Reprinted from Enzyme Therapy in Genetic Diseases. Birth Defects Original Article Series
March 1973, Vol. IX, No. 2. Copyright © The National Foundation
Printed in the United States of America

278

Hepatic Transplantation in Wilson Disease*

CARL G. GROTH, M.D.; REUBEN S. DUBOIS, M.D.; JACQUES CORMAN, M.D.; CHARLES HALGRIMSON, M.D.; DENIS O. RODGERSON, Ph.D. AND THOMAS E. STARZL, M.D., Ph.D.

Two teen-age males with Wilson disease underwent orthotopic liver transplantation 32 and 12 months ago. One of the patients had normal serum ceruloplasmin and copper before as well as after operation. In the other case, these measures rose from low to normal values after transplantation. Both boys had increased cupriuresis after the operation. Biopsy specimens of the graft in one of the patients have shown no accumulation of copper.

Wilson disease is an inborn error of metabolism characterized by an elevated copper content in the liver, brain and other organs, a low level of the copper-binding plasma protein ceruloplasmin, low total serum copper and elevated urinary copper excretion. Pigmentation of the cornea with copper is visible on slit-lamp examination as the so-called Kayser-Fleischer ring. Any or all of these diagnostic criteria except the first mentioned may, however, be absent and the primary genetic abnormality in Wilson disease remains obscure.[1] Earlier, clinical emphasis was usually on neurologic symptoms but in more recent years it has become apparent that almost all patients suffering from this disease have cirrhosis of the liver.

Two teen-age boys with advanced Wilson disease have been treated with orthotopic hepatic transplantation at our institution. One of them was in terminal hepatic failure[2] while in the other the indication for the procedure was cirrhosis of the liver and severe neurologic involvement not controlled by conventional chelating therapy.

* Aided by research grants from the Veterans Administration, by Grants RR-00051 and RR-00069 from the general clinical research centers program of the Division of Research Resources, National Institutes of Health and by USPHS Grants A1-10176-01, A1-AM-08898, AM-07772, GM-01686 and HE-09110.

Groth—Associate Professor of Surgery, University of Colorado School of Medicine, Denver.
Dubois—Assistant Professor of Pediatrics, University of Colorado School of Medicine.
Corman—Assistant Professor of Surgery, University of Colorado School of Medicine.
Halgrimson—Assistant Professor of Surgery, University of Colorado School of Medicine.
Rodgerson—Assistant Professor of Pediatrics, University of Colorado School of Medicine.
Starzl—Professor and Chairman of Surgery, University of Colorado School of Medicine.

CASE REPORTS

Case 1. Clinical Course. An 11-yr-old boy was admitted in July 1969, in hepatic precoma. The diagnosis of a liver disorder had been established at the age of 8 when an open liver biopsy showed "postnecrotic" cirrhosis. At that time serum copper and urinary copper excretion were normal. In April 1969, he was admitted to another hospital with symptoms of advanced liver disease and a biopsy again showed cirrhosis with the additional finding of Mallory bodies. This biopsy was interpreted as being consistent with Wilson disease. There were no Kayser-Fleischer rings and serum ceruloplasmin was within normal limits. When the patient was transferred to our institution 2 mo later, he had massive ascites. The serum bilirubin was 20.6 mg per 100 ml, the serum albumin 1.5 gm per 100 ml, the prothrombin time 13% of normal and blood ammonia 432 μg nitrogen per 100 ml. Serum ceruloplasmin values were 26–31 μg per 100 μl using an enzymatic assay (normal 22–43 μg per 100 μl). Shortly after arrival the patient developed upper gastrointestinal hemorrhage and became agonal. At this time the patient's liver was removed and replaced with an orthotopic hepatic homograft from a cadaveric donor.[3]

Posttransplantation there was an immediate clearing of the sensorium, a fall in the serum bilirubin and blood ammonia levels, an increase in the total serum protein, and a normalization in the prothrombin time (Fig. 1). The patient was treated with an immunosuppressive regimen that included azathioprine, prednisone and antilymphocyte globulin. Two early rejection episodes occurred, 1 after a few days and the other after 3 wk. At the time of the 2nd episode there was an extreme degree of hyperbilirubinemia and raised alkaline phosphatase (Fig. 1). Reversal of the rejection was followed by 1 yr of normal graft function but the succeeding yr again saw 2 episodes of moderate graft dysfunction. Presently, 2 yr and 8 mo after transplantation, the patient is clinically well with a bilirubin of 1.8 mg per 100 ml. He has had no demonstrable neurologic impairment after transplantation. No dietary limitations have been imposed and chelating agents have never been administered except during a brief test.

Studies of the Copper Metabolism after Transplantation. The patient's diseased liver contained 216 μg copper per gm wet wt (normal less than 20). Following the transplantation there was a massive cupriuresis which declined to normal (less than 30 μg per 24 hr) after several mo (Fig. 2). At the end of 7 mo a 3-day course of D-penicillamine (1.5 g/day) was given and there was a 20-fold increase in urine copper excretion, which then rapidly returned to normal (Fig. 2). This increase is somewhat higher than that found in normal persons. From 15 mo onwards urine excretion has again been slightly to moderately elevated (maximum 255 μg per 24 hr).

During the 2 yr and 8 mo of follow-up, serial serum ceruloplasmins have varied from 29.5 to 55 mg per 100 ml and coincidentally measured total serum coppers have ranged from 80 to 171 μg per 100 ml (normal 70–118).

Homograft biopsies obtained 6, 17 and 28 mo after transplantation contained 15, 13 and 7 μg copper per gm wet wt.

Case 2. Clinical course. This boy was found to have cirrhosis of the liver at 11 yr of age when he presented with ascites and a serum bilirubin of 9.5 mg per 100 ml. The following yr he showed an improvement but at 13 yr he was admitted to our institution following 2 episodes of hematemesis. At this time, Kayser-Fleischer rings were detected and serum ceruloplasmin was found to be distinctly subnormal at 1.0–1.7 mg per 100 ml. Total serum copper was low, 22.4–35 μg per 100 ml, while the urinary excretion of the metal was elevated to 340–520 μg per 24 hr. An open liver biopsy revealed "postnecrotic" cirrhosis, the copper content of the specimen was 392 μg per gm wet wt. The diagnosis of Wilson disease was thus established and the patient was put on a low-copper diet and chelating therapy was instituted with D-penicillamine and triethyline tetramine dihydrochloride.[4] In spite of increased cupriuresis the patient's neurologic status deteriorated, with athetotic movements, dysarthria and mental disturbance.

At 14 yr of age, in March 1971, the patient underwent orthotopic hepatic transplantation. At this time the serum bilirubin was 2.9 mg per 100 ml, serum albumin was 2.9 gm per 100 ml, and prothrombin time 44% of normal. Postoperative immunosuppression was the same as in *Case 1*, except that cyclophosphamide was given instead of azathioprine during the 1st 9 mo. Following 1 mo of normal graft function, the serum bilirubin and the alkaline phosphatase rose rapidly to reach a maximum of 9.7 mg per 100 ml and 952 IU, respectively (Fig. 3). The concurrent finding of Australia antigenemia suggested serum hepatitis. The bilirubin returned to normal in 1 mo while the alkaline phosphatase required several mo to recover (Fig. 3). Presently, 12 mo after transplantation, graft function is normal.

During the 1st postoperative mo there was an improvement in the patient's neurologic status but subsequently the symptoms from the nervous system have recurred intermittently. The Kayser-Fleischer rings have not changed during the 12 mo of follow-up.

Studies of Copper Metabolism after Transplantation. The removed, native liver contained 184 μg copper per gm wet wt. After the hepatic transplantation, serum cerulo-

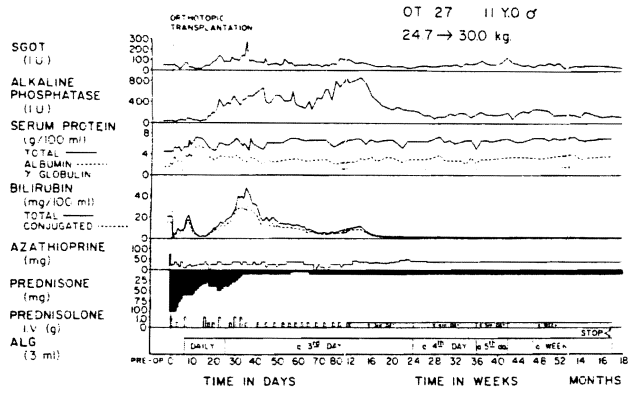

Fig. 1. The course and the immunosuppressive treatment in *Case 1*. (Adapted from *Lancet* **i**:505, 1971.)

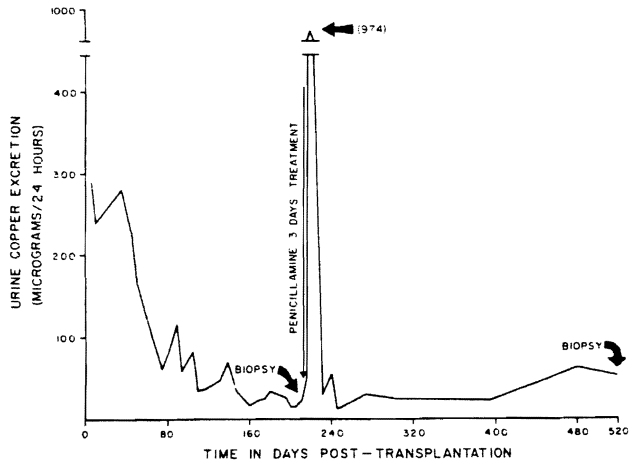

Fig. 2. Urinary excretion of copper after transplantation in *Case 1*. (Adapted from *Lancet* **i**:505, 1971.)

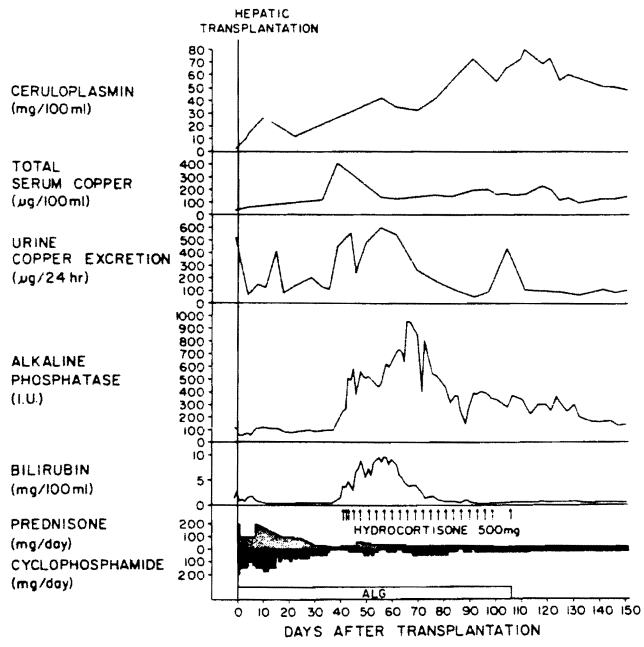

Fig. 3. The course and the immunosuppressive treatment in *Case 2*.

plasmin and copper rose, to reach normal levels after 2 wk (Fig. 3). Urinary copper excretion fluctuated between 60 and 600 μg per 24 hr for 4 mo and then stabilized around 100 μg (Fig. 3).

Discussion

Since most of the symptoms and signs of Wilson disease were lacking in the first of these two patients, the diagnosis was missed and chelating therapy had never been instituted. Following operation, the high copper concentration in the native liver and the presence of Mallory bodies in the specimen established the diagnosis. In addition, indirect evidence of extensive copper deposition in extrahepatic tissues was provided by the cupriuresis which followed operation.

In contrast, the second patient had every classic manifestation of Wilson disease and low-copper diet and therapy with chelating drugs had been tried for more than 1 year. In spite of this, the patient's neurologic symptoms progressed to a stage where he was severely crippled.

Following hepatic transplantation, both patients had an increased excretion of copper. In the second patient, low serum ceruloplasmin and copper rose to normal levels. Biopsy specimen of the graft in one of the patients has shown no accumulation of the metal. These findings are consistent with the hypothesis that the metabolic defect in Wilson disease is liver based. However, the facts that urinary copper excretion has stayed moderately elevated in both cases, and that the Kayser-Fleischer rings of the second patient are unchanged, indicate that the extrahepatic copper stores remain abnormal in these patients.

REFERENCES

1. Bearn, A. G.: Wilson's disease. In *The Metabolic Basis of Inherited Disease*. 3rd Ed, eds, J. B. Stanbury, J. B. Wyngaarden and D. S. Fredrickson. McGraw-Hill, New York, 1033, 1972.
2. Dubois, R. S.; Giles, G.; Rodgerson, D. O.; Lilly, J.; Martineau, G.; Halgrimson, C. G.; Shroter, G.; Starzl, T. E.; Sternleib, I. and Scheinberg, I. H.: Orthotopic liver transplantation for Wilson's disease. *Lancet* **i**:505, 1971.
3. Starzl, T. E. and Putnam, C. W.: *Experience in Hepatic Transplantation*, W. B. Saunders, Philadelphia, 1969.
4. Dubois, R. S.; Rodgerson, D. O.; Slovis, T. L.; Hambidge, K. M. and Bianili, T. A.: Use of triethylene tetramine dihydrochloride in the management of Wilson's disease. *Lancet* **ii**:775, 1970.