Homotransplantation of the liver in a patient with hepatoma and hereditary tyrosinemia

A girl with hereditary tyrosinemia, diagnosed at 6 months of age, was treated with a diet restricted in phenylalanine and tyrosine. At 9½ years of age she developed an acutely enlarged liver and spleen, and the diagnosis of hepatocarcinoma was made. The patient received a liver transplant and tyrosine metabolites became normal while she was receiving a regular diet. Three months later, an infected thrombosis of the portal vein caused her death. Liver transplant appears to be an effective method of enzyme replacement in tyrosinemia and should be considered for prevention of hepatoma.

Robert O. Fisch, M.D.,* Minneapolis, Minn.,
Edward R. B. McCabe, M.D., Ph.D., Denver, Colo., Doris Doeden, M.S.,
Minneapolis, Minn., Lawrence J. Koep, M.D., Jerry G. Kohlhoff, B.A.,
Arnold Silverman, M.D., and Thomas E. Starzl, M.D., Denver, Colo.

Hereditary tyrosinemia is a disorder characterized by hypertyrosinemia, tyrosinuria, marked excretion of tyrosine metabolites in the urine (tyrosyluria), liver disease, and renal tubular dysfunction. p-Hydroxyphenylpyruvic acid oxidase (4-hydroxyphenylpyruvate: oxygen oxidoreductase [hydroxylating, decarboxylating], EC 1.13.11.27) has been shown to be deficient in the livers of patients with hereditary tyrosinemia, but it is not clear that this is the primary enzymatic deficiency. Recently, evidence has been presented suggesting a deficiency of another enzyme in tyrosine catabolism, fumarylacetoacetase (4-fumarylacetoacetate fumarylhydrolase, EC 3.7.1.2), in this disease. Tyrosinemia and tyrosyluria can be found in liver disease due to other causes, notably, hereditary fructose intolerance.1,2

The liver disease in hereditary tyrosinemia features progressive hepatocytic atrophy with fibrosis and nodular regeneration.3 Hepatoma is a significant contributor to death in patients surviving beyond infancy.4 Although dietary restriction of phenylalanine and tyrosine will lead to improvement of tyrosinemia, tyrosyluria, growth, and renal tubular dysfunction,5 it is not clear that this will alter progression of pathologic changes in the liver that lead ultimately to the development of hepatocarcinoma.4

Abbreviations used
ALA: delta-aminolevulinic acid
ALA-D: ALA-dehydratase
pHPPA: p-hydroxyphenylpyruvic acid
pHPLA: p-hydroxyphenylactic acid

CASE REPORT

The patient weighed 3,458 gm at birth; pregnancy and delivery were uncomplicated. She began vomiting at 2 months of age. Later she developed abdominal distention, periorbital edema, and increasing ascites. At six months of age she was admitted to the University of Minnesota Medical Center.

Exploratory laparotomy revealed enlargement of the liver and kidneys. The spleen was normal. Biopsies revealed cirrhosis of the liver and focal calcification of the kidneys.
Abnormal liver function tests included clotting studies uncorrected by vitamin K. Metabolic studies revealed hyponatraemia, tyrosuria, and aminoaciduria, suggesting a diagnosis of "hereditary tyrosinemia" (Table I). She was given a diet low in tyrosine and phenylalanine (AB-3200, Mead Johnson) at 7 months of age. She was hospitalized twice during her first year of life for dietary readjustment and was followed at approximately monthly intervals for clinical and laboratory evaluation which included routine assessment of serum tyrosine and urinary tyrosine metabolites. With the exception of two episodes of urinary tract infection, her course was uncomplicated over the first nine years. Intellectual development was normal and activity was unrestricted. Ambulatory dietary management in her ninth year provided tyrosine 35 mg/day, phenylalanine 41 mg/kg/day, and protein 2.1 gm/kg/day. Growth measures at the last outpatient evaluation at 9% years included weight 27.3 kg (twenty-fifth percentile), height 130.9 cm (twenty-fifth percentile), and head circumference 52 cm (fortieth percentile). At that time the liver was 2 to 3 cm below the right costal margin and the spleen was 10 cm below the left costal margin.

The family history was unremarkable; the parents and three siblings are in good health.

She was admitted two weeks later to the University of Minnesota Medical Center with acute onset of abdominal pain and an enlarging spleen. There was no preceding history of hepatitis or infection. On physical examination a nodular liver was palpable 3.5 cm below the right costal margin, and the spleen extended 16 cm below the left costal margin with a 10 cm width.

Laboratory findings at this time included hemoglobin 9.1 gm/dl, 2,000 white blood cells/mm³, 51,000 platelets/mm³, BUN 21 mg/dl, and creatinine 0.1 mg/dl.

A liver-spleen scan revealed a discrete filling defect in the right lobe of the liver and an enlarged spleen. An angiogram of the liver and spleen showed abnormal vasculature in the right lobe of the liver and massive splenomegaly without evidence of a splenic vascular accident. Bone marrow examination and multiple x-ray examinations did not demonstrate metastases. The patient was subjected to exploratory laparotomy and open liver biopsy. Findings at surgery included regenerative macronodular cirrhosis and an area of firm tumor on the right lobe of the liver. Biopsies of the mass confirmed a diagnosis of hepatocellular carcinoma of the right lobe of the liver. Severe macronodular cirrhosis precluded resection.

Additional laboratory results included negative alpha fetoprotein, elevated gamma glutamyltranspeptidase (54 IU/l), alkaline phosphatase 578 IU/l, SGOT 78 IU/l, and negative heterophil antibody test. Serum electrophoresis revealed a twice normal elevation of alpha-1 fraction (0.41 gm/dl), trypsin inhibitory capacity 2.06 mg (normal 0.25 to 1.2 mg), and carcinoembryonic antigen 0.1/1 ng/ml (normal < 2.0/1 ng ml).

She was transferred to the University of Colorado Medical Center. Additional investigation revealed no evidence of metastatic disease, and two weeks after admission she underwent total hepatectomy and orthotopic liver transplantation. The liver, weighing 1,450 gm, was cirrhotic with hepatocellular carcinoma invading the portal vein. Blood pressure gradually rose to a high of 192/124 on the second postoperative day; this responded to

---

Table I. Results of serum and urinary tyrosine metabolites, urinary ALA, ALA-D, and protoporphyrin in red blood cells

<table>
<thead>
<tr>
<th></th>
<th>Normal values</th>
<th>On regular diet 5-6 mo of age (N = 3)</th>
<th>On restricted diet 6 mo 9 yr (N = 52)</th>
<th>1 wk prior to transplant on restricted diet (N = 1)</th>
<th>2 days after transplant (N = 1)</th>
<th>0.5-11 wk after transplant (N = 7-10)</th>
<th>12 wk after transplant (week prior to death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum tyrosine (mg/dl)</td>
<td>Mean 2.47 ± 0.97</td>
<td>Mean 13.2 Range 0.7-6.3 Mean 3.29 SD ± 1.16</td>
<td>3.83 Range 0.59-1.25 Mean 0.79</td>
<td>73.5 Range 62.5-223.0 Mean 136</td>
<td>0 Range 0-0.16 Mean 0.11</td>
<td>9.4 Range 3.1-10.0 Mean 4.94</td>
<td>1.1-1.2</td>
</tr>
<tr>
<td>Urine tyrosine (μmol/24 hr)</td>
<td>(3-12 yr) Range 40-168</td>
<td>Mean 19.0 Range 12-24.0 Mean 2.62 SD ± 4.0</td>
<td>6.85 Range 0.1-2.0 Mean 0.72</td>
<td>0 Range 0-0.16 Mean 0.11</td>
<td>0.19 Range 0-0.16 Mean 0.11</td>
<td>0.05 Range 0-0.16 Mean 0.11</td>
<td>0.19</td>
</tr>
<tr>
<td>Urine pHHPA and pHLA (μmol/ml)</td>
<td>Range 0.0-0.3 Mean 5.57</td>
<td>Mean 5.57 Range 3.0-37.0 Mean 20.5 SD ± 3.34</td>
<td>34.4 Range 3.1-10.0 Mean 4.94</td>
<td>9.4 Range 3.1-10.0 Mean 4.94</td>
<td>9.4 Range 3.1-10.0 Mean 4.94</td>
<td>9.4 Range 3.1-10.0 Mean 4.94</td>
<td>9.4</td>
</tr>
<tr>
<td>RBC ALA-D (μmol) ALA/min/liver RBC</td>
<td>Range 22.4-44.5 Mean 33 SD ± 4.8</td>
<td>Mean &lt;6.0 Mean 6.0 SD ± 4.8</td>
<td>9.4 Range 3.1-10.0 Mean 4.94</td>
<td>9.4 Range 3.1-10.0 Mean 4.94</td>
<td>9.4 Range 3.1-10.0 Mean 4.94</td>
<td>9.4 Range 3.1-10.0 Mean 4.94</td>
<td>9.4</td>
</tr>
<tr>
<td>RBC protoporphyrin (μg/dl)</td>
<td>Range 22.0-87.0 Mean 46.0 SD ± 14</td>
<td>Mean 93.3 Mean 93.3 SD ± 10.4</td>
<td>9.4 Range 3.1-10.0 Mean 4.94</td>
<td>9.4 Range 3.1-10.0 Mean 4.94</td>
<td>9.4 Range 3.1-10.0 Mean 4.94</td>
<td>9.4 Range 3.1-10.0 Mean 4.94</td>
<td>9.4</td>
</tr>
</tbody>
</table>
Demonstration of normal aldolase activity in patient's native liver after hepatectomy*  

<table>
<thead>
<tr>
<th>Liver</th>
<th>Fructose-1,6-diphosphate</th>
<th>Fructose-1-phosphate</th>
<th>FDP/F-1-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>26.7</td>
<td>22.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Patient</td>
<td>37.4-43.5</td>
<td>30.2-26.8</td>
<td>1.2-1.6</td>
</tr>
</tbody>
</table>

*Enzyme activity is expressed as nanomoles NAD formed/mg protein min at 37° utilizing the assay of bolstein and Rutter.

Zinc concentrations in urine, plasma, and red blood cells  

<table>
<thead>
<tr>
<th>Normal*</th>
<th>Period 1974-1975</th>
<th>Range</th>
<th>N</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine zinc (mg/24*)</td>
<td>0.4-0.6</td>
<td>0.006-0.05</td>
<td>5</td>
<td>0.036</td>
</tr>
<tr>
<td>Plasma zinc (μg/ml)</td>
<td>0.89 ± 0.13</td>
<td>0.64-0.58</td>
<td>2</td>
<td>0.61</td>
</tr>
<tr>
<td>RBC zinc (gm/ml)</td>
<td>10.1 ± 1.2</td>
<td>10.7-15.4</td>
<td>2</td>
<td>13.0</td>
</tr>
</tbody>
</table>

DISCUSSION  
This patient's presentation and physical and laboratory findings are typical of hereditary tyrosinemia, with improvement of the metabolic studies after dietary restriction of tyrosine and phenylalanine. Hereditary fructose intolerance (hepatic aldolase deficiency) can present in a similar fashion, but this patient's liver had normal aldolase activity (Table II). and she responded biochemically to a diet restricted in tyrosine and phenylalanine unrestrained in fructose. Although our patient did not have evidence of vitamin D-resistant rickets, she did have intermittent porphyria, elevated urinary ALA values, and evidence of ALA-D deficiency (Table I). The patient is among the first with tyrosinemia in whom decreased red cell activity of zinc-dependent enzyme ALA-D, and zinc deficiency as measured by diminishing levels in plasma and urine, have been documented (Table III). The appearance of hepatoma is characteristic of patients with hereditary tyrosinemia, even in those treated with tyrosine and phenylalanine restricted diets.

Hepatocarcinoma usually appears in children over the age of 5 years; one third of the cases are associated with cirrhosis: 37% of patients with hereditary tyrosinemia surviving beyond 2 years of age develop hepatocarcinoma. The median age at the time of death has been 15 years, with a range of 4 to 25 years. Hepatocarcinoma was
Homotransplantation of the liver

...death in 66% of the females and 57% of the males. Incidence of tumor among patients with hereditary tyrosinemia is far greater than the incidence of this tumor autopsied adults with cirrhosis (4.4% of adult and 17.5% of adult males, for an overall incidence 2%), suggesting that factors other than the mere presence of cirrhosis are associated with the induction of hepatoma in tyrosinemia. The coexistence of cirrhosis and hepatocarcinoma also distinguishes the tyrosinemic child from others with this tumor, since in contrast to this association is relatively infrequent in the general population. A hepatocarcinoma is uniformly fatal. The time from the diagnosis of 47 untreated with primary cancer of the liver ranged from one to 24 months, with a mean of five months. A series of 47 pediatric patients who had been managed with surgical resection of hepatocarcinoma: 27 were alive, 15 without metastasis, seven of these patients were well at least five years after their resection. A recent survey of 16 pediatric clinics indicated that the two-year survival with cellular carcinoma was only one out of eight, with survival beyond five years rare. Radiation and cancer drugs usually had little effect on these hepatic tumors: lobectomy, hemihepatectomy, or extended hepatectomy were the operations of choice. The nodular cirrhosis of patients with hereditary tyrosinemia and hepatoma markedly increases the operative risk in our patient, precludes surgical resection. Lives in these patients are then to do nothing, to modalities (i.e., radiation and drugs) which appear to be of no value, or to consider liver transplantation in the first liver transplantation in 1963, 119 have been reported. In one report, more than half of the patients were children. Hepatoma was the most common cause for liver transplantation for adults, and second for children. Replacement through orthotopic liver transplantation for inherited metabolic disorders has been newly reported for Wilson disease (two patients), α-1 antitrypsin deficiency (one patient), and for Niemann-Pick disease (one patient). These patients have remarkable one-year survival of 100% and successful treatment of the metabolic defect. The patient with Niemann-Pick disease was operated on at 2 years of age; following liver transplantation, not only did enzymatic function resume, but clouding of the cornea quickly disappeared, together with a definite regression of the lipid infiltrate in the retinas.

In the current management of hereditary tyrosinemia, the only supportive measure is dietary restriction; enzymatic replacement therapy is not available. In spite of the rejection symptoms and the terminal outcome, our patient demonstrates that hepatic transplantation does alleviate the metabolic abnormalities of the liver and kidney in this disorder. A recommendation for routine liver transplantation in this disease might be considered, understandingly, an overly aggressive posture. However, increasing experience, improving technical skill, better preservation of livers, and immunologic support will inevitably produce more successful hepatic transplants.

Appropriate timing of transplantation would not only restore normal tyrosine function and other liver functions, but ideally could prevent the complications of severe cirrhosis and portal hypertension, and might help prevent hepatoma.

We thank Mr. William H. Scruton for his assistance with heavy metal determinations by the Minnesota Department of Health.

REFERENCES

11. Tomokuni K, and Ogata M: Simple method for determina-