Metabolic Effects of Hepatic Replacement in Wilson's Disease

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WILSON's disease is an inborn disorder of metabolism characterized by progressive accumulation of copper in tissues with subsequent degenerative changes that affect mainly the brain and the liver. Discoloration of the cornea by the metal is observable on split-lamp examination as the Kayser–Fleischer ring. Abnormal biochemical findings may include elevated albumin-bound serum copper, increased urinary excretion of copper, low level of the copper-containing serum protein ceruloplasmin, and low total serum copper. The nature of the primary metabolic defect remians obscure.[1]

The frequency and significance of severe hepatic involvement in Wilson's disease has become increasingly apparent in the last years.[2,3] Clinically, the hepatic disorder is indistinguishable from other forms of chronic hepatitis. Histologically, there is "postnecrotic" cirrhosis with alcoholic hyaline bodies of Mallory.

Two teen-age boys with liver cirrhosis due to Wilson's disease have been treated with orthotopic hepatic transplantation at our institution. Studies of the copper metabolism in these patients has provided important information concerning the role of the liver in Wilson's disease.

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CASE REPORTS

Patient No. 1: An 11-yr-old boy was admitted for hepatic transplantation in July 1969. His liver disease dated back to the age of 8 when he was found to have abnormal liver-function tests and a liver biopsy showed "postnecrotic" cirrhosis. In April 1969 he developed symptoms of hepatic failure. A liver biopsy showed cirrhosis with Mallory bodies; the findings were interpreted as being consistent with Wilson's disease. There were no neurological symptoms and no Kayser–Fleischer rings. Two months later the patient was transferred to our institution in precoma. At this time he had massive ascites and anasarca. The serum bilirubin was 20.6 mg/100 ml, the serum albumin 1.5/100 ml, the prothrombin time 13% of normal, and blood ammonia 432 μg nitrogen/100 ml. A few hours after arrival the patient developed upper gastrointestinal hemorrhage and became agonal. Shortly afterward a cadaveric donor became available and the patient underwent an orthotopic hepatic transplantation.[4] Posttransplantation immunosuppression included azathioprine or cyclophosphamide, prednisone, and antilymphocyte globulin[4,5] (Fig. 1).

After the operation there was a clearing of the sensorium and a fall in the blood ammonia level. The serum bilirubin diminished (Fig. 1), and total serum protein and the prothrombin time normalized. Two early rejection episodes occurred. At the time of the second, there was an extreme degree of hyperbilirubinemia and alkaline phosphatmia (Fig. 1). Reversal of the rejection was followed by 1 yr of normal graft function but in the succeeding years there has been moderate elevation of SGPT and some episodes of hyperbilirubinemia (Fig. 1). Presently, 3 yr 2 mo after transplantation, the bilirubin is 2.2 mg/100 ml, alkaline phosphatase is 292 IU, and SGPT is 210 IU. Tests for Australia antigen in serum has consistently been negative. The patient is clinically well. No dietary limtations have been imposed and chelating agents have never been administered except for two brief tests.

Patient No. 2. This boy was admitted in March 1971 at the age of 14 yr for hepatic transplantation. At 11 yr of age liver disease had been diagnosed when he presented with ascites

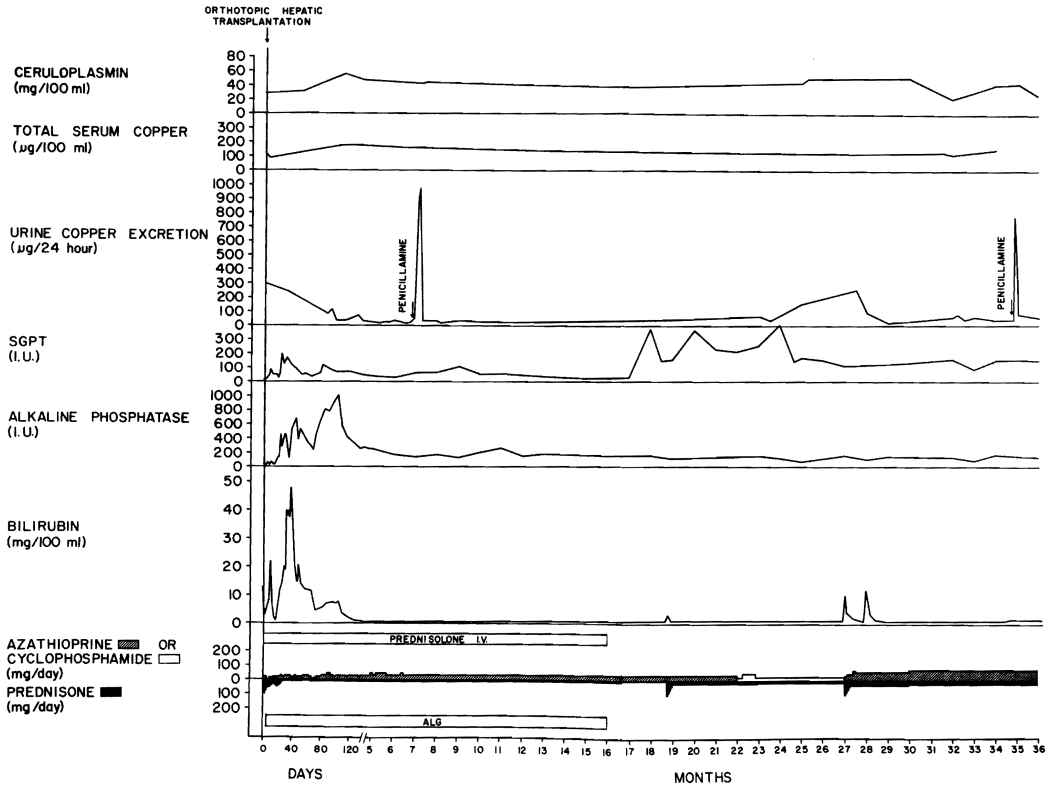

Fig. 1. The course in the first patient.

and a serum bilirubin of 9.5 mg/100 ml. In the next year there was an improvement but at 13 yr he had two episodes of hematemesis. At this time there was moderate neurological involvement with tremor and athetotic movements. Split-lamp examination revealed Kayser–Fleischer rings. An open liver biopsy showed postnecrotic cirrhosis. The finding of an elevated copper content in the liver specimen as well as typical abnormalities in the serum and urine copper established the diagnosis of Wilson's disease. A low-copper diet was instituted and chelating therapy was attempted initially with D-penicillamine and later with triethylene tetramine dihydrochloride. In spite of increased cupriuresis the patient's neurological status deteriorated and he became severely crippled with chorea and dysarthria.

At the time of transplantation the serum bilirubin was 2.9 mg/100 ml, serum albumin was 2.9 g/100 ml, and prothrombin time 44% of normal. Postoperative immunosuppression was as in the first patient except that cyclophosphamide was given instead of azathioprine during the first 9 mo (Fig. 2). After 1 mo of normal graft function there was a sudden rise in the serum bilirubin (maximum 9.6 mg/100 ml), the alkaline phosphatase (maximum 952 IU), and the SGPT (maximum 300 IU) (Fig. 2). The concurrent development of Australia antigenemia suggested serum hepatitis. Over the next few months liver function became normal (Fig. 2). Presently, 17 mo after transplantation, serum bilirubin is 0.64 mg/100 ml, alkaline phosphatase is 94 IU, and SGPT 30 IU, all within normal limits of our laboratory.

After transplantation the chelating therapy was not resumed and the dietary limitation in copper intake was abolished.

During the first 12 mo postoperative the patient's neurological status was intermittently improved but in intervening periods chorea and dysarthria was prominent. On the most recent neurological evaluation 17 mo after operation a definite improvement was noted, although the symptoms had not cleared completely.

Repeated examinations of the corneas showed unchanged Kayser–Fleischer rings during the first

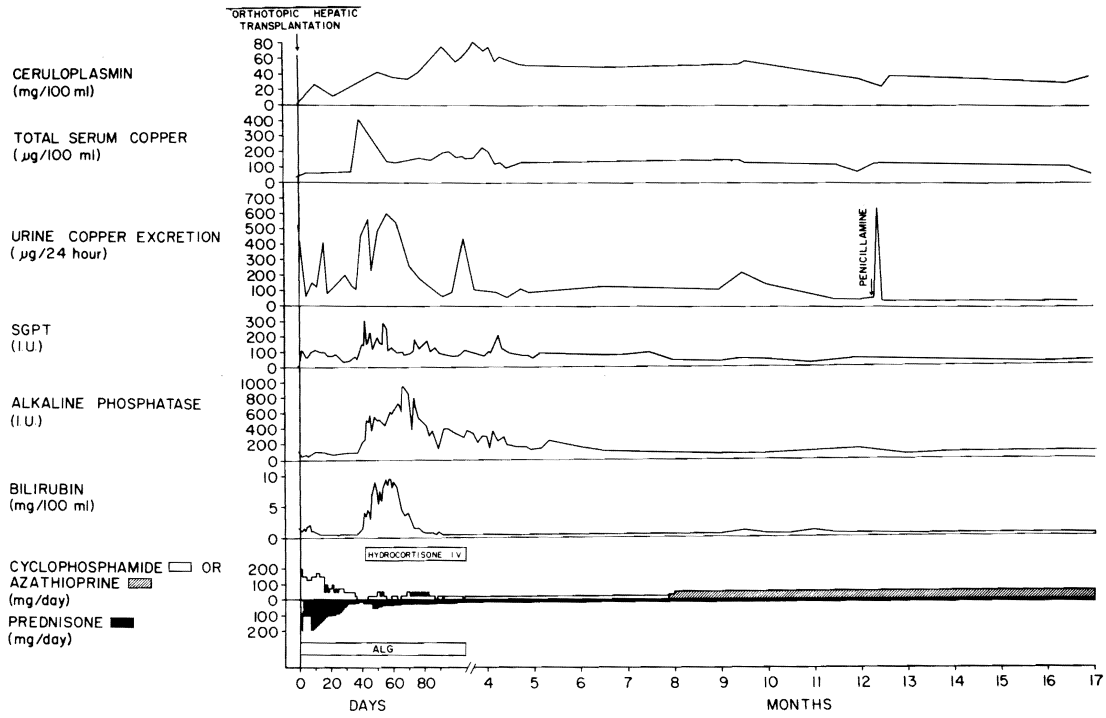

Fig. 2. The course in the second patient.

12 mo of postoperative follow-up. At 17 mo, however, a distinct decrease in coloration was noted.

STUDIES OF THE COPPER METABOLISM

Liver Copper: The diseased native livers both had an abnormally high copper content. The copper concentration in the removed liver of the first patient was 216 μg/g wet weight (normal < 20 μg). In the second patient a biopsy specimen obtained 12 mo before transplantation contained 329 μg copper/g wet weight. After therapy with chelating agents the removed liver contained 184 μg/g wet weight.

Biopsy specimens of the hepatic homograft obtained in the first patient at 6, 17, and 28 mo after transplantation contained 15, 13, and 17 μg of copper/g wet weight. Histopathologically, these tissues had minor abnormalities as previously reported.[6] In the second patient the liver copper concentration was 48, 30, and 45 μg in biopsy specimens obtained after 12, 13, and 17 mo, respectively. Histopathologically, these liver specimens were normal.

Urinary Copper Excretion: The first patient had normal urinary copper excretion when studied at another hospital several months before transplantation. In contrast, the second patient had an elevated copper excretion of 340 μg 24 hr (normal < 30 μg) before institution of chelating therapy. At the time of transplantation when chelating agent had been given for 1 yr 540 μg was excreted in 24 hr.

During the first several months after the hepatic replacement, the urinary copper excretion increased to high levels in the first patient and it remained elevated in the second patient. After approximately 5 mo a decrease toward normal was noted in both patients (Figs. 1 and 2). In the last year the first patient has occasionally excreated increased amounts of copper (maximum 225 μg/24 hr) (Fig. 2).

A 3-day course of D-penicillamine (1.5 g/day) given to the first patient at 7 and again at 35 mo after transplantation increased the copper excretion to 974 and 770 μg/24 hr, respectively. A similar test in the second patient at 12 mo posttransplantation resulted in an excretion of 646 μg, as compared with 1412 μg/24 hr 1 yr before the operation.

Serum Ceruloplasmin and Copper: In the first patient, preoperative serum ceruloplasmin was within normal range except for one sample in which it was diminished to 15 mg/100 ml (normal 22–43 mg/100 ml). Serum copper was normal in one specimen obtained at a previous admission to another hospital. In the seond patient serum ceruloplasmin was almost absent with concentrations of 1.0–1.7 mg/100 ml, and total serum copper concentration was low at 22.4–35 μg/100 ml (normal 70–118 μg).

After hepatic transplantation serum ceruloplasmins and total serum coppers have been normal or slightly above normal during the 3 yr 2 mo of follow-up in the first patient (Fig. 1). In the second patient, these measures rose within the first weeks after transplantation to reach normal levels. The levels have been subsequently within or above normal range (Fig. 2).

DISCUSSION

The early work-up of the first patient had revealed postnecrotic cirrhosis with Mallory bodies suggesting Wilson's disease, but the lack of neurologic impairment and the absence of Kayser–Fleischer rings as well as the normal serum ceruloplasmin and copper made the diagnosis equivocal. As a consequence, chelating therapy was never instituted in spite of the progressive deterioration in liver function. When the patient presented at our institution his condition was no longer amenable to medical treatment and hepatic transplantation was carried out.[6]

The second patient had all the classical clinical and biochemical manifestations of Wilson's disease. Consequently, low-copper diet and therapy with chelating drugs had been tried for more than 1 yr. During this time the liver copper decreased somewhat but there was no evidence of corollary improvement in hepatic function. Furthermore, the patient's chorea and dysarthria progressed to a stage where he was severely crippled. When hepatic transplantation was carried out it was hoped that the provision of a normal liver would improve the copper metabolism with consequent amelioration of the extrahepatic manifestations of the disease.

Several findings indicate that the handling of copper was indeed favorably affected by the hepatic replacement. There was no accumulation of the metal in the new liver of the first patient. In the second patient, the serum ceruloplasmin and copper normalized shortly after transplantation and biopsy specimens of the graft have shown only a slightly elevated copper concentration. The initial high urinary excretion of copper is consistent with clearing of tissue copper stores, although both patients had concurrent hepatic dysfunction with cholestasis which might interfere with biliary excretion of copper and cause a compensatory capriuresis. When later in the course D-penicillamine was administered over 3 days, both patients showed a copper excretion only slightly exceeding that seen in normal persons. Finally, the fact that the neurologic symptoms have abated and that the Kayser–Fleischer rings have become less prominent in the second patient indicates that the extrahepatic manifestations are being favorably affected by the hepatic transplantation. The present findings are consistent with the hypothesis that the metabolic defect in Wilson's disease is liver based. Hopefully, the future course of these two patients will provide grounds for a definite conclusion concerning the role of the liver in the pathogenesis of the disease.

SUMMARY

Two boys with Wilson's disease had liver replacement 3 and 1½ yr ago for terminal hepatic failure and moderate cirrhosis plus severe neurologic involvement, respectively. Both patients had a high liver copper value but only the second boy had low ceruloplasma and total serum copper and increased urinary copper excretion. Biopsy specimen of the grafts have shown copper

levels that are normal or only slightly elevated. The serum and urine findings in the second patient have normalized, his neurologic symptoms have abated, and the Kayser–Fleischer rings have become less prominent. The findings are consistent with the hypothesis that the metabolic defect in Wilson's disease is liver based.

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