Excess Copper Chelating Therapy for Wilson Disease Induces Anemia and Liver Dysfunction

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Abstract

A 37-year-old man was diagnosed with Wilson disease at the age of 14. His first manifestations were neurological. He was treated with trientine for more than 10 years and suffered from anemia and liver dysfunction. Wilson disease is a genetic disorder characterized by accumulation of copper in the body. Excess copper is toxic, but copper is an essential trace element. Copper-binding ceruloplasmin is important for iron metabolism. Excess copper chelating treatment-induced anemia and iron deposition in the liver was suspected. Proper monitoring of copper status is important for the management of Wilson disease.

Key words: ceruloplasmin, chelating therapy, hemochromatosis, Wilson disease

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Introduction

Wilson disease is an autosomal recessive disorder characterized by the progressive accumulation of copper in the body. The failure of the hepatocytes to excrete copper into bile and the decreased copper incorporation into ceruloplasmin causes copper to accumulate in the body (1-3). The disease affects about one in 30,000 individuals and was first described by Samuel A.K. Wilson in 1912 (1, 2, 4). Wilson disease gene was identified and designated \( \text{ATP7B} \) (5-7). The gene product is expressed mainly in hepatocytes and functions in biliary copper excretion via the late endosome and the lysosome (8, 9). Failure of this system results in copper accumulation in the body. Previously no effective treatment for this progressively fatal disorder was available, however, the clinical outcome of patients with Wilson disease has improved owing to the introduction of various drugs that reduce the copper in the body (10). Therefore, Wilson disease is now one of the rare inherited disorders for which effective pharmacologic treatment is available (1, 2).

Case Report

A 37-year-old man visited our hospital due to prolonged anemia and liver function abnormality during the treatment with trientine for Wilson disease. He was diagnosed with Wilson disease at a local hospital when he was 14 years old. His first manifestations were drooling, dysarthria, gait disturbance and rigid dystonia. He had been hospitalized for 2 years after the initial diagnosis and had been treated with trientine. His neurological symptoms gradually improved. However, he eventually began to suffer from anemia and his liver function tests had been abnormal. He had received 2,500 mg/day of trientine for more than 10 years. On examination, he had mild dysarthria and rigid dystonia. Physical examinations demonstrated a temperature of 36.4°C, heart rate of 72 beats/min and blood pressure of 120/80...
mmHg. The abdomen was soft, not tender, and without organomegaly. Edema was not recognized. Laboratory findings are shown in Table 1. Serum antinuclear antibody, granomegaly. Edema was not recognized. Laboratory findings are shown in Table 1. Serum antinuclear antibody, anemia rapidly improved. Thereafter, serum concentrations of aminotransferases and ferritin gradually decreased. Now we prescribe low dose zinc acetate for the disease. The clinical course is shown in Fig. 2.

**Discussion**

We describe a case with Wilson disease in whom excess copper chelating therapy induced anemia and iron deposition in the liver. Copper is an essential trace element in all organisms and mediates various cellular processes, including mitochondrial energy generation (cytochrome c oxidase), neurotransmitter biosynthesis (dopamine β-hydroxylase), melanin production (tyrosinase), cross-linking of collagen (lysyl oxidase), oxygen-radical scavenging (superoxide dismutase) and iron metabolism (ceruloplasmin) (11, 17). Copper is very important for the body, because Menkes disease, a copper deficiency disease, is a lethal multysystemic disorder caused by the mutation of ATP7A (11). Although, the redox property of copper is essential for various cellular functions, excess copper deposition is harmful for the cells. Wilson described a familial copper storage disorder as progressive lenticular degeneration in 1912 (4). After the first description of Wilson disease, no effective treatment was available for this fatal disease for half a century. But now several therapies for this disease have been developed. Pharmacological treatments of Wilson disease are copper chelating agents to promote copper excretion from the body and zinc to reduce copper absorption. They are sometimes used simultaneously (1).

The recommended initial treatment for symptomatic patients is copper chelating therapy using penicillamine or trientine (1). The first manifestations in the present patient were neurological. Trientine seems favorable for patients with neurological manifestation (1). Usually after the stabilization with initial chelating treatment, the choice for maintenance therapy is the reduction of the dose of chelating agent or zinc monotherapy. The typical doses of initial treatment with trientine are 750 to 1,500 mg/day and the maintenance doses are 750 or 1,000 mg/day (1). However, the present patient had received 2,500 mg/day of trientine for about 10 years. Serum ceruloplasmin is low in about 90% of patients.
with Wilson disease, because copper incorporation to ceruloplasmin is impaired in Wilson disease (2, 3, 18). Non-copper binding ceruloplasmin, apo-ceruloplasmin, is unstable and the half-life is very short (19). While hepatocytes synthesize the secreted form of ceruloplasmin (3, 18), other cells synthesize glycosylphosphatidylinositol (GPI)-linked ceruloplasmin anchored to the plasma membrane (13, 20). Ferroportin is the only known mammalian protein that exports iron from the cells and ceruloplasmin stabilizes ferroportin in the plasma membrane of various cells (20). In the absence of ceruloplasmin, ferroportin is rapidly internalized and degraded in the lysosomes (20, 21). Therefore, iron is accumulated in various organs in patients with aceruloplasminemia (16). In some patients with Wilson disease especially male patients, iron is accumulated in the liver before treatment (22, 23). Chelating agents further decrease the serum concentrations of copper and ceruloplasmin. Therefore, the iron content in the liver is increased following chelating treatment in some patients with Wilson disease (22). It is important to monitor the copper status of such patients and also examine compliance with the treatment. Usually we examine concentrations of ceruloplasmin and copper, and urinary copper excretion. In the present patient these concentrations were very low and the daily urinary copper excretion was near the normal range. Therefore, the copper must have been sufficiently removed from the body of the present patient.

A mutant ceruloplasmin G969S, detected in a patient with hemochromatosis, cannot bind copper. In patients with ceruloplasmin G969S mutant, failure of iron efflux caused by dysfunction of ferroxidase activity of the mutant ceruloplasmin, induces iron deposition in the liver, pancreas, brain and retina (19). Therefore, copper binding to ceruloplasmin is essential for proper iron metabolism.

Inflammation affects iron metabolism via induction of hepcidin, which is also important for iron metabolism, from hepatocytes (24, 25). However, serum CRP concentration and erythrocyte sedimentation rate of this patient were normal and there was no symptom indicating the complication of any inflammation. Therefore, we believe that copper depletion by long-term treatment with high-dose of trientine and the consequent decrease of copper-binding holoceruloplasmin induced anemia, iron deposition and liver function abnormality in the patient. Indeed anemia has been reported in patients with Wilson disease treated with trientine (22, 26, 27).

Copper chelating therapy using penicillamine or trientine is very useful to excrete copper, but it also inhibits the bioactivity of copper, and induces anemia and iron accumulation in some patients with Wilson disease. Therefore it is important to carefully monitor the status of copper and iron in patients being treated for Wilson disease.

The authors state that they have no Conflict of Interest (COI).

References

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