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Treatment of a Presymptomatic 14-year-old Girl with Wilson's Disease

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ABSTRACT

A 14-year-old girl with presymptomatic Wilson's disease was treated with D-penicillamine during seven years. A prompt effect with an increased urinary copper excretion was seen. The liver function tests were normalized. The girl is still asymptomatic seven years after the initiation of D-penicillamine treatment.

INTRODUCTION

Wilson's disease (hepatolenticular degeneration) is an autosomal recessively inherited disorder characterized by cirrhosis of the liver associated with degeneration of the corpus striatum. The disease usually appears towards the end of the second decade, but occasional cases have been seen in the first decade and onset in the third and forth decade is not unusual. The main symptoms are neurological and psychiatric and caused by liver-insuffiency. (7) In children with early onset of the disorder, liver-insufficiency is the first symptom. The basic cause of the disorder is unknown, but the biochemical errors are very characteristic. There is a low concentration of ceruloplasmin in serum (less than 10 μmol per liter). Ninty-five per cent of the serum copper is bound to this α_1-globulin. The serum copper concentration is usually low and the urinary excretion of copper is high (more than 1.6 μmol per 24 hours), and there is a high concentration of copper in liver (more than 250 μg per g dry weight) as well as in kidneys and brain. An increased urinary amino acid excretion is usually seen. At liver biopsy a multilovular cirrhotic liver is usually seen. Another typical observation is the Kayser- Fleischer ring in the outer zone of cornea. In fulminant cases neurological symptoms are also seen as spastic dystonia, but bulbar symptoms may also appear. Psychiatric symptoms may appear from time to time. Variations in consciousness is seen, as well as changes in personality. There is usually a progressive demensis. In the brain major anatomical changes are mainly seen in the corpus striatum.

This part of the brain may be excavated, and collapsed and sometimes also brownish disexcavated, and collapsed and sometimes also brownish discolored. Changes in thalamus, nuclei in the medulla oblongata cortex cerebri and in cerebellum may also be seen. Wilson's disease when not treated, is invariably fatal. Treatment is available and effective when started before the terminal stages of the disease.

The aim of the treatment is to prevent the accumulation of copper by restricting dietary copper and to remove the excessive amounts already deposited in the tissues by the administration of copperbinding agents which promote rapid excretion.

BAL (2,3 dimercaptopropanol) was first used by Cumings in 1947 in the treatment of the disease. (1) This drug was replaced by a more non-toxic drug, penicillamine, in 1956. (8) Recently trials have been made to replace penicillamine treatment in Wilson's disease with oral zinc therapy. Preliminary results with oral zinc sulphate in a patient with Wilson's disease suggest that this therapy may not only prevent further accumulation of copper in the tissues but also contribute to the gradual removal of copper already deposited. (3)

In 1969 Falkmer et al. (2) showed that a complete remission of liver-cirrhosis could be achieved in a 11 year-old girl with Wilson's disease after the administration of D-penicillamine, Sternlieb and Scheinberg in 1968 (8) Werlin et al. 1978 (10) found that clinical manifestations of the disease can be prevented by treatment during the presymptomatic phase.

In the present study a 14 year-old girl remains asymptomatic after 7 years treatment with penicillamine. To our knowledge this is the first Scandinavian case of Wilson's disease treated prior to symptoms.

CASE REPORT

M H, a girl, 14 years of age. An elderly sister was diagnosed as a case of Wilson's disease and died at 10 years of age due to liver cirrhosis and liver insufficiency. A remote relative of her father also was a diagnosed case of Wilson's disease.

The pregnancy delivery and neonatal period and the first year of life was uneventful. Birth weight 3 400 g. Since Wilson's disease was diagnosed in her sister, chemical analyses were started when she was 7 years of age to find out whether she was a presymptomatic case of Wilson's disease.

The physical examination at 7 years of age revealed no signs of Wilson's disease, such as the Kayser-Fleischer corneal ring, hepatomegaly or neurological symptoms.

Laboratory examinations

An increased urinary excretion of copper, 4,3 µmol per 24 hours (normal value less than 0.25 µmol/24) and a low serum ceruloplasmin level, 1.5 mg/100 ml was seen. The serum copper was however normal, 15 µmol/liter (normal value 11-22).

Routine haematological examinations as well as analyses for bleeding- and coagulation time were normal. Analyses for serum preotein were normal as well. Liver function tests were slightly increased: GOT 67 U/L (normal value: 5-17 U/L), GPT 107 U/L (normal value: 2-17 U/L), LDH 282 U/L (normal value: 50-150 U/L).

A normal urinary excretion of aminoacids was seen when analysed by high-voltage paper electrophoresis.

Incorporation of 64 Cu into ceruloplasmin as described by Falkmer et al (2) was performed in the girl and her father and mother. According to Fig 1, an abnormal incorporation of the isotope was seen in the girl, supporting the diagnosis Wilson's disease. Heterozygote curves were seen in her parents.

To confirm the diagnosis, laparotymy was performed. The edge of the liver was seen 4 cm (1 1/4 inch) below the arcus. The gross anatomy of the liver was normal.

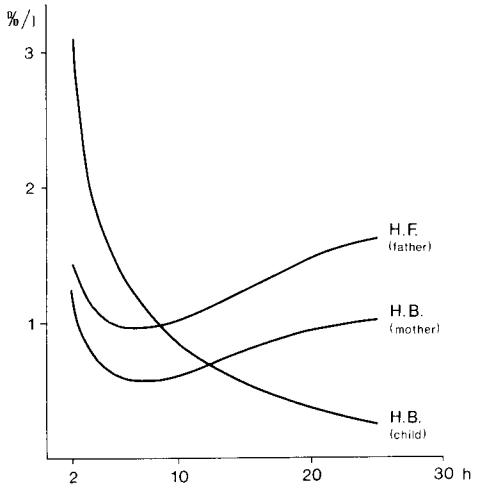

Fig 1. Concentration of ^{64}Cu in the plasma after intravenous injection of 0.3 µC ^{64}Cu, of the patient H B, her father (H F) and her mother H B.

The histo-pathological examination showed slight fatty infiltration but no signs of cirrhosis. Histochemical analysis of copper by the rubean acid method

was negative. Analysis for hepatic copper concentration was not performed. To summarize, there was no histochemical support for the diagnosis Wilson's disease.

The diagnosis presymptomatic Wilson's disease was based on

1) increased urinary copper excretion
2) low serum ceruloplasmin concentration
3) abnormal results on liver-function tests
4) results of a ^{64}Cu incorporation test characteristic of Wilson's disease

To avoid progress of the symptoms, treatment with D-penicillamine was introduced one year after the diagnosis presymptomatic Wilson's disease.

RESULTS

A daily administration of 250 mg of D-penicillamine resulted in an increase of urinary copper to a mean of 4.5-5.8 umol/24h. Three years later the daily dose of penicillamine was increased to 250 mg two times a day, and an increase in urinary copper to mean 6.0 µmol/24 h was seen. (Fig 2) The liver function tests were normalized in a few months.

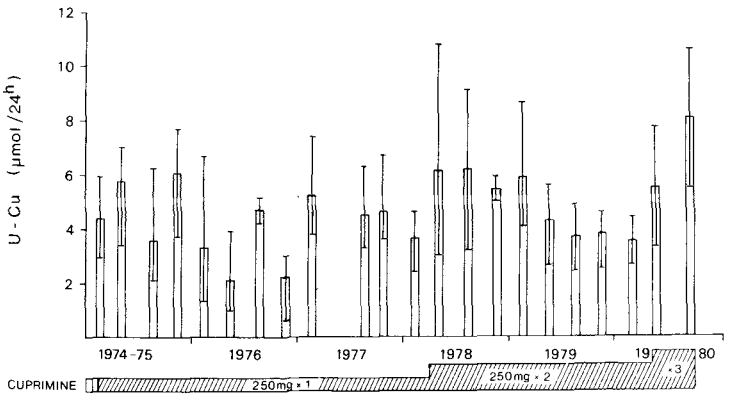

Fig 2. 24-hour-urinary copper excretion of the girl on 3-4 sampling-occasions a year during the period 1974 - 1980.

After 7 years of treatment the daily dose of penicillamine was increased to 750 mg, with a further increase of the urinary copper excretion. In Fig 2 the urinary copper excretion determined 3-4 times a year during seven years is visulized.

At 14 years of age (4 years more than the age when her sister died in liver-insufficiency due to Wilson's disease) she had no clinical symptoms of Wilson's disease, and her liver function tests were quite normal.

DISCUSSION

There is of great importance to make an early diagnosis of Wilson's disease in order to introduce treatment with D-penicillamine. This diagnosis should be made already in presymptomatic patients (4, 10). Sternlieb and Scheinberg in 1968 (8) treated forty-two presymptomatic patients with Wilson during a period of observation of 142 patient years. Presymptomatic treatment has also been described by Powell and Tolman (6).

All these patients treated remained asymptomatic during the observation period.

An early diagnosis was possible in our case because of the fatal death of her sister in Wilson's disease. Penicillamine was administrated at 7 years of age. It is hard to tell if there has been any beneficial effect of the treatment, but still seven years after the initiation of the therapy she is asymptomatic.

In the present case no side-effect due to the penicillamine treatment was seen, such as skin rash, proteinuria or signs of bone marrow depression.

Since Wilson's disease is an autosomal recessively inherited disorder, the risk is 25 % in sibs of Wilson patients to be affected. Consequently efforts should be made to make early diagnosis in these individuals at risk and treatment introduced.

Wilson's disease should be suspected in all cases of liver cirrhosis or liver insufficiency in infancy and childhood (2, 5).

Our patient represents the first reported Scandinavian presymptomatic case of Wilson's disease in which prophylactic treatment with penicillamin has been performed. Besides the reports from USA by Sternlieb and Scheinberg (8) and Werlin et al (10), there are not many published instances of treatment of pre-symptomatic Wilson's disease from other parts of the world.

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