatment or failure of compliance (2). On zinc therapy, urinary copper excretion usually falls to less than 150 μg/day. Unfortunately, the reported patient was not consulted by a hepatologist and the effectiveness of the therapy was evaluated only on neurological basis, ignoring the evidence that pure neurological phenotypes of Wilson's disease do not exist and the course of hepatic damage in Wilson's disease may be surreptitious.

Conclusions

1. Monitoring of therapeutic effectiveness by serum free copper levels is mandatory even in symptom-free patients.
2. Liver injury in Wilson's disease may be clinically covert, therefore patients with primary neurological manifestation of this disease should remain under the care of a team of specialists. Liver biopsy should be performed even in the absence of abnormal hepatic tests.
3. Allergic reactions to penicillamine should not be regarded as absolute contraindication to this drug (if trientine is not accessible). In such cases a desensitizing therapy with increasing doses of penicillamine or use of corticosteroid protection should be considered.
4. Therapy with zinc salts may be ineffective as initial treatment of Wilson's disease.

REFERENCES

1. Brewer GJ. Zinc acetate for the treatment of Wilson's disease. Expert Opin Pharmacother 2001; 2: 1473-1477.
2. Brewer GJ, Askari FK. Wilson's disease: clinical management and therapy. J Hepatol 2005; 42 Supl: S13-21.
3. Brewer GJ. Novel therapeutic approaches to the treatment of Wilson's disease. Expert Opin Pharmacother 2006; 7: 317-324.
4. Ferenci P. Review article: diagnosis and current therapy of Wilson's disease. Aliment Pharmacol Ther 2004; 19: 157-165.
5. Hoogenraad TU. Paradigm shift in treatment of Wilson's disease: zinc therapy now treatment of choice. Brain Dev 2006; 28: 141-146.
6. Lee VD, Northup PG, Berg CL. Resolution of decompensated cirrhosis from Wilson's disease with zinc monotherapy: a potential therapeutic option? Clin Gastroenterol Hepatol 2006; 4: 1069-1071.

Correspondence to:
Prof. dr hab. Marek Hartleb, Klinika Gastroenterologii, CSK,
ul. Medyków 14, 40-752 Katowice, Poland
E-mail: lakmus@poczta.wprost.pl